Note: This is a three-article spread with a shared commentary. Please scroll down for the second and third articles.

Irbesartan was renoprotective in patients with type 2 diabetes, hypertension, and microalbuminuria

Parving H-H, Lehnert H, Bröchner-Mortensen J, et al., for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. **The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.** N Engl J Med. 2001 Sep 20;345:870-8.

QUESTION

In patients with type 2 diabetes mellitus, hypertension, and persistent microalbuminuria, what is the effectiveness of the angiotensin-II–receptor antagonist (ARA) irbesartan for delaying or preventing the development of nephropathy?

DESIGN

Randomized {allocation concealed*}†, blinded {clinicians, patients, and outcome assessors}†,* placebo-controlled trial with 2-year follow-up.

SETTING

96 centers worldwide.

PATIENTS

611 patients between 30 and 70 years of age who had type 2 diabetes; hypertension defined as systolic blood pressure > 135 mm Hg or diastolic blood pressure > 85 mg Hg or both; persistent microalbuminuria defined as an albumin excretion rate of 20 to 200 µg/min; and a serum creatinine level ≥ 133 µmol/L for men or ≥ 97 µmol/L for women. Exclusion criteria were nondiabetic kidney disease, cancer, fatal disease, or indication for angiotensin-converting enzyme (ACE) inhibitors or ARAs. 590 of 611 (97%) patients (mean age 58 y, 68% men) completed follow-up.

INTERVENTION

Patients were allocated to receive irbesartan, 150 mg/d (n = 195) or 300 mg/d (n = 194), or placebo (n = 201). Patients were treated with antihypertensive drugs as needed, but ACE inhibitors were not allowed. Patients continued their usual diabetes care. Dietary salt and protein were not restricted.

MAIN OUTCOME MEASURE

Development of nephropathy, defined by a urinary albumin excretion rate > 200 µg/min that is at least 30% higher than the baseline rate.

MAIN RESULTS

Analysis was by intention to treat. At 2 years, unadjusted analyses showed that placebo was associated with a higher incidence of progression to nephropathy than was irbesartan, 300 mg/d (P < 0.001), but not irbesartan, 150 mg/d (P = 0.08). After adjusting for baseline microalbuminuria and blood pressure during the study, placebo was associated with a higher incidence of progression to nephropathy than was irbesartan, 300 mg/d (P < 0.001), and irbesartan, 150 mg/d (P = 0.05) (Table).

CONCLUSION

In patients with type 2 diabetes mellitus, hypertension, and persistent microalbuminuria, irbesartan delayed progression to nephropathy independent of its effect on blood pressure.

Sources of funding: Sanofi-Synthelabo and Bristol-Myers Squibb.

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*See Glossary.

†Information provided by author.

Irbesartan vs placebo for progression to nephropathy in type 2 diabetes, hypertension, and persistent microalbuminuria at 2 years‡

Irbesartan dose	Irbesartan	Placebo	Adjusted hazard ratio (95% CI)	NNT (CI)
150 mg/d	9.7%	14.9%	0.56 (0.31 to 0.99)	16 (10 to 728)
300 mg/d	5.2%	14.9%	0.32 (0.15 to 0.65)	11 (8 to 21)

‡Abbreviations defined in Glossary; NNT and its CI calculated by using hazard ratios provided in the article; hazard ratios adjusted for baseline microalbuminuria and blood pressure during the study.

COMMENTARY

Type 2 diabetes mellitus causes microvascular and macrovascular complications that pose public health concerns worldwide. The end organ damage resulting from microvascular complications clinically manifests as retinopathy, neuropathy, and nephropathy. Diabetic nephropathy causes almost 40% of all incident dialysis cases in the United States. Once ESRD has developed, the median survival of patients with type 2 diabetes is 2 years, and most of these deaths are from cardiovascular disease (1).

In the spectrum of renal disease complicating diabetes, microalbuminuria precedes overt diabetic nephropathy. This stage is readily detectable, is associated with an increased risk for progression to diabetic nephropathy, and is potentially reversible.

Parving and colleagues have shown that treating patients who have type 2 diabetes, hypertension, and microalbuminuria with irbesartan, 300 mg/d, reduced progression to overt nephropathy at 2 years; lower doses (e.g., 150 mg/d) were less effective. This beneficial effect of irbesartan was independent of blood pressure lowering and glycemic control. In addition, irbesartan was more likely than placebo to cause regression to normoalbuminuria. The findings support the role of renin-angiotensin system blockade with irbesartan in preventing progression to albuminuria.

The Microvascular Heart Outcomes Prevention Evaluation (MICRO-HOPE) study (2) enrolled 3577 patients with diabetes, 32% of whom had microalbuminuria. The rate of progression to overt nephropathy was lower in the ramipril group than in the placebo group (relative risk reduction [RRR] 24%). Although the effects of irbesartan (RRR 66%) seemed to be greater in preventing progression to overt nephropathy, no study exists with clinically important outcomes comparing ARAs to ACE inhibitors.

The study of Mogensen and colleagues (3) provides a preliminary assessment of the role of combination therapy with ARAs and ACE inhibitors in the candesartan and lisinopril microalbuminuria (CALM)

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Irbesartan reduced progression of nephropathy caused by type 2 diabetes independent of the effect on blood pressure

Lewis EJ, Hunsicker LG, Clarke WR, et al., for the Collaborative Study Group. **Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes.** N Engl J Med. 2001 Sep 20;345:851-60.

QUESTION

In patients with type 2 diabetes mellitus, diabetic nephropathy, and hypertension, what effect does the angiotensin-II–receptor antagonist (ARA) irbesartan and the calcium-channel blocker amlodipine have on renal disease?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, outcome assessors, and statisticians),* placebo-controlled trial with mean follow-up of 2.6 years (the Irbesartan Diabetic Nephropathy Trial [IDNT]).

SETTING

210 clinical centers worldwide.

PATIENTS

1715 patients between 30 and 70 years of age (mean age 59 y, 66% men) who had type 2 diabetes, hypertension, proteinuria defined as a urinary protein excretion rate ≥ 900 mg/24 hours, and serum creatinine levels between 88 and 265 µmol/L in women and between 106 and 265 µmol/L in men. Follow-up was 99%.

INTERVENTION

Patients were allocated to irbesartan, titrated to 300 mg/d (n = 579); amlodipine, titrated to 10 mg/d (n = 567); or placebo (n = 569). Treatment targeted a systolic blood pressure ≥ 135 mm Hg and a diastolic blood pressure ≥ 85 mm Hg by using drugs other than angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, and calcium-channel blockers, if necessary.

MAIN OUTCOME MEASURES

The primary outcome was the composite of a doubling of the baseline serum creatinine level, onset of end-stage renal disease, or all-cause mortality. The secondary outcome was the composite of cardiovascular mortality, nonfatal myocardial infarction, heart failure resulting in hospitalization, neurologic deficit caused by a cerebrovascular event, or above-ankle lower-limb amputation.

MAIN RESULTS

Analysis was by intention to treat. After adjusting for mean blood pressure, irbesartan lowered the risk for the primary composite outcome more than did amlodipine (P = 0.005) or placebo (P = 0.03); this outcome did not differ for amlodipine and placebo (P = 0.47) (Table). The 3 groups did not differ for the secondary composite outcome.

CONCLUSION

In patients with type 2 diabetes, nephropathy, and hypertension, irbesartan was more effective in reducing progression of nephropathy independent of the effect on blood pressure than was amlodipine or placebo.

Sources of funding: Bristol-Myers Squibb Institute for Medical Research and Sanofi-Synthelabo.

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*See Glossary.

Irbesartan, amlodipine, or placebo for risk for a composite outcome in diabetic nephropathy and hypertension at mean 2.6 y†

Comparisons	Event rates	Adjusted RRR (95% CI)	NNT (CI)
Irbesartan vs amlodipine	33% vs 41%	24% (8 to 37)	12 (7 to 35)
Irbesartan vs placebo	33% vs 39%	19% (1 to 33)	16 (8 to 121)
		Adjusted RRI (CI)	NNH
Amlodipine vs placebo	41% vs 39%	7% (–11 to 29)	Not significant

†Composite outcome = doubling of baseline serum creatinine level, end-stage renal disease, or all-cause mortality. Abbreviations defined in Glossary; RRR, RRI, and CI adjusted for mean arterial blood pressure; NNT, NNH, and CI calculated from data in article.

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study. Candesartan combined with lisinopril for 24 weeks resulted in greater reductions in blood pressure and in the albumin-to-creatinine ratio than either drug given alone.

Once overt nephropathy develops, the goal of therapy is to slow the rate of progression to ESRD. The IDNT and the RENAAL trials, which used irbesartan and losartan, respectively, showed that patients treated with ARAs had a lower incidence of the composite outcome of doubling of serum creatinine, ESRD, or death. The effect of amlodipine on progression to the composite end point was neutral. After the baseline visit, mean systolic blood pressure levels ranged from 140 to 150 mm Hg, and diastolic blood pressure levels ranged from 74 to 77 mm Hg. A mean of 3 to 4 additional nonstudy medications were needed to achieve these blood pressure levels. Mean proteinuria levels decreased by 33% to 35% in the ARA-treated groups. These trials provide convincing evidence that irbesartan and losartan reduce the risk for progression of renal disease.

Preventing progression of diabetic nephropathy should not be considered in isolation from macrovascular complications associated with type 2 diabetes. In middle-aged and elderly persons with type 2 diabetes, fatal and nonfatal cardiovascular events occur at a rate of 4% to 5% per year. The HOPE study (4) strongly supports a protective effect of ramipril (RRR 22%) on future cardiovascular events in high-risk patients, including those with diabetes and ≥ 1 additional cardiovascular risk factor. Although the HOPE trial excluded patients with overt proteinuria, patients with proteinuria and type 2 diabetes would probably have a similar benefit.

Both the IDNT and RENAAL studies used prespecified secondary outcome clusters to measure morbidity and mortality from cardiovascular causes. Secondary outcomes occurred in 24% of patients in the IDNT study and 34% of patients in the RENAAL study. Neither losartan nor irbesartan reduced the risk for this composite outcome. Losartan was associated, however, with a lower rate of first hospitalization for congestive heart failure.

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Losartan was renoprotective in diabetic nephropathy independent of its effect on blood pressure

Brenner BM, Cooper ME, de Zeeuw D, et al., for the RENAAL Study Investigators. **Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy.** N Engl J Med. 2001 Sep 20;345:861-9.

QUESTION

In patients with type 2 diabetes mellitus and nephropathy, what is the renoprotective effect of the angiotensin-II–receptor antagonist (ARA) losartan?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, outcome assessors, and statisticians),* placebo-controlled trial with mean follow-up of 3.4 years (the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL] Study).

SETTING

250 centers worldwide.

PATIENTS

1513 patients between 31 and 70 years of age (mean age 60 y, 63% men) who had type 2 diabetes and nephropathy defined as a urinary albumin-to-creatinine ratio ≥ 300 mg/g and a serum creatinine level between 115 and 265 µmol/L (≥ 133 µmol/L for men weighing > 60 kg). Exclusion criteria included type 1 diabetes and nondiabetic renal disease. Follow-up was 99.8%.

INTERVENTION

After stratification by baseline level of proteinuria, patients were allocated to receive losartan, 50 to 100 mg/d (n = 751), or placebo (n = 762). Conventional antihypertensive therapy (excluding angiotensin-I–converting enzyme inhibitors and ARAs) was adjusted to target a systolic and diastolic blood pressure < 140 and < 90 mm Hg, respectively.

MAIN OUTCOME MEASURES

The primary outcome was the composite of a doubling of the baseline serum creatinine level, end-stage renal disease (ESRD), or death. The secondary outcome was the composite of cardiovascular morbidity or mortality.

MAIN RESULTS

Analysis was by intention to treat. Losartan reduced the risk for the primary composite outcome (unadjusted P = 0.02; P = 0.03 after adjustment for blood pressure), doubling of the baseline serum creatinine level (unadjusted P = 0.006), and ESRD (unadjusted P = 0.002) more than did placebo (Table). However, losartan and placebo did not differ for incidence of death (unadjusted P = 0.88) (Table) or the secondary composite outcome of cardiovascular morbidity or mortality (P = 0.26).

CONCLUSIONS

Losartan was renoprotective in patients with type 2 diabetes mellitus and nephropathy. This effect was beyond that attributable to blood pressure control.

Source of funding: Merck and Company.

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*See Glossary.

Losartan vs placebo for type 2 diabetes and nephropathy at mean 3.4 years†

Outcomes	Losartan	Placebo	RRR (95% CI)‡
Composite outcome§	44%	47%	16% (2 to 28)
Doubling of serum creatinine level	22%	26%	25% (8 to 39)
End-stage renal disease	20%	26%	28% (11 to 42)

†Abbreviations defined in Glossary.
‡Based on Cox regression model.
§Composite outcome = doubling of baseline serum creatinine level, end-stage renal disease, or death.

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Patients and their clinicians must now consider using these 2 classes of drugs. Therapy for individual patients should consider the risk for progression of renal disease, risk for future cardiovascular events, and blood pressure.

The treatment of type 2 diabetes should start early in the course of the disease process. At the normoalbuminuric or microalbuminuric stage, ACE inhibitors should be considered first-line agents because of their proven efficacy in preventing progression to overt nephropathy and reducing cardiovascular events. Attention should also focus on blood pressure control and modification of other risk factors for cardiovascular disease.

Once nephropathy has developed, the importance of reninangiotensin system blockade persists, but the choice of drug is less clear. Clinicians should expect to use 3 to 4 different drugs to achieve a good blood pressure reading. Although further research using clinically important outcomes is required, dual blockade of the renin-angiotensin system with a combined ACE inhibitor and ARA seems promising. This combination may offer the best of both treatment strategies and result in lower incidence rates of devastating microvascular and macrovascular complications in persons with type 2 diabetes.

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