Treatment of Diabetic Nephropathy and Proteinuria

**Background**

- End stage renal disease is a major cause of death and disability among diabetics
- BP reduction is important to slow the progression of diabetic nephropathy
- Outcomes trials that demonstrate a clear renoprotective benefit of ACE inhibitors in diabetes have been conducted primarily in type 1 diabetics
- Three recently completed randomized blinded trials address the previously unanswered questions of whether ARBs delay the progression of diabetic nephropathy (RENAAL, IDNT) or reduce proteinuria (IRMA II) in patients with type 2 diabetes

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**IRMA 2: Study Design**

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

**IRMA 2: Blood Pressure Response**

- **Double-blind Treatment**
  - Placebo/Control group
  - Irbesartan 150 mg
  - Irbesartan 300 mg

- **Screening/Enrollment**
  - 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 Primary Endpoint**

- **Time to Overt Proteinuria**

- **IRMA 2 Normalization of Urinary Albumin Excretion Rate**

- **IRMA 2: Blood Pressure Response**


Angiotensin II Receptor Blockers (ARBs) in Type 2 Diabetes

### Angiotensin II Receptor Blockers in Type 2 Diabetes With Nephropathy

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>Randomized Double-blind PL controlled study of 1531 type 2 diabetics enrolled for mean of 3.4 yrs</td>
</tr>
<tr>
<td>IDNT</td>
<td>Study Design</td>
</tr>
<tr>
<td>IDNT</td>
<td>Blood Pressure Response</td>
</tr>
</tbody>
</table>

#### Summary of Findings (I)

- **RENAAL, IDNT and IRMA II present the strongest evidence to date for the efficacy of specific types of treatment to slow the progression of nephropathy in type 2 diabetes**
  - The ARBs losartan and irbesartan compared to placebo* have been shown to reduce the progression of renal insufficiency beyond the benefit of similarly achieved blood pressures
  - Irbesartan compared to placebo* has been shown to reduce the progression of microalbuminuria to diabetic nephropathy

*In combination with conventional antihypertensive therapy (excluding ACE inhibitors)

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**Angiotensin II Receptor Blockers**

**Progression of Microalbuminuria†**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRMA II (n=590)</td>
<td>Irbesartan 150mg vs placebo* ↓ 39% (P=0.080)</td>
</tr>
<tr>
<td>IRMA II (n=590)</td>
<td>Irbesartan 300mg vs placebo* ↓ 70% (P=0.001)</td>
</tr>
</tbody>
</table>

*Albumin excretion rate of 20 to 200 µg per minute in 2 of 3 consecutive, sterile, overnight urine samples

‡Urinary albumin excretion rate >200 µg per minute and at least 30% higher than baseline in at least 2 consecutive measurements

*In combination with conventional antihypertensive therapy (excluding ACE inhibitors)

**Progression of Renal Insufficiency**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>Losartan 50-100 mg vs placebo* ↓ 16% (P=0.02)</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan 150-300 mg vs placebo* ↓ 20% (P=0.02)</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan 150-300 mg vs Amlodipine* ↓ 23% (P=0.006)</td>
</tr>
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*In combination with conventional antihypertensive therapy (excluding ACE inhibitors)

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**Randomized Double-blind PL controlled study of 1531 type 2 diabetics enrolled for mean of 3.4 yrs**

- Patients initiated on Losartan 50mg: elective titration up to 100mg (based on BP target) and then additional therapy as needed
  - 27.8% patients on losartan 50mg
  - 71.2% patients on losartan 100mg
- most common other agents were CCBs ~90% in both groups

**Results:**

- 16% RR reduction in losartan group vs. PL for morbidity and mortality from CV causes, proteinuria and rate of progression of renal disease.


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**1,715 patients with hypertension, type 2 diabetes, and proteinuria ≥ 900 mg/day**

**Screening/Enrollment**

- Double-blind Treatment
  - Irbesartan
  - Placebo/Control group
  - Amlodipine

**Average Duration**

- Primary Endpoint: Composite of doubling of serum creatinine, end stage renal disease, or death

- Duration

- RENAAL (n=1,514)
  - Losartan 50-100 mg vs placebo* ↓ 16% (P=0.02) 3.4 yrs

- IDNT (n=1,715)
  - Irbesartan 150-300mg vs placebo* ↓ 20% (P=0.02) 2.6 yrs
  - Irbesartan 150-300mg vs Amlodipine* ↓ 23% (P=0.006) 2.6 yrs

*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.


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**Blood Pressure Response**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>On Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>158</td>
<td>158</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>140</td>
<td>140</td>
</tr>
</tbody>
</table>