Impact of Achieved Blood Pressure on Cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial


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tients with diabetes have an enhanced risk for cardiovascular (CV) events (1–3). The treatment of the increased BP decreases CV events in diabetic (4–7) and in nondiabetic patients (8,9). Target BP have been progressively lowered. However, there remains controversy about which component of BP is important. Patients with microalbuminuria, proteinuria, or elevated serum creatinine have an increased CV risk compared with patients without renal disease (10,11), but no BP goals that have been demonstrated to reduce CV risk in such patients have been established. This is because studies that have examined the benefits of lowering BP on CV risk excluded patients with overt renal disease. The Irbesartan Diabetic Nephropathy Trial (IDNT), conducted in patients with type 2 diabetes and proteinuria, provides opportunity to assess the relationship of BP control to the development of CV outcomes. The IDNT reported the association of achieved follow-up BP with renal outcomes and an increase in all-cause mortality in patients with systolic BP (SBP) <120 mmHg (12). This report aimed to determine the association of achieved SBP with specific CV events and the association of achieved diastolic BP (DBP) with all-cause mortality and CV events and to analyze the association of different levels of SBP, DBP, and pulse pressures with CV outcomes.

Materials and Methods

Study Patients

This study is based on data from the IDNT trial (13) (Appendix 1). The methods and baseline characteristics of the 1715 participate have been published (13,14). Entry criteria included age between 30 and 70 yr; documented type 2 diabetes; and hypertension defined as seated office SBP >135 mmHg, seated office DBP >85 mmHg, or documented
treatment with antihypertensive agents. All patients had overt proteinuria (>900 mg/24 h) and serum creatinine between 1.0 and 3.0 mg/dl in women and between 1.2 and 3.0 mg/dl in men. Institutional review board or appropriate ethics committee at each center approved the protocol. All patients gave written informed consent.

**Treatment and Randomization**

Patients were randomly assigned centrally by computer to receive irbesartan 300 mg/d (Avapro; Bristol-Myers Squibb, Princeton, NJ), amlodipine 10 mg/d (Norvasc, Pfizer, NY), or matched placebo. Randomization was blocked by center. All patients had BP controlled with a BP goal of <135/85 mmHg. For the analysis of CV end points, patients were followed to initiation of treatment for end-stage renal failure (dialysis, renal transplantation, or a serum creatinine level ≥530.4 μmol/L [6.0 mg/dl]), death, or administrative censoring in December 2000 (median follow-up, 1082 d; range, 121 to 1721 d).

**Medical Management**

Patients were seen in hypertension or renal clinics at 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. SBP and DBP were determined at baseline and throughout the trial per study protocol. Office BP were performed 1 min apart in triplicate after the patient remained quiet and seated for 10 min, followed by triplicate measurements after standing for 2 min. More frequent visits were required when the recorded BP was not at treatment goal. Visits to bring BP under control took place at 2-wk intervals until goal BP was reached. A clinical management committee (CMC) reviewed achieved BP and therapeutic regimens on a quarterly basis after the eighth study week on any patient who did not meet the BP goal. The CMC recommended BP management in accordance with JNC VI (15). Telephone contact and written correspondence occurred regularly between the CMC or centers that had difficulty meeting BP goals.

**Outcomes**

The primary outcome was time to occurrence of a composite renal outcome of doubling of entry serum creatinine, ESRD, or all-cause mortality (13). We also established CV outcomes, defined in Appendix 2.

**Ascertainment of CV Events**

All hospitalizations and adverse events were screened at Bristol-Myers Squibb (Princeton, NJ) by trained, blinded clinical research associates to identify potential CV events. Investigators reported all CV events. For all potential events, hospital discharge summaries and records including laboratory values, electrocardiograms (EKG), and radiographic reports were obtained. A central EKG reading center was established at Brigham and Women’s Hospital (Boston, MA), where two cardiologists reviewed every EKG. Electrocardiography was performed at baseline, 6 mo, 12 mo, and annually thereafter. A total of 5698 EKG were reviewed at the center. All new Q-wave infarctions found on these EKG were correlated with clinical events.

**Adjudication of CV Events**

An Outcomes Confirmation and Classification Committee (Appendix 3) reviewed potential CV outcomes in a blinded manner. Investigators at each center reported CV events. The information on all potential events was also referred to one member of the Outcomes Confirmation and Classification Committee. When the committee member agreed with the classification of the center investigator, the classification was accepted. When the center investigator and the committee member differed, the case material was adjudicated by the entire committee membership, with a simple majority rule. Deaths were adjudicated by a mortality committee. Each death was reviewed by two committee members and presented to the membership, whose decision was accepted as final.

**Statistical Analyses**

BP fell in all randomization groups during the first 6 mo of follow-up but was stable in all groups thereafter. We defined the mean achieved BP for each patient as the simple mean of all SBP and DBP obtained on that patient at regularly scheduled 3-month visits on or after the 6-mo visit; 1590 patients reached such a visit. On average, the mean follow-up achieved BP were determined from the three BP recordings at each of nine follow-up visits, with a range from one to 17 visits. Continuous baseline variables were compared between groups by t test, and categorical variables were compared by the χ² test. For the determination of hazard ratios, we used proportional hazards modeling with BP variables and randomized treatment assignment as covariates. BP variables were considered either continuously (as linear covariates) or by increasing 10 mmHg categories. For achieving stable analyses, patients with the highest and lowest BP categories were consolidated into single categories designated less than or greater than the stated boundary value. For all-cause mortality and CV death outcomes, we used standard proportional hazards analysis. For the other CV outcomes, which could occur more than once, we used the Anderson-Gill formulation of the proportional hazards model in which patients are considered at risk for the first event from randomization to the time of the first event, at risk for the second event from the day after the first event to the time of the second event, and so forth, permitting use of all of the data. In accordance with the method of Lee et al. (16), we used a robust variance estimate that takes into account the possibility of correlation of risk for multiple events within a patient. We believed that occurrence of a first event increases the likelihood of a subsequent similar event. Therefore, in these analyses, we included as an independent covariate, in addition to BP variables and treatment assignment, a time-dependent covariate indicating whether the event was the first of its type or a subsequent event. Patients were included in these analyses only when they had at least one BP measurement at or after the 6-mo follow-up visit, so relative risk (RR) for all-cause mortality and CV death was computed conditional on survival for 6 mo. Among patients who survived to the 6-mo visit, all congestive heart failure (CHF), myocardial infarction (MI), and stroke events from randomization to death or censoring were included in the analysis. Data management and computations were performed using SAS for Windows, Version 8 (SAS Institute, Cary, NC) or S-Plus for Windows, Version 6.2 (Insightful Corp., Seattle, WA). Statistical tests were two-sided. P ≤ 0.05, unadjusted for the multiple comparisons, was considered to be statistically significant.

**Role of the Funding Sources**

The funding sources were involved in the data collection but not in the analysis or interpretation or the decision to submit the manuscript for publication.

**Results**

Baseline BP (mean ± SD) for the 1590 patients was 159/87 ± 20/11 mmHg and was similar among treatment groups. BP was controlled in the irbesartan group to a mean of 141/78 ± 14/8 mmHg (n = 537), in the amlodipine group to 142/77 ± 13/8 mmHg (n = 523), and in the placebo (usual care) group to 144/80 ± 13/8 mmHg (n = 530). Thirty percent of participants reached the 135-mmHg SBP goal, and 81% achieved the DBP goal (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 nonstudy drugs (17). Overall, the use of other antihypertensive agents was similar in the three groups. However, there was a significantly greater use of sympathetic agents in the placebo group. There was no statistically significant difference in the use of thiazide or loop diuretics among the three study cohorts (17).

**CV Event and Characterization of Patients with SBP <120 mmHg**

Fifty-three patients whose follow-up mean SBP were <120 mmHg had increased all-cause mortality (12). Table 1 summarizes deaths and CV events in this population. The increased RR for all-cause mortality (3.05; 95% confidence interval [CI] 1.80 to 5.17; P < 0.0001) was mimicked by a similar increase in CV mortality (RR 4.06; 95% CI 2.11 to 7.80; P < 0.0001). Likewise, the RR for episodes of CHF was increased in this group of patients (1.80; 95% CI 1.17 to 2.80; P = 0.008). There was no significant increase in risk for MI and a nonsignificant trend to more strokes. Table 2 summarizes the baseline variables that differentiated this group of 53 patients from the 1537 others. More than 40 baseline variables were analyzed. The patients whose mean achieved SBP was ≤120 mmHg had a higher fraction than the other patients with a history of heart disease and with CHF at entry into the study. However, the adverse risks of death and CV death in this group, compared with patients with an average SBP >120 mmHg, remained significant and were not substantially reduced after accounting for the different frequencies of these two comorbidities. The patients with SBP <120 mmHg were younger. Fewer of them were on calcium channel blockers. These patients also had lower serum creatinines, lower baseline seated SBP and DBP, and higher standing pulse rates and were on fewer antihypertensive drugs. Because of its limited size and the multiple differences between these patients and the rest of the cohort, all further analysis were undertaken solely in the patients who achieved a mean SBP >120 mmHg.

**Effect of Achieved SBP on CV Outcomes**

Figure 1A depicts the effect of the achieved SBP on the risk for CV death adjusted for treatment assignment variables. There was a progressive decrement in the risk for death from a CV event as achieved SBP decreased from >170 mmHg to 120 to 130 mmHg. In this range, a 20-mmHg lower achieved mean SBP was associated with a 39% reduction in CV mortality (P = < 0.002). The attainment of lower SBP to 120 mmHg was also associated with fewer CHF events. A 20-mmHg decrease in SBP reduced the risk by 25% (P = 0.001; Figure 1B). SBP was not significantly related to the risk for nonfatal MI (RR 0.96/10-mmHg increase; P = 0.61). A nonsignificant trend for a relationship was seen for stroke (RR 1.15/10-mmHg increase; P = 0.12).

**Effect of Assignment to Treatment Group and Achieved SBP on the Risk for CHF**

We have previously reported that assignment to irbesartan significantly decreased the risk for CHF (17) compared with either amiodipine or placebo. We therefore analyzed the independent contribution of lowering SBP and treatment assignment on CHF. At almost every point of the SBP spectrum, assignment to irbesartan was associated with a lower rate of CHF events when compared with amiodipine or placebo, and the effects of BP and treatment assignment were statistically independent (test for interaction P = 0.51). Assignment to irbesartan and lower SBP reduced the risk for CHF to an extent greater than either alone. We

### Table 1. CV outcomes in patients with mean achieved SBP > and ≤120 mm/Hg

<table>
<thead>
<tr>
<th>BP &gt; 120 mmHg (n = 1537)</th>
<th>BP ≤ 120 mmHg (n = 53)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Events</td>
<td>Patients (%)</td>
<td>Events</td>
</tr>
<tr>
<td>CV mortality</td>
<td>192 (12%)</td>
<td>15 (28%)</td>
<td>4.06 (2.11 to 7.80)</td>
</tr>
<tr>
<td>CHF</td>
<td>289 (19%)</td>
<td>23 (25%)</td>
<td>1.80 (1.17 to 2.86)</td>
</tr>
<tr>
<td>MI</td>
<td>120 (7%)</td>
<td>3 (6%)</td>
<td>0.91 (0.29 to 2.78)</td>
</tr>
<tr>
<td>Stroke</td>
<td>65 (4%)</td>
<td>4 (6%)</td>
<td>2.12 (0.77 to 5.84)</td>
</tr>
</tbody>
</table>

aCV, cardiovascular; SBP, systolic BP; RR, relative risk; CI, confidence interval; CHF, congestive heart failure; MI, myocardial infarction.

bNumber of patients with at least one event.

cRR of patients with mean achieved SBP of 120 mmHg compared with those with mean achieved SBP >120 mmHg. For all-cause mortality and CV mortality, the risk period is limited to follow-up after 6 mo. For CHF, MI, and strokes, the risk period includes the entire period from randomization to death or censorship in patients who survived at least to the 6-mo visit.

### Table 2. Baseline variables that differed in patients with mean achieved SBP > and ≤120 mm/Hg

<table>
<thead>
<tr>
<th>BP &gt; 120 mmHg</th>
<th>BP ≤ 120 mmHg</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1537</td>
<td>53</td>
</tr>
<tr>
<td>Age</td>
<td>59.0</td>
<td>56.6</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>44%</td>
<td>60%</td>
</tr>
<tr>
<td>History of CHF</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>36%</td>
<td>21%</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Baseline SBP (mmHg)</td>
<td>159</td>
<td>140</td>
</tr>
<tr>
<td>Baseline DBP (mmHg)</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>Standing pulse (per min)</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>BP drug classes</td>
<td>1.45</td>
<td>0.98</td>
</tr>
</tbody>
</table>

aCCB, calcium channel blockers; DBP, diastolic BP.
also reported that assignment to amlodipine significantly reduced the risk for MI (17), compared with either irbesartan or placebo. The effect of assignment to amlodipine was not altered by adjustment for SBP. No other treatment-specific effects on CV outcomes were noted (Table 3) (17).

Effect of Achieved DBP on All-Cause Mortality and CV Events

In contrast to the observations made with SBP, there was a statistically insignificant trend to an inverse relationship between DBP and all-cause and CV mortality, seen primarily at DBP <85 mmHg. This more or less neutral impact of achieved DBP on mortality seems to be the result of opposing effects of lower DBP to be associated with increased risks for MI and CHF but with a decreased risk for stroke. The association with MI was highly significant ($P < 0.0001$), with a 61% increase in RR per 10 mmHg lower DBP (Figure 2). This effect was independent of treatment assignment. The beneficial impact of assignment to amlodipine and the adverse association with lower DBP remained essentially unchanged and significant in a model that contained both variables. A more modest increment in risk was noted for CHF. In contrast, the risk for stroke paralleled changes in SBP, with a lower stroke incidence at lower DBP (Table 4).

Effect of Pulse Pressure on All-Cause Mortality and CV Outcomes

Figure 3 reflects the effect of increasing pulse pressure on all-cause mortality. For each 10-mmHg increase in pulse pressure, the RR for death increased by 27%. This effect is particularly striking when pulse pressure exceeded 90 mmHg. As shown in Table 5, an increase of 10 mmHg in pulse pressure significantly enhanced the risk for CV death, MI, and CHF as the impact on CV deaths approached significance. There was no significant effect of pulse pressure on strokes.

Discussion

Numerous studies have shown that the lowering of BP with a variety of antihypertensive agents reduces CV morbidity and mortality (18–21). This is also reflected in the consistent superiority of any active drug intervention when compared with placebo (22,23). It is less clear whether treatment with one class of agents is superior to another, with the exception of prevention of heart failure by angiotensin-converting enzymes (ACE),

Table 3. Simultaneous impact of achieved SBP and treatment assignment to irbesartan (versus amlodipine or placebo) on risk for CHF

<table>
<thead>
<tr>
<th>Independent Variable(s)</th>
<th>RR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower achieved SBP (per 20 mmHg)</td>
<td>0.75 (0.63 to 0.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>Assignment to irbesartan (compared with placebo or amlodipine)</td>
<td>0.71 (0.54 to 0.93)</td>
<td>0.013</td>
</tr>
<tr>
<td>Both lower SBP and irbesartan</td>
<td>0.53 (0.38 to 0.73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
We conclude that for SBP patients who had BP measurements on a mean of nine occasions. We analyzed the impact of BP achieved after 6 mo in 1590 blockers on CV events with the exception of CHF hospitalization.

Angiotensin II Antagonist Losartan (RENAAL) (24) unveiled neither IDNT (17) nor Reduction of Endpoints in NIDDM with an effect of assignment to treatment with angiotensin receptor blockers (23). These conclusions were drawn from studies with a broad range of hypertensive patients with and without diabetes at varying stages of their disease. The great majority of the patients with diabetes in these trials had little or no renal disease. The IDNT trial provides an opportunity to assess, in a group of patients with overt diabetic nephropathy, the impact of BP on the occurrence of CV events. This is fitting because neither IDNT (17) nor Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) (24) unveiled an effect of assignment to treatment with angiotensin receptor blockers on CV events with the exception of CHF hospitalization.

We analyzed the impact of BP achieved after 6 mo in 1590 patients who had BP measurements on a mean of nine occasions. We conclude that for SBP >120 mmHg, increments of SBP are associated with a significantly higher rate of CV death and CHF. No such relation could be established for either nonfatal MI or strokes. The association of achieved SBP on strokes was indeterminate. However, at SBP <120 mmHg, the risk for CV death rate and CHF hospitalization was increased. Because assignment to the angiotensin receptor blocker irbesartan was associated with a decrease in CHF hospitalization, we examined the interaction between BP lowering and assignment to irbesartan. The analysis revealed a significant protective effect of irbesartan on this CV event that was independent of BP lowering (Table 3).

Our study also revealed significant effects of changes in DBP. At DBP <85 mmHg, we observed a trend to increase in all-cause mortality. A lower DBP had a profound effect to increase the risk for MI and marginally of CHF while concurrently protecting against strokes. Because mean arterial pressure closely tracks with DBP, its impact was similar to that of DBP, with decreases in mean arterial pressure enhancing the risk for MI but decreasing stroke risk. In view of the similar effects of SBP >120 mmHg and DBP <85 mmHg, the impact of pulse pressure on all-cause mortality and CV outcomes was assessed. Increasing pulse pressure, particularly when it exceeds 90 mmHg, markedly increases the RR of mortality, MI, and CHF but not of stroke. The impact of these changes in SBP and DBP on the risk for various CV events relates solely to BP achieved during the study. It is of note that neither the level of baseline SBP or baseline DBP was a predictor of CV outcomes after accounting for the mean achieved BP (25).

The results of our study suggesting an increase event rate at achieved DBP <85 mmHg reopens the question as to whether there is a J effect. Its existence is championed by some (26) and questioned by others (27). On the basis of his own data (28–30) and those of others (31,32), Cruickshank made an argument that at DBP <85 mmHg, there may be a J effect, particularly in patients with underlying ischemic heart disease. An impaired coronary circulation may be particularly sensitive to decreases in DBP. An analysis of the International Verapamil-Trandolapril Study (INVEST) in which the CV effects of a calcium channel blocker were compared with that of a β blocker (33), a J effect with a nadir at a DBP of 84 mmHg was reported in this population of hypertensive patients with coronary artery disease (34). Likewise, a meta-analysis of seven large, randomized trials revealed a J effect with a nadir at 84 mmHg for all-cause mortality (35). Arguments against the J point have also been set forth on the basis of the Multiple Risk Factor Intervention Trial (MRFIT) (36,37) and of several interventional trials (6,10,21). In our study, DBP, particularly <85 mmHg, were associated with increased risk for MI. Elderly patients with type 2 diabetes represent a population that is highly enriched with underlying coronary artery disease and may be more prone than others to display the J-curve effects. The association of lower DBP with increased risk for MI was particularly striking and not paralleled by the risk for strokes. In fact, most studies on the effect of BP on the risk for stroke suggest a continuous increment as BP increases (36). Likewise, analysis of the Hypertension Optimal Treatment data also fails to reveal a J effect for strokes (6).

Furthermore, in the analysis of the INVEST (33), in contrast to its findings vis à vis MI, failed to reveal an effect for strokes.

The association of the low SBP (<120 mmHg) with increased all-cause mortality and CV mortality and CHF deserves some
comment. A systolic J effect at 119 mmHg is also suggested in the INVEST (33) and at a higher level of SBP in the large meta-analysis (35). It must be noted, however, that in our study, there were only 53 patients in this subgroup and therefore the number of events from which the data are derived is modest. These patients had a higher baseline prevalence of heart disease and CHF, but these baseline factors did not explain their increased mortality. No increase in renal end points occurred in this subgroup as the risk for renal end points progressively dropped with decreasing achieved SBP (12). A similar effect of lower BP on GFR was seen in the Modification of Diet in Renal Disease study of nondiabetic patients in the subgroup with >1 g protein/24 h (38) but not in the African American Study of Kidney Disease and Hypertension (39). It must be noted that this study represents an observation and not a randomized analysis of the IDNT data, as patients were not a priori randomized with the goal of achieving different SBP or DBP. It is not possible, therefore, to determine whether the increased mortality in this group of patients is due in part to the very low achieved BP, the low BP were the consequence of other baseline comorbidities, or both. A randomized study that provides a similar number of patients in each BP range would be needed to confirm the treatment guidelines suggested by the present analysis.

Our data may leave the clinician whose goal is to prevent cardiac events, strokes and renal failure in a difficult dilemma of attempting to prevent the latter two at the expense of the first. It would appear, however, that the present guidelines that target a SBP of 120 and a DBP of approximately 80–85 mmHg are reasonable and likely to provide significant protection from the above renal and CV events.

Appendix 1: Flow Diagram for the IDNT
Appendix 2: Classification for Fatal and Nonfatal CV Events

I. CV deaths
II. MI defined as either:
   A. A clinical report of a MI from the investigator and the presence of one of the following:
      1. elevation of creatine kinase (CK) to \( \geq 2.0 \times \) the upper limit of normal for the given hospital in the absence of other explanation supported by an elevation of a cardiac enzyme above the normal range (e.g., MB fraction of CK, cardiac troponin T, or cardiac troponin I), or
      2. in the absence of cardiac-specific enzyme determination, a typical evolutionary pattern defined as elevation of CK to 2.0 times the upper limit of normal for the given hospital followed by a fall of at least 50%
   B. The appearance of new pathologic (>30 ms) Q waves in two or more contiguous leads or the appearance of an R wave (>30 ms) with R/S ratio in lead V1>1.0 (in the absence of other causes, e.g., right ventricular hypertrophy or right bundle branch block) in patients with or without a clinical report of MI from the center and without one of the following conditions on their baseline ECG: Pathologic waves, Wolf-Parkinson-White, intraventricular conduction defects, or left ventricular hypertrophy
   C. MI requiring hospitalization and documented by a clinical report of an MI from the investigator but lacking confirmation of elevated cardiac enzymes

III. Heart failure (HF)
   A. Requiring hospitalization. Hospital records were reviewed for supporting documentation that indicates that the patient was admitted for dyspnea or other symptoms of HF and required therapy with an inotropic agent, vasodilator, or ACE inhibitor or required an increase in the dose of diuretic or required ultrafiltration or dialysis.
   B. HF not requiring hospitalization but requiring therapy with an ACE inhibitor or angiotensin II receptor antagonist.
IV. Permanent neurologic deficit of at least 24 h duration attributed to stroke and requiring hospitalization and either confirmed or not confirmed by radiographic imaging (e.g., computed tomography scan, magnetic resonance imaging)
V. Unplanned (at the time of randomization) coronary artery revascularization procedure (coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty that includes laser therapy, atherectomy, standard balloon dilation, or stent placement).

Appendix 3
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 Kloocker, MD, Heidelberg, Germany; Project Coordinator: Beatrix Spiller, PharmD, 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 Bartholomew, PhD, Clayton, Victoria, Australia.

European Country Coordinators:
- UK: Rudolf W. Bilous, MD; Sweden, Denmark and Finland: Lennart Hulthén, 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 Kloocker, 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; and 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 Kloocker, MD; José B. Lopes de Faria, MD; Ruggiero Mangili, MD; Efrain Reisin, MD; Roger A. Rodby, MD; Guntram Schemthaner, MD; Samuel Spitaletwitz, 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 Stroiek, MD; Robert Toto, MD; Philippe Vanhille, MD; Thomas B. Wiegmann, MD; and 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; and Jean-Lucien Rouleau, MD.

Collaborating Clinics/Investigators

North America:
- United States: 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. Blumen- thal, 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;
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. Pernro, MD; Ospedale Luigi Sacco, Milano: G. Norbiato, MD; Ospedale S. Battista LeMolinette, Torino: G. Piccoli, MD; Instituto Scienzifico S. Raffaele, Milano: G. Pozza, MD, R. Mangili, MD; Ospedale Giovanni Bosco, Torino: F. Quarello, MD; Ospedale Mauriziano Umberto Primo, Torino: A. Ramello, MD; Ospedaliero Mutizionale, Bari: F. Paolo Schena, MD; Viremecate Hospital, Viremecate: A. Sessa, MD; Policlinico Universitario S. Orsola, Bologna: S. Stefoni, MD; Clinia CNR, Reggio Calabria: C. Zoccali, MD.

Poland: Klinika Endokrinologii Akademii Mediczne, Szczecin: S. Czekalski, MD, H. Fuchs, K. Pynka, MD; Medical University of Lodz, Lodz: J. Drezwoski, MD; Departament 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 Caudaongad, Oviedo: R. Marin Iranzo, MD; Dr. J. Truea 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. Ruijlo, MD; Hospital de Cruces, Cruces: J.A. Vazquez, MD.

Sweden: Universitetsjukhuset, 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. Dorman, MD, J. New, MD; Leeds General Infirmary, Leeds: P. Grant, MD; Central Middlesex Hospital, London: D. Hopkins, MD, A. Grenfell, MD; Maerol 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. Vaughan, 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. Simmons, 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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