Cost-Effectiveness of Early Irbesartan Treatment Versus Control (Standard Antihypertensive Medications Excluding ACE Inhibitors, Other Angiotensin-2 Receptor Antagonists, and Dihydropyridine Calcium Channel Blockers) or Late Irbesartan Treatment in Patients With Type 2 Diabetes, Hypertension, and Renal Disease

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OBJECTIVE — The aim of this study was to determine the most cost-effective time point for initiation of irbesartan treatment in hypertensive patients with type 2 diabetes and renal disease.

RESEARCH DESIGN AND METHODS — This study was a Markov model–simulated progression from microalbuminuria to overt nephropathy, doubling of serum creatinine, end-stage renal disease, and death in hypertensive patients with type 2 diabetes. Two irbesartan strategies were created: early irbesartan 300 mg daily (initiated with microalbuminuria) and late irbesartan (initiated with overt nephropathy). These strategies were compared with control, which consisted of antihypertensive therapy with standard medications (excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) with comparable blood pressure control, initiated at microalbuminuria. Transition probabilities were taken from the Irbesartan in Reduction of Microalbuminuria-2 study, Irbesartan in Diabetic Nephropathy Trial, and other published sources. Costs and life expectancy, discounted at 3% yearly, were projected over 25 years for 1,000 simulated patients using a third-party payer perspective in a U.S. setting.

RESULTS — Compared with control, early and late irbesartan treatment in 1,000 patients were projected to save (mean ± SD) $11.9 ± 3.3 million and $3.3 ± 2.7 million, respectively. Early use of irbesartan added 1,550 ± 270 undiscounted life-years (discounted 960 ± 180), whereas late irbesartan added 71 ± 40 life-years (discounted 48 ± 27) in 1,000 patients. Early irbesartan treatment was superior under a wide-range of plausible assumptions.

CONCLUSIONS — Early irbesartan treatment was projected to improve life expectancy and reduce costs in hypertensive patients with type 2 diabetes and microalbuminuria. Later use of irbesartan in overt nephropathy is also superior to standard care, but irbesartan should be started earlier and continued long term.

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

Abbreviations: DSC, doubling of serum creatinine; ESRD, end-stage renal disease; IDNT, Irbesartan in Diabetic Nephropathy Trial; IRMA-2, Irbesartan in Reduction of Microalbuminuria-2; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Diabetic nephropathy develops in ~40% of patients with type 2 diabetes and is the leading cause of end-stage renal disease (ESRD) in Europe and the U.S. (1,2). ESRD is projected to

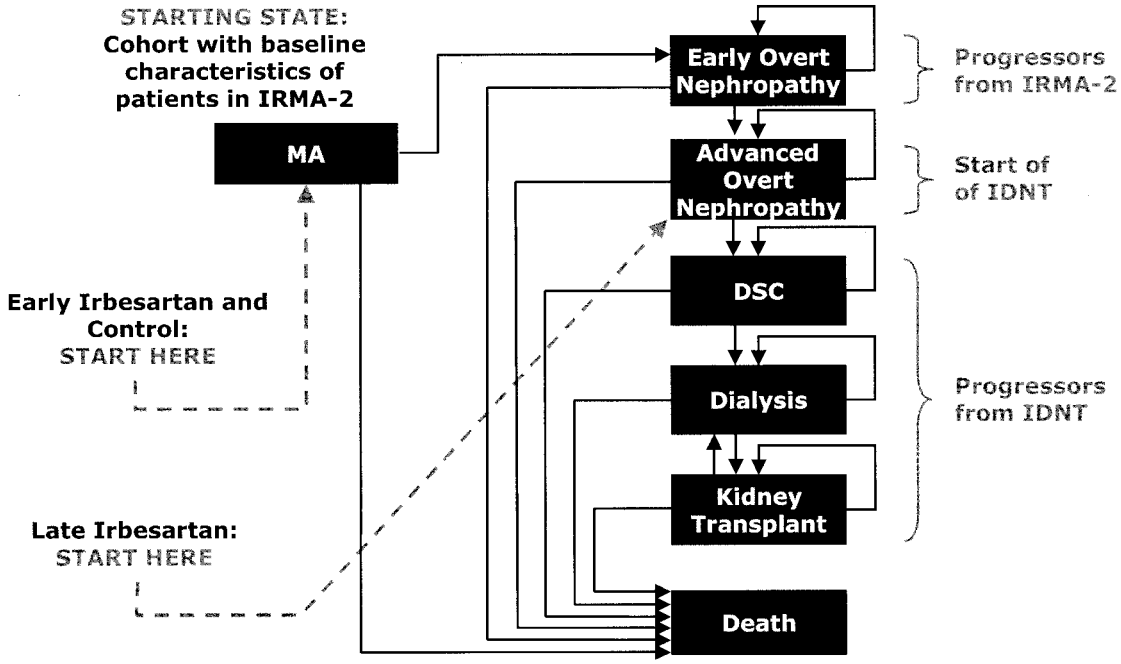

Figure 1—*Overview of model structure. Control refers to standard antihypertensive medications, including β-blockers, α/β-blockers, diuretics, peripheral vasodilators, peripheral adrenergic blockers, and central adrenergic blockers, but excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers, as required to achieve a target blood pressure of <135/85 mmHg, started when patients were in the state of microalbuminuria. Early irbesartan refers to 300 mg irbesartan daily, which was started when patients were in the state of microalbuminuria. Late irbesartan refers to control therapy when patients were in the states of microalbuminuria and early overt nephropathy, with 300 mg irbesartan daily added once patients reached the state of advanced overt nephropathy.*

cost ~$28 billion per year in 2010 in the U.S. (3).

Several trials have recently reported on the blood pressure–independent renoprotective effects of angiotensin receptor antagonist treatment on the progression of various stages of renal disease in patients with hypertension and type 2 diabetes (4–6). In the Irbesartan in Reduction of Microalbuminuria-2 (IRMA-2) study (4), a renoprotective effect of the angiotensin-2 receptor antagonist irbesartan was demonstrated in type 2 diabetic patients with microalbuminuria, protecting patients against the transition from microalbuminuria to overt nephropathy. The Irbesartan in Diabetic Nephropathy Trial (IDNT) (5) demonstrated that irbesartan is renoprotective in type 2 diabetic patients with advanced nephropathy, preventing doubling of serum creatinine (DSC) and ESRD. Both trials showed that renal events could be postponed considerably, which could have impacts on both life expectancy as well as health care costs. The aim of the present post hoc cost-consequence analysis was to identify at which stage of diabetic renal disease the initiation of treatment with irbesartan would be most efficient, i.e., would result in the greatest reductions in the development of ESRD, greatest improvements in projected life expectancy, and lowest overall costs. We used the data from the IRMA-2 (early intervention) and IDNT (late intervention) for this analysis.

RESEARCH DESIGN AND METHODS

Model structure

We developed a Markov computer-simulation model using DATA Pro software (TreeAge Software, Williamstown, MA). The Markov model consisted of seven disease states that reproduced the progression of type 2 diabetic patients from microalbuminuria (24-h urinary albumin excretion [UAE] 20–199 μg/min) to early overt nephropathy (UAE 200 μg/min to median UAE 1,900 mg per 24 h), advanced overt nephropathy (median UAE on entry 1,900 mg per 24 h), DSC, ESRD treated with dialysis, ESRD treated with renal transplant, and death (Fig. 1). A distinction was made between early and advanced overt nephropathy to bridge the gap that existed between patients reaching the end point of the IRMA-2 study (UAE 200 μg/min with minimum of 30% increase in UAE from baseline) (4) and patients included in the IDNT (median UAE 1,900 mg per 24 h) (5). Second-order Monte Carlo analysis was performed to calculate the mean, median, and 95% CI of the total costs and life expectancy by randomly drawing probabilities of key events from distributions taken from the IRMA-2 trial and the IDNT (for details of Monte Carlo simulation methods, see SENSITIVITY ANALYSIS).

Transition probabilities

Transition probabilities for progression from microalbuminuria to early overt nephropathy were taken from the IRMA-2 study (see online appendix [available at http://care.diabetesjournals.org]) (4). The annual probabilities of progressing from early overt nephropathy to advanced overt nephropathy were calculated by linear extrapolation of the rate of increase of UAE in all patients in the IRMA-2 trial who reached the end point (UAE >200 μg/min with minimum 30% increase from baseline) and by calculating the conditional probability of reaching

the threshold for entry into the IDNT (advanced overt nephropathy) stage of the model (online appendix). A threshold of UAE of 1,100 mg per 24 h was chosen to reproduce the baseline characteristics of the IDNT. Indeed, using this threshold value, the median UAE of those patients crossing this threshold at any time corresponds to the median baseline value in IDNT (UAE 1,900 mg per 24 h) (5). Because of the lack of published data, it was conservatively assumed that the rate of progression from early overt nephropathy to advanced overt nephropathy was the same in both treatment arms. Sensitivity analysis was performed on the UAE value for entry into the IDNT state (advanced overt nephropathy) by using the cutoff threshold of 585 mg/day, which represented the minimum UAE required for inclusion in the IDNT.

Mortality calculations

Mortality in the states microalbuminuria, early overt nephropathy, advanced overt nephropathy, and DSC was calculated from age- and sex-specific all-cause mortality tables, adjusted by state-dependent relative risks (RRs) for all-cause mortality in each state. Therefore, mortality was independent of treatment arm and was entirely dependent on the level of renal disease reached by a simulated patient. The RR for all-cause mortality in the state microalbuminuria was calculated from the Steno-2 study in Denmark (7) by comparing the annual death rates for patients with microalbuminuria who did not progress to overt nephropathy or ESRD (2.1% per year), and comparing that to age- and sex-matched mortality in the general Danish population (8). The RR of mortality for patients with type 2 diabetes, hypertension, and microalbuminuria was calculated to be 2.03. The RR of mortality in both overt nephropathy states was calculated in a similar way by comparing the annual probability of death in patients with overt nephropathy (who did not progress to ESRD) (5.4% per year) in the Hvidöre Hospital in Denmark (9) with the age- and sex-matched general Danish population (8). The RR for mortality in type 2 diabetic patients, hypertension, and overt nephropathy was calculated to be 4.4 compared with the general population. Because of the absence of data, the RR for all-cause mortality in both the early and the advanced overt nephropathy states as well as the DSC state were conservatively assumed to be the same. Once simulated patients reached the state of ESRD, mortality was dependent on the type of renal replacement therapy received (i.e., dialysis or transplantation). ESRD outcome data, including mortality rates in the ESRD states, were taken from published U.S. sources (1) and have been described previously (10).

Cohort and treatment groups

The model simulated a hypothetical cohort of patients with type 2 diabetes, hypertension, and microalbuminuria (UAE 20–199 μg/min on two of three consecutive occasions) similar to the baseline characteristics of patients in the IRMA-2 study (4). Three treatment choices were simulated: *1*) "control," which consisted of standard antihypertensive medications (including diuretics, β-blockers, α/β-blockers, peripheral vasodilators, peripheral adrenergic blockers, and central adrenergic blockers but excluded ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) as required to achieve a target blood pressure of <135/85 mmHg, started when patients were in the state of microalbuminuria; *2*) 300 mg of irbesartan daily, started when patients were in the state of microalbuminuria (termed "early irbesartan" treatment); and *3*) "late irbesartan" treatment, which consisted of control therapy as in the first treatment described when patients were in the states of microalbuminuria and early overt nephropathy with 300 mg of irbesartan daily added once patients reached the state of advanced overt nephropathy.

Costs included in the model

A third-party reimbursement perspective was taken with costs expressed in U.S. dollars reflecting year 2000 values. We focused this analysis on the incremental costs of adding irbesartan therapy to otherwise standard blood pressure control (as listed under the control treatment arm previously) and the costs of ESRD treatment that would develop in a simulated cohort of patients. It was assumed that the cost of other medications, including all other antihypertensive agents, did not differ between treatment regimens and were therefore not included in the analysis. This assumption might be considered as conservative and biased against the irbesartan treatment strategies, because the cost of standard antihypertensive therapy in the control arm is not included in the model. The costs of ESRD treatment (dialysis and transplantation) were taken from the U.S. Renal Data Service (1). For dialysis, these costs amounted to $60,133 per patient per year. In the first year after transplantation, costs per patient were $62,442. In maintenance years, costs after transplantation were $27,600 per patient per year. Annual costs of 300 mg of irbesartan daily were taken from the *Drug Topics Red Book* (11), using the average wholesale price, and amounted to $573.05 per patient per year.

Sensitivity analysis

Second-order Monte Carlo simulation is a well-accepted method commonly used in health economics modeling to account for uncertainty in multiple parameters (12). In our model, this was executed by calculating the transition probabilities for the irbesartan treatment arms by applying the placebo arm probabilities and multiplying them with a value drawn from the distribution of RR of progression from microalbuminuria to early overt nephropathy (RR 0.30 [95% CI 0.14–0.61], $P < 0.001$), from advanced overt nephropathy to DSC (0.71 [0.54–0.92], $P = 0.009$), and from advanced overt nephropathy or DSC to ESRD (0.83 [0.62–1.11], $P = 0.19$) taken from the 300-mg irbesartan treatment arms of the IRMA-2 trial and the IDNT (4,5).

Further sensitivity analysis was performed on the level of UAE at which patients would enter the IDNT part of the model (i.e., the advanced overt nephropathy state). In the base-case analysis, we obtained a median UAE for those patients who progressed to advanced overt nephropathy of 1,900 mg per 24 h, using a threshold of 1,100 mg per 24 h for entering the IDNT state. As mentioned previously, this was chosen to reproduce the baseline characteristics of the IDNT trial for those patients who enter in this state. We also tested the effect on projected costs and life expectancy of using an IDNT threshold of 585 mg per 24 h (the minimum UAE required for inclusion in the IDNT). Additionally, we ascertained the impact of using different assumptions on the annual probability of dying in the states of microalbuminuria, early overt nephropathy, and advanced overt nephropathy. The annual probabilities of dying for the newly diagnosed patients

Table 1—*Summary results*

Treatment	Years free of ESRD	Cumulative incidence ESRD (%)	Life expectancy (years)	Life-years gained vs. control (years)	Life-years gained: early vs. late irbesartan (years)	25-year costs	Cost savings vs. control	Cost savings: early vs. late irbesartan
Control	12.4	20.0	13.19 (10.50)	—	—	$28,782	—	—
Early irbesartan	14.4	7.0	14.75 (11.46)	1.55 (0.96)	1.48 (0.92)	$16,859	$11,922	$8,670
Late irbesartan	12.7	16.0	13.27 (10.54)	0.07 (0.05)	—	$25,529	$ 3,252	—

Data are mean (discounted results) unless otherwise indicated. Undiscounted life expectancy is shown (with discounted life expectancy in parentheses). Costs are discounted at 3% annually. Control treatment consisted of standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers with equivalent blood pressure control.

with type 2 diabetes and no renal disease, microalbuminuria, or overt nephropathy have recently been assessed in the U.K.; these were 1.4, 3.0, and 4.6%, respectively (13). We applied these values as constant age- and sex-independent mortality rates and observed the effects on costs and life expectancy. A further extreme form of sensitivity analysis was performed on the RR of mortality in the states leading up to ESRD by setting them to a value of 1.0, thereby only incorporating the effects of treatment on delaying the onset of ESRD and its associated increase in mortality.

RESULTS — Compared with control, both early and late use of irbesartan delayed the onset of ESRD, reduced the cumulative incidence of ESRD, increased life expectancy, and led to overall cost savings (Table 1). Early use of irbesartan was most efficient with the greatest improvements in clinical outcomes and cost savings.

Cumulative incidence and years free of ESRD

The cumulative incidence of ESRD was reduced by 64% with early irbesartan and 20% with late irbesartan compared with control. Cases of ESRD began to be avoided after 3–4 years for both early and late irbesartan versus the control and for early versus late irbesartan (Fig. 2*A*). After 25 years, early irbesartan led to the avoidance of ~130 cases of ESRD per 1,000 patients treated versus the control, and 86 cases per 1,000 patients treated versus late irbesartan. Approximately 50% of the ESRD cases avoided were seen after 12 years. Late irbesartan led to 45 cases of ESRD avoided per 1,000 patients treated versus the control.

The onset of ESRD was delayed by 2.1 years with early use of irbesartan compared with control, by 0.3 year with late irbesartan versus the control, and by 1.8 years for early versus late irbesartan.

Projected improvements in life expectancy

Mean undiscounted life expectancy per patient was improved by 1.55 and 0.07 years for early and late irbesartan treatment versus the control, respectively. Discounted life expectancy was improved by 0.96 and 0.05 years, respectively. Early irbesartan versus late irbesartan improved undiscounted life expectancy by 1.48 years and discounted life expectancy by 0.92 years. Improvements in life expectancy were seen after 4 years for early irbesartan versus control and after 10 years for late irbesartan versus control. Improvements in life expectancy were seen after 5 years for early versus late irbesartan (Fig. 2*B*).

Projected 25-year costs

Early irbesartan treatment led to 25-year costs savings of $11,922 per patient versus the control and $8,670 versus late irbesartan, whereas late irbesartan therapy led to a cost savings of $3,252 over 25 years (Table 1). The cost savings became evident after 10 years with early irbesartan treatment versus the control, after 5 years with late irbesartan treatment versus the control, and after 11 years for early versus late irbesartan (Fig. 2*C*).

Sensitivity analysis

Second-order Monte Carlo simulation of 1,000 individual patients allowed the calculation of mean, median, SD, and 95% CI of the changes in life expectancy and costs projected for early irbesartan and late irbesartan versus the control and for early versus late irbesartan treatment. For 1,000 simulated patients, early irbesartan versus the control led to undiscounted mean life-years gained of (mean ± SD) 1,550 ± 270 years (median 1,570 [95% CI 900–2,080]). Discounted improvements in life expectancy were 960 ± 180 years (median 972 [588–1,261]). The mean 25-year costs were decreased by $11.9 ± 3.3 million (median $12.0 million [5.4–17.6 million]).

For late irbesartan versus control, the mean number of undiscounted life-years gained in the 1,000 simulated patients were 71 ± 40 years (median 77 [95% CI 22–146]). When discounted life expectancy was calculated, late irbesartan versus control led to increased life expectancy of 48 ± 27 years (median 50 [2–97]). The mean 25-year costs were decreased by $3.3 ± 2.7 million (median $3.3 million [95% CI savings of 8.5 million to increased costs of 1.9 million]).

For early versus late irbesartan, the mean number of undiscounted life-years gained in the 1,000 simulated patients were 1.48 ± 0.27 years (median 1.50 [95% CI 0.96–2.01]). When discounted life expectancy was calculated, early irbesartan versus late irbesartan led to increased life expectancy of 0.91 ± 0.18 years (median 0.93 [0.56–1.23]). The mean 25-year costs were decreased by $8.67 ± 2.78 million (median $8.99 million [95% CI savings of 3.45–14.23 million]).

When the impact of using different assumptions on the annual probability of dying in the states of microalbuminuria, early overt nephropathy, and advanced overt nephropathy was assessed, the relative results remained stable under all conditions tested. When UKPDS (U.K. Prospective Diabetes Study)-derived constant age- and sex-independent annual mortality rates for the state-specific mortality rates were applied (3.0% in microalbuminuria and 4.6% in early and

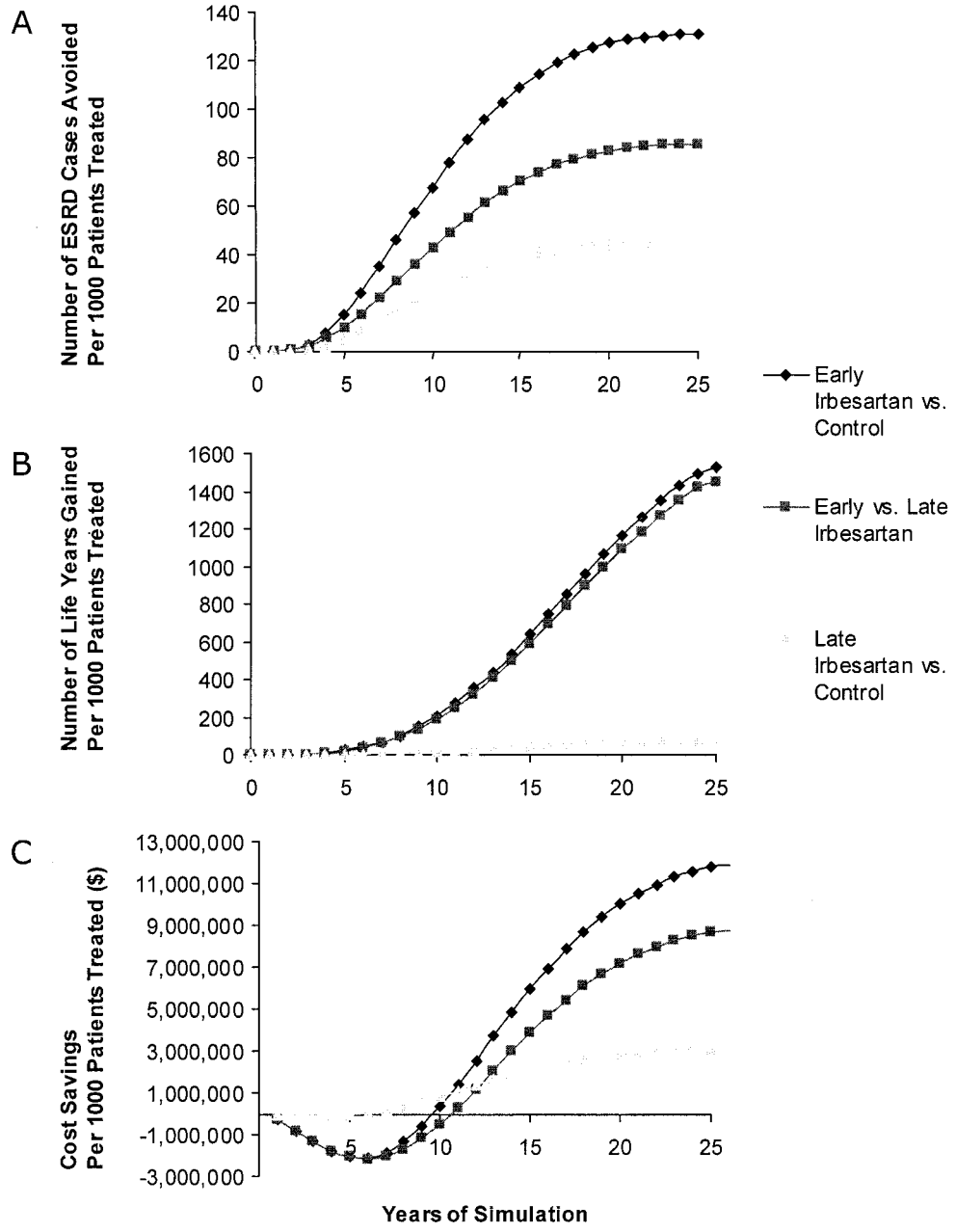

Figure 2—*A: Number of ESRD cases avoided.* B*: Number of life-years gained. C: Cost savings per 1,000 patients treated for early irbesartan versus control, late irbesartan versus control, and early versus late irbesartan.*

advanced overt nephropathy and DSC), early treatment with irbesartan improved discounted life expectancy/patient by 0.9 years and reduced 25-year costs/patient by $18,099. Late irbesartan treatment improved discounted life expectancy by 0.2 year and reduced 25-year costs by $6,531/patient.

When only the effects of treatment on delaying the onset of ESRD and its associated increase in mortality were assessed by setting the RR of mortality in the states of microalbuminuria, early overt nephropathy, advanced overt nephropathy, and DSC to 1.0, the incremental life expectancies were similar to those observed in the base case (0.78 and 0.27 life-years gained for early or late irbesartan versus the control, respectively). The incremental cost savings versus the control were projected to decrease slightly (by $2,845) for late irbesartan compared with control alone. However, the cost savings were observed to increase substantially (by $11,478) for early irbesartan compared with standard blood pressure control alone.

Choosing a different UAE threshold for entry into the IDNT section of the model (i.e., the point at which patients were deemed to have progressed to advanced overt nephropathy) had no effect on the relative outcomes. If the threshold was set to the minimum inclusion level for the IDNT (UAE of 585 mg per 24 h), both early and late irbesartan treatments

were projected to be cost saving and lifesaving compared with control, with early irbesartan treatment having a more positive impact than late.

CONCLUSIONS — This study identified the most efficient time point at which angiotensin-2 receptor antagonist treatment with irbesartan for renal disease associated with type 2 diabetes and hypertension should be initiated. The study demonstrated the importance of early treatment of patients with type 2 diabetes, hypertension, and microalbuminuria. Treating these patients with irbesartan when they first develop microalbuminuria was projected to extend life and reduce costs. Late use of irbesartan (when overt nephropathy develops) is also better and less costly than standard care, but irbesartan should be started earlier and continued long term to maximize the impact on prevention of ESRD, reduction in mortality, and cost savings. As technology improves health care, it usually does so at an increased cost. Sometimes these costs are substantial and expensive procedures, and medications may be unavailable to a patient in need because of denial of approval for payment by payers. Although the purpose of this study was primarily a health economic analysis, our results predict not only substantial economic savings when irbesartan is used to treat diabetic nephropathy but life-changing improvements in patient outcome. Thus, both payers, as a group responsible for providing economically responsible health care, and patients, whose lives are prolonged by delaying or avoiding ESRD, benefit from irbesartan use.

Encouragingly, the results were robust under a wide range of plausible assumptions. The RR of dying in the states of microalbuminuria and overt nephropathy had a large impact on the absolute values calculated for life expectancy but had no impact on the relative results (i.e., early treatment with irbesartan resulted in reduced costs and was lifesaving compared with either later treatment with irbesartan or the control under the range of values used). In the base-case analysis, the RR for overall mortality in the microalbuminuria state was assumed to be 2.03, calculated from the Steno-2 trial versus the Danish general population. This is similar to an RR of 2.0 reported in a U.K.-based study (14). In the overt nephropathy and DSC states, the RR of mortality compared with the general population of 4.4 was used in the base-case analysis. This was calculated from the mortality rates observed in a Danish study for patients with overt nephropathy (who did not progress to ESRD) versus the age- and sex-matched mortality in the general Danish population (9). If the values derived from the UKPDS were used in the model in place of the adjusted general population mortality values, the relative results remained unchanged with irbesartan treatment started in the state of microalbuminuria leading to cost savings in comparison with irbesartan treatment started in the state of advanced overt nephropathy and the control.

Monte Carlo simulation demonstrated that the projected improvements in life expectancy and cost savings are not likely to have been generated by random chance. Only the incremental costs of irbesartan and the costs of ESRD treatment were included in this analysis. This would be considered conservative and should bias against irbesartan because the cost of standard antihypertensive therapy was not considered in the model. Previous studies have shown that other costs, like the costs of additional concomitant medications and cardiovascular disease events, have only a relatively small impact compared with the costs of ESRD on total costs in patients with advanced overt nephropathy (10).

Lack of direct clinical comparisons limited our ability to compare our results with outcomes of treatment with ACE inhibitors or other angiotensin-2 receptor antagonists. The placebo arm of the IRMA-2 and IDNT studies included commonly used antihypertensive treatment like diuretics, β-blockers, calcium channel blockers (except dihydropyridines), and central α-antagonists to achieve the target blood pressure of <135/85 mmHg (4,5). The evidence supporting a specific renoprotective effect of ACE inhibitors, i.e., a beneficial effect of ACE inhibitors on kidney function beyond the hypotensive effect in hypertensive patients with type 2 diabetes and microalbuminuria, is conflicting in the nine studies published to date (15–22). The relatively long-term U.K. Prospective Diabetes Study suggested that there was no difference in the effects of the β-blocker atenolol and the ACE inhibitor captopril in patients with type 2 diabetes, and it provided no evidence that either drug has any specific beneficial or deleterious effect (23). Our analysis did not include a comparison with a treatment arm containing an ACE inhibitor because of the lack of evidence-based data derived from head-to-head comparative trials between ACE inhibitors and irbesartan. However, other modeling studies in type 1 diabetes and nondiabetic nephropathy in a number of country-specific settings have shown that treatment of nephropathy with ACE inhibitors may lead to long-term cost savings (24–29). Future health economic comparisons between ACE inhibitors and angiotensin-2 receptor antagonists would be of great interest if evidence-based data derived from direct comparative clinical trials become available.

In conclusion, our model supports the use of irbesartan in hypertensive type 2 diabetic patients with microalbuminuria (early intervention) or overt nephropathy (late intervention). Both led to life and cost saving. However, early intervention with irbesartan was predicted to lead to the greatest decreases in the incidence of ESRD, prolongation of life, and savings of money. These findings are robust under a wide range of assumptions.

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