Renal Protection in Hypertensive Patients at Cardiovascular Risk

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Glomerular Histopathology in Type 2 Diabetic Nephropathy
Development of ESRD in Type 2 Diabetes After Diagnosis of Proteinuria

Cumulative incidence of ESRD (%)

Years from diagnosis of persistent proteinuria

Typical Course of Diabetic Nephropathy

Duration of diabetes

Glomular Filtration Rate (mL/min)

Stage I  Stage II  Stage III  Stage IV  Stage V

Protein Excretion (g/24 h)

Microalbuminuria

Proteinuria

Primary prevention
Secondary prevention
Life support
Definitions: Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Stage of nephropathy</th>
<th>Urine dipstick for protein</th>
<th>Urine ACR (mg/mmol/L)</th>
<th>24 hour urine collection for albumin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Negative</td>
<td>&lt; 2.0 (men)</td>
<td>&lt; 30 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 2.8 (women)</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Negative</td>
<td>2.0–20.0 (men)</td>
<td>30–300 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.8–28.0 (women)</td>
<td></td>
</tr>
<tr>
<td>Overt nephropathy (macroalbuminuria)</td>
<td>Positive</td>
<td>&gt; 20.0 (men)</td>
<td>&gt; 300 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 28.0 (women)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels
ACR = Albumin to creatinine ratio
Potential role of hyperglycemic spikes in diabetic complications

Hyperglycemia

- Polyol pathway
- Antioxidative defenses
- Glucose auto-oxidation
  - Protein glycation
  - Oxidative factors

Glucose auto-oxidation $O_2/NO$

- NO-dependent vasodilation
- Intracellular $Ca^{2+}$
- VSMC proliferation
- LDL oxidation
- Hemorheologic disturbances
  - Activation of coagulative pathway

MACROANGIOPATHY
RETINOPATHY
NEUROPATHY
NEPHROPATHY

NCV Endoneural blood flux

Heparin-sulphate

VSMC = Vascular smooth muscle cell
NCV = Nerve conduction velocity

Diabetic nephropathy: Albuminuria

- Diabetic nephropathy is the #1 cause of end-stage renal failure in Canada and in the western world.

Radioimmunoassay

Albustix-positive

Normal range  Microalbuminuria  Macroalbuminuria

mg/day  Albumin excretion rate (AER)

μg/min

10  30  300

7  20  200

Total urinary protein ~ 500 mg/day

Hypertension & Diabetes

Prevalence of HNT (%)

Type 1
Type 2

No Proteinuria
Proteinuria
Renal Failure

Epstein M et al., Hypertension. 1992: 19; 403-418
Mechanism of diabetic nephropathy

Normal
Glomerular capillary pressure 35 mm Hg

Early nephropathy
Glomerular capillary pressure 45 mm Hg

Advanced nephropathy
Glomerular capillary pressure 45 mm Hg

- Albumin
- IgG

---

Capillary lumen
GBM
Urinary space

55 Å

Normoalbuminuria
Microalbuminuria
Macroalbuminuria

Intraglomerular Pressures

Afferent Arteriole dilated

\[ P_G \]

Efferent Arteriole constricted
Intraglomerular Pressures

Afferent Arteriole dilated

Efferent Arteriole constricted

$P_G$
Effect of RAAS Interruption

- Afferent Arteriole
- Efferent Arteriole

Vasodilate with ACE-I or ARB
Effect of ACE-I or ARB Treatment

GFR vs. Months on ACEi
Effect of ACE-I or ARB Treatment

GFR

Hemodynamic effect

Months on ACEi
Effect of ACE inhibitor Treatment

GFR

Months on ACEi

Hemodynamic effect

Non-hemodynamic effect
Renal Injury

- Decreased nephron mass
  - Glomerular capillary hypertension
    - Increased glomerular permeability to macromolecules
      - Increased filtration of plasma proteins
        - Excessive tubular reabsorption of protein
          - Proteinuria

- Increased generation of Angiotensin II
  - Tubular cell hypertrophy
    - Tubular cells transformed into fibroblasts
      - Fibroblast proliferation
        - Interstitial inflammatory reaction
          - Fibrogenesis and renal scarring

- Increased synthesis of Type IV collagen
  - Nuclear signals for vasoactive and inflammatory genes; release of vasoactive and inflammatory substances into the interstitium
What is the association between albuminuria and CV disease?
## HOPE Trial - Independent Predictors of Primary Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated serum creatinine</td>
<td>1.40 (1.16-1.69)</td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
<td><strong>1.59 (1.37-1.84)</strong></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.51 (1.22-1.85)</td>
</tr>
<tr>
<td>PVD</td>
<td>1.49 (1.29-1.70)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.42 (1.23-1.65)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.20 (1.01-1.43)</td>
</tr>
<tr>
<td>Ramipril use</td>
<td>0.79 (0.69-0.89)</td>
</tr>
<tr>
<td>Age (1 yr increase)</td>
<td>1.03 (1.02-1.05)</td>
</tr>
</tbody>
</table>

Elevated serum creatinine = > 122 micromoles/L

Mann JFE et al. Ann Intern Med 2001;629-636
CVD Events by Decile of Albuminuria

HOPE Study
- patients with dipstick proteinuria were excluded

Gerstein HC. JAMA 2001;286:421-26
Effect of ACE Inhibition in Normotensive Diabetics

* * P ≤ 0.05; †P ≤ 0.01.
Effect of ACEI vs Placebo in Type I and Type II with Normotension and Microalbuminuria (2 years)

Captopril group
122/74 mmHg

Placebo group
126/76 mmHg

4/2 mmHg difference (p<.05)

Effect of ACEI vs Placebo in Normotensive, Normoalbuminuric Patients with Type II DM (5 years)

Long-Term Benefits of ACE Inhibition in Normotensive Type 2 Diabetics with microalbuminurinuria

* * * ** *  
* p < 0.05; ** p < 0.01; † p < 0.02; *** p < 0.005, et al. Ann Intern Med. 1993;118(8):577-581.
Effect of ACEI vs Placebo in Normotensive, Normoalbuminuric Patients with Type II DM (5 years)

MAP increased from 96.1 to 102 mmHg on placebo

MAP increased from 98.2 to 100 mmHg on enalapril

# ACE Inhibitors vs Non-ACE Inhibitors in Type 2 Diabetes and Proteinuria

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Treatment</th>
<th>Follow-up (y)</th>
<th>Proteinuria</th>
<th>Decline in GFR (mL/min/y)</th>
<th>ACE inhibitor</th>
<th>Non-ACE inhibitor</th>
<th>ACE inhibitor</th>
<th>Non-ACE inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker et al (n=86)</td>
<td>ACE inhibitor vs conventional therapy</td>
<td>3</td>
<td>↓↓</td>
<td>↓</td>
<td>3.0</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebovitz et al (n=46)</td>
<td>ACE inhibitor vs conventional therapy</td>
<td>3</td>
<td>↓</td>
<td>→</td>
<td>6.4</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bakris et al (n=52)</td>
<td>ACE inhibitor vs CCB vs beta blocker</td>
<td>5</td>
<td>↓↓</td>
<td>↓↓(CCB)</td>
<td>1.0</td>
<td>1.4 (CCB)</td>
<td>3.3 (BB)</td>
<td></td>
</tr>
<tr>
<td>Nielsen et al (n=36)</td>
<td>ACE inhibitor vs beta blocker</td>
<td>3</td>
<td>↓↓</td>
<td>→</td>
<td>7.0</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estacio et al (n=83)</td>
<td>ACE inhibitor vs CCB</td>
<td>5</td>
<td>↓</td>
<td>↓</td>
<td>5.5</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fogari et al (n=51)</td>
<td>ACE inhibitor vs CCB</td>
<td>2</td>
<td>↓↓</td>
<td>↓</td>
<td>2.0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nonb ACE inhibitor or Decline in GFR (mL/min/y)

Follow-up (y) Treatment Investigator

Why do drugs which block the renin-angiotensin system delay the progression of renal disease?
Benefits of RAAS Blockade for Renal Protection

Hemodynamic Effects

- Reduction in systemic BP
- Reduction in glomerular capillary pressure
- Reduction in proteinuria

Non-hemodynamic Effects

- Stimulation of extracellular matrix degradation
- Inhibition of macrophage/monocyte infiltration
Relative Importance of MAU

Odds ratio

- Microalbuminuria: 10.02
- Smoking: 6.52
- Diastolic BP: 3.20
- Cholesterol: 2.32

Proteinuria and Risk of Stroke and CHD Events in Type 2 Diabetes

U-Prot, urinary protein concentration.

UKPDS 64: Annual Nephropathy Transition Rates From Stage to Stage

No nephropathy

- 0.1% (0.1% to 0.2%)
- 2.0% (1.9% to 2.2%)

Microalbuminuria

- 0.1% (0.0% to 0.1%)
- 2.8% (2.5% to 3.2%)

Macroalbuminuria

- 0.3% (0.1% to 0.4%)
- 2.3% (1.5% to 3.0%)

Elevated plasma creatinine or RRT

- 1.4% (1.3% to 1.5%)
- 3.0% (2.6% to 3.4%)
- 4.6% (3.6% to 5.7%)
- 19.2% (14.0% to 24.4%)

Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause.

UKPDS: United Kingdom Prospective Diabetes Study
RRT: renal replacement therapy

What should the target BP be for patients with diabetic nephropathy?
HOT Study: Effect of intensive treatment according to diabetes status

Major cardiovascular events/1,000 patient-years

Patients with diabetes, number of drugs and mean blood pressure at final visit

Target blood pressure groups (mm Hg)

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>≤ 90</th>
<th>≤ 85</th>
<th>≤ 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>147/84</td>
<td>146/82</td>
<td>143/81</td>
<td></td>
</tr>
</tbody>
</table>

No diabetes

| 143/85   | 141/83| 139/81|

- Monotherapy
- 2 drugs
- ≥ 3 drugs
UKPDS: Results

- **Intensive glucose control** reduces risk of
  - Any diabetes-related endpoints: 12% (p = 0.029)
  - Diabetes-related deaths: 10% (p = 0.340)
  - Microvascular endpoints: 25% (p = 0.010)

- **Tight blood pressure control** with captopril- or atenolol-based therapy reduces risk of
  - Any diabetes-related endpoints: 24% (p = 0.005)
  - Diabetes-related deaths: 32% (p = 0.019)
  - Stroke: 44% (p = 0.013)
  - Microvascular endpoints: 37% (p = 0.009)

* Mean blood pressure achieved: 144/82 vs. 154/87 mm Hg.

United Kingdom Prospective Diabetes Study (UKPDS): Risk Reduction

*Mean BP achieved: 144/82 vs. 154/87 mm Hg*


Cardiovascular-Renal Protection

Blood Pressure Control

RAAS Interruption

NIDDM with Hypertension
IRMA 2
Study Design

• 590 patients with hypertension, type 2 diabetes, microalbuminuria (albumin excretion rate 20–200 µg/min), and normal renal function

Screening/Enrollment

Double-blind Treatment

Control group*

Irbesartan 150 mg*

Irbesartan 300 mg*

Up to 5 weeks

Follow-up: 2 years

* Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor antagonists, and dihydropyridine calcium channel blockers) could be added to all groups to help achieve equal blood pressure levels.

IRMA 2
Clinical Outcome Measures

• Primary outcome:
  – Time to occurrence of overt proteinuria (AER > 200 µg/min)

• Secondary outcomes:
  – Change in AER
  – Regression to normoalbuminuria (AER < 20 µg/min)
  – Change in creatinine clearance
  – Clotting factors and lipid profile

IRMA 2 Primary Endpoint
Time to Overt Proteinuria

Subjects (%)

Follow-up (mo)

Control
Irbesartan 150 mg
Irbesartan 300 mg

IRMA 2
Normalization of Urinary Albumin Excretion Rate

IRMA-2

Change in UAER

ARB Therapy in Diabetic Microalbuminuria

- The maximum recommended dose of Avapro is the only effective dose of Avapro.
- Whether the maximum recommended dose of other ARBs provides similar benefit is not proven, only assumed.
Before prescribing pharmaceutical preparations containing telmisartan or any of the products mentioned in this slide resource, please consult the manufacturers’ prescribing information as approved in your country. The pharmaceutical preparations containing telmisartan by Boehringer Ingelheim are
Prospective, randomized, double-blind, forced-titration, multicentre, parallel-group, 1-year treatment

Run-in period

E → R

Telephone

4 weeks

2 weeks

2 weeks

Telmisartan 20 mg

Telmisartan 40 mg

Telmisartan 40 mg

Telmisartan 80 mg

Placebo

48 weeks

Transition to overt nephropathy

All patients

- Placebo
- Telmisartan 40mg
- Telmisartan 80mg

Month

0 3 6 9 12 15 18 21 24 27 30

Transition rate

0 0.2 0.4 0.6 0.8

RRR: relative risk reduction
NNT: number needed to treat to prevent 1 transition

Makino et al. Diabetes Care 2007; in press
Remission of microalbuminuria

* P<0.001 versus placebo

Makino et al. Diabetes Care 2007; in press
## BLOOD PRESSURES

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Start</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>137/77</td>
<td>132/74</td>
</tr>
<tr>
<td>Micardis 40mg</td>
<td>137/78</td>
<td>128/72</td>
</tr>
<tr>
<td>Micardis 80mg</td>
<td>138/78</td>
<td>128/72</td>
</tr>
</tbody>
</table>
Conclusions

• Both Telmisartan 40mg and 80mg were beneficial in reducing progression to overt nephropathy and in increasing regression of microalbuminuria

• Blood pressure was the same in both treatment group, but was 4/2 higher in the placebo group
RENAAL

Altering the Course of Renal Disease in Hypertensive Patients with Type 2 DM and Nephropathy with the A II Antagonist Losartan
Long-term treatment with losartan versus placebo (alone or in combination with conventional antihypertensive therapy*) in Type 2 diabetic patients with nephropathy will increase the time to first event and decrease the incidence of doubling of sCr, ESRD or death.

* Excluding ACEIs and other AIIAs

RENAAL- Study Design

**Losartan** 100 mg qd (+CT)

**Losartan** 100 mg qd

**Losartan** 50 mg qd

Maintain conventional antihypertensive therapy (CT)*

(excluding ACEI, AIIA)

n=1513

Goal trough BP: < 140/<90 mmHg

Placebo (+CT)

Placebo (+CT)

Placebo (+CT)

6 Wks 4 Wks 8 Wks

Mean follow-up 3.4 years

*CT=conventional therapy: Open-label calcium-channel blocker, diuretic, beta blocker, alpha blocker, or centrally acting agents.

# RENAAL-Primary Composite Endpoint & Components

<table>
<thead>
<tr>
<th>Composite and Components</th>
<th>Losartan (+CT) (n=751) n (%)</th>
<th>Placebo (+CT) (n=762) n (%)</th>
<th>P-Value</th>
<th>% Risk Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DsCr, ESRD, Death</td>
<td>327 (43.5)</td>
<td>359 (47.1)</td>
<td>0.02</td>
<td>16</td>
<td>(2, 28)</td>
</tr>
<tr>
<td>Doubling of sCr</td>
<td>162 (21.6)</td>
<td>198 (26.0)</td>
<td>0.006</td>
<td>25</td>
<td>(8, 39)</td>
</tr>
<tr>
<td>ESRD</td>
<td>147 (19.6)</td>
<td>194 (25.5)</td>
<td>0.002</td>
<td>28</td>
<td>(11, 42)</td>
</tr>
<tr>
<td>Death</td>
<td>158 (21.0)</td>
<td>155 (20.3)</td>
<td>0.88</td>
<td>-2</td>
<td>(-27, 19)</td>
</tr>
<tr>
<td>ESRD or Death</td>
<td>255 (34.0)</td>
<td>300 (39.4)</td>
<td>0.01</td>
<td>20</td>
<td>(5, 32)</td>
</tr>
</tbody>
</table>

RENAAL- Change from Baseline in Proteinuria

Median Percent Change

0 12 24 36 48 Months

P

L

p<0.001

35% Overall Reduction

Proteinuria measured as the urine albumin:creatinine ratio from a first morning void.

RENAAL - Occurrence of CV endpoint according to baseline proteinuria

Baseline Proteinuria

% with CV endpoint

Month

0 12 24 36 48

≥3.0 g/g
≥1.5<3.0 g/g
<1.5 g/g

RENAAL - Baseline proteinuria predicts outcome

**CV Endpoint**

- Heart Failure

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with CV endpoint</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

- Heart Failure

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with heart failure endpoint</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

**Hazard ratio relative to lowest proteinuria**

- Albuminuria (g/g)

<table>
<thead>
<tr>
<th>&lt;.5</th>
<th>2.0</th>
<th>2.95</th>
<th>4.4</th>
<th>≥5.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.0</td>
<td>4.0</td>
<td>6.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

- Albuminuria (g/g)

<table>
<thead>
<tr>
<th>&lt;.5</th>
<th>2.0</th>
<th>2.95</th>
<th>4.4</th>
<th>≥5.25</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>2.0</td>
<td>4.0</td>
<td>6.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>
RENAAL- Percentage reduction of proteinuria predicts outcome
Objectives

• To compare the long-term effect of Telmisartan 80 mg versus Losartan 100 mg in patients with type 2 diabetes and overt nephropathy on:
  – Proteinuria (primary endpoint)
  – Other renal parameters (secondary endpoint)
  – Cardiovascular protection (secondary endpoint)
  – Safety
Outcomes

Primary endpoint
• Change in proteinuria after 1 year of treatment

Secondary endpoints
• Creatinine clearance
• Surrogate renal protection endpoints

Patient characteristics

- 860 patients

**Inclusion criteria**

- Type 2 diabetes
- Hypertension (seated SBP/DBP >130/>80 mmHg)
- Macroproteinuria
  \( \geq 700 \text{ mg/g creatinine (first morning voided urine), equivalent to 900 mg/24 hours} \)
- Serum creatinine
  - women \( \leq 265 \text{ µmol/L (} \leq 3.0 \text{ mg/dL)} \)
  - men \( \leq 285 \text{ µmol/L (} \leq 3.2 \text{ mg/dL)} \)

Study design

Prospective, randomized, double-blind, double-dummy, forced-titration, multicentre, parallel-group, 1-year treatment

Run-in period

E

R

4 weeks

2 weeks

50 weeks

Telmisartan 80 mg

(n = 419)

(n = 441)

Losartan 50 mg

Losartan 100 mg

≥130/≥80 mmHg

<130/<80 mmHg

≥130/≤80 mmHg

<130/<80 mmHg

Telmisartan 80 mg + add on

E = enrollment, R = randomization

a <130/<80 mmHg recommended target recommended by JNC7 for patients with diabetic nephropathy (Chobanian et al. Hypertension 2003;42:1206–1252).
# Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan 40/80 mg (N=419)</th>
<th>Losartan 50/100 mg (N=441)</th>
<th>Total (N=860)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male, N (%)</strong></td>
<td>256 (61.1)</td>
<td>279 (63.3)</td>
<td>535 (62.2)</td>
</tr>
<tr>
<td><strong>Age, yrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>60.0 (9.2)</td>
<td>60.5 (9.4)</td>
<td>60.3 (9.3)</td>
</tr>
<tr>
<td><strong>Race, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>188 (44.9)</td>
<td>217 (49.2)</td>
<td>405 (47.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>172 (41.1)</td>
<td>180 (40.8)</td>
<td>352 (40.9)</td>
</tr>
<tr>
<td>Black</td>
<td>59 (14.1)</td>
<td>43 (9.8)</td>
<td>102 (11.9)</td>
</tr>
</tbody>
</table>
## Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan 40/80 mg (N=419)</th>
<th>Losartan 50/100mg (N=441)</th>
<th>Total (N=860)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI, mean (SD) [kg/m^2]</strong></td>
<td>30.1 (6.8)</td>
<td>29.9 (6.2)</td>
<td>30.0 (6.5)</td>
</tr>
<tr>
<td><strong>Smokers, N (%)</strong></td>
<td>63 (15.0)</td>
<td>71 (16.1)</td>
<td>134 (15.6)</td>
</tr>
<tr>
<td><strong>Duration hypertension, mean (SD) [yrs]</strong></td>
<td>9.0 (8.9)</td>
<td>9.7 (9.9)</td>
<td>9.3 (9.4)</td>
</tr>
<tr>
<td><strong>Duration diabetic nephropathy, mean (SD) [yrs]</strong></td>
<td>2.7 (5.3)</td>
<td>2.3 (3.5)</td>
<td>2.5 (4.5)</td>
</tr>
<tr>
<td><strong>Duration type 2 diabetes, mean (SD) [yrs]</strong></td>
<td>14.6 (8.4)</td>
<td>14.1 (8.1)</td>
<td>14.3 (8.3)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan (n= 419)</th>
<th>Losartan (n = 441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP/DBP (mmHg)</td>
<td>144 ± 16/ 80 ± 9</td>
<td>143 ± 15/80 ± 10</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.1 ± 6.8</td>
<td>29.9 ± 6.2</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>16.6 ± 8.4</td>
<td>14.1 ± 8.1</td>
</tr>
<tr>
<td>HbA₁C (%)</td>
<td>7.93 ± 1.30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.85 ± 1.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>UPC (mg/gCr)</td>
<td>1970.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2010.5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum creatinine (gmean, mg/dL)</td>
<td>1.54&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.55&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>n = 418,  <sup>b</sup>n = 439,  <sup>c</sup>n = 413,  <sup>d</sup>n = 437,  <sup>e</sup>n = 419,  <sup>f</sup>n = 441
# Patient Participation at Conclusion

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan 40/80 mg N (%)</th>
<th>Losartan 50/100mg N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td></td>
<td></td>
<td>1567</td>
</tr>
<tr>
<td>Entered</td>
<td>419</td>
<td>441</td>
<td>860</td>
</tr>
<tr>
<td>Treated</td>
<td>419 (100.0)</td>
<td>441 (100.0)</td>
<td>860 (100.0)</td>
</tr>
<tr>
<td>•Completed Study</td>
<td>345 (82.3 )</td>
<td>342 (77.6)</td>
<td>687 (79.9)</td>
</tr>
<tr>
<td>•Prematurely Discontinued</td>
<td>74 (17.7)</td>
<td>99 (22.4)</td>
<td>173 (20.1)</td>
</tr>
<tr>
<td></td>
<td>Telmisartan 80 mg</td>
<td>Losartan 100 mg</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Actual</td>
<td>Change</td>
<td>Actual</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>414</td>
<td></td>
<td>428</td>
</tr>
<tr>
<td><strong>SYSTOLIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>144</td>
<td></td>
<td>143</td>
</tr>
<tr>
<td>Final high dose</td>
<td>140</td>
<td>-4</td>
<td>141</td>
</tr>
<tr>
<td><strong>DIASTOLIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80</td>
<td>-3</td>
<td>79</td>
</tr>
<tr>
<td>Final high dose</td>
<td>77</td>
<td>-3</td>
<td>77</td>
</tr>
</tbody>
</table>
Reduction in proteinuria

p = 0.0284 for treatment ratio in favour of telmisartan

Telmisartan
(n = 407)

Baseline
Endpoint
29%

Losartan
(n = 420)

Baseline
Endpoint
20%
Overall Renal and Cardiovascular Composite Endpoints
Overall Renal and Cardiovascular Composite Endpoints

- **Overall composite**
  - Telmisartan
  - Losartan
  - P = 0.083

- **CV Composite**
  - P = 0.037

---

**Legend:**
- Telmisartan
- Losartan

---

**Notes:**
- *a* Doubling of serum creatinine, ESRD or all-cause death.
- *b* Myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization.
Conclusions

- The AMADEO study confirms the renoprotective profile of ARBs
- Telmisartan provides superior reduction in proteinuria compared with Losartan, despite no significant differences in blood pressure control
- Continuous use of Telmisartan may slow the progression to ESRD in patients with diabetic nephropathy and reduce the risk of cardiovascular events
- Pharmacological differences in ARBs may have implications in renal and cardiovascular protection
Conclusions

• The renin-angiotensin system plays an important role in diabetic kidney disease
• ARBs reduce proteinuria and the rate of deterioration of renal function
• The reduction in proteinuria predicts the reduction in ESRD and cardiovascular events in these diabetic patients
• Greater reduction in proteinuria should provide greater reduction in the risk of ESRD and cardiovascular events

Study Design

**The ONTARGET Trial Programme**

**Screening**

**ONTARGET**

Randomisation (n = 23,400)*

- n = 7,800
- Telmisartan 80 mg/day + Placebo
- n = 7,800
- Ramipril 10 mg/day + Placebo
- n = 7,800
- Telmisartan 80 mg/day + Ramipril 10 mg/day

Follow-up at 6 weeks

Follow-up every 6 months for 5.5 years

**TRANSCEND**

Randomisation (n = 6,000)†

- n = 3,000
- Telmisartan 80 mg/day
- n = 3,000
- Placebo

Follow-up at 6 weeks

Follow-up every 6 months for 5.5 years

* Planned. Actual = 25,620
† Planned. Actual = 5,926
The ONTARGET Trial Programme

Primary Endpoint

• Primary composite cardiovascular endpoint:
  – Cardiovascular mortality
  – Non-fatal myocardial infarction
  – Non-fatal stroke
  – Hospitalisation for congestive heart failure
The ONTARGET Trial Programme

Secondary Endpoints

• Newly diagnosed congestive heart failure
• Cardiovascular revascularisation procedure
• Newly diagnosed diabetes
• Cognitive decline/dementia
• New onset of atrial fibrillation
• Nephropathy
The ONTARGET Trial Programme

Other Endpoints

• Non-cardiovascular death, total mortality
• Unstable, new and worsening angina
• Transient ischaemic attack
• Microvascular complications of diabetes (laser therapy for diabetic retinopathy)
• Non-fatal malignancy
The ONTARGET Trial Programme

Substudies

- Arterial stiffness
- Blood markers
- Cardiac MRI
- Oral glucose tolerance test (OGTT)
- Erectile dysfunction
- Ambulatory blood pressure measurement (ABPM)
- Health economics

Yusuf S., Am J Cardiol 2002;98 (suppl):18A–26A
Unger T., Am J Cardiol 2003;91 (suppl):28G–34G
Zimmerman M., Unger T., Expert Opin Pharmacother 2004;5:1201-8
Cardiovascular-Renal Protection

- Blood Pressure Control
- RAAS Interruption
AMADEO-Percent reduction in proteinuria

- Losartan
- Telmisartan

p = 0.0284
AMADEO - Systolic & Diastolic BPs

Systolic BP

Diastolic BP

Initial | Final

Telmisartan

Losartan

Initial | Final

Losartan

Telmisartan
RENAAL- Occurrence of CV endpoint according to reductions after 6 months

Change from Baseline by Month 6

RENAAL:

Predictors of Renal Outcomes

- Baseline level of proteinuria was a significant predictor of renal outcomes, ESRD
- Reduction in proteinuria at 6 months is also a significant predictor
- These are predictors regardless to which treatment the patient is randomized
Public Health Implications of RENAAL

• For diabetic patients at risk over a 3.5 year period, it is estimated:
  – one case of ESRD can be prevented for every 16 patients treated
  – the reduction in days with ESRD saves $5,300 (p=0.03) per treated patient (savings increase to $7,400 at 4 years)

* Assumes annual cost of ESRD is $56,000 based on Medicare (USRDS 2000). Drug cost based on AWP.
** NHANES III diagnosed diabetic patients with proteinuria (≥ 300 mg/g) assumed to have Type 2 diabetes based on age of diagnosis ≥ 30 years
• 1,715 patients with hypertension, type 2 diabetes, and proteinuria ≥ 900 mg/day

**Screening/Enrollment**

**Double-blind Treatment**

- Irbesartan*
- Control group*
- Amlodipine*

**Up to 5 weeks**

- Minimum follow-up: approximately 2 years (average follow-up 2.6 years)

* Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor antagonists, and calcium channel blockers) could be added to all groups to help achieve equal blood pressure levels.

IDNT Primary Endpoint
Time to Doubling of Serum Creatinine, ESRD, or Death

Objective

• To demonstrate that Telmisartan is effective against progression of renal disease by reducing proteinuria in hypertensive diabetic patients and possibly superior compared with Losartan

Prospective, randomized, double-blind, double-dummy, forced-titration, multicentre, parallel-group, 1-year treatment

Study design

Prospective, randomized, double-blind, double-dummy, forced-titration, multicentre, parallel-group, 1-year treatment

4 weeks 2 weeks 50 weeks

Telmisartan 80 mg

≥130/≥80 mmHg

<130/<80 mmHg

Telmisartan 80 mg

Losartan 100 mg

≥130/≥80 mmHg

<130/<80 mmHg

Losartan 100 mg

(n = 419)

(n = 441)

E

Run-in period

R


Weber.
Losartan

Telmisartan

p = 0.0284

% reduction in UPCR after 50 weeks

-20%

-29%
# RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Telmisartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
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</tbody>
</table>