Diabetic Nephropathy
A new hope

Joel Michels Topf, MD
Assistant Professor of Medicine
Oakland University William Beaumont School of Medicine
Judah is going to cure cancer in two years.
Judah is going to cure cancer in two years.

Dr. James D. Watson
Already, Dr. Folkman said, he gets hundreds of calls a day from cancer patients, pleading for the drugs.

...one call had come from an old friend from medical school with prostate cancer that had spread to his bones.
Already, Dr. Folkman said, he gets hundreds of calls a day from cancer patients, pleading for the drugs.

...one call had come from an old friend from medical school with prostate cancer that had spread to his bones.
Bardoxolone was my Judah Folkman moment
Bardoxolone methyl

- Antioxidant inflammatory modulator
  - Activates Keap1-Nf2 pathway
  - Maintains kidney function and structure
  - Inhibits NF-kappa β
Enrolled patients with GFR 20-45

Type 2 DM

On a stable dose of ACEi or ARB unless not tolerated

227 patients randomized to:
- Placebo
- 25 mg daily
- 75 mg daily
- 150 mg daily

For 52 weeks
- Primary outcome: Change in GFR at 24 weeks
- Secondary outcome: Change in GFR at 52 weeks
- Primary outcome: Change in GFR at 24 weeks
- Secondary outcome: Change in GFR at 52 weeks
Increased in GFR
Increased in GFR

This should be good. Right?
Increased in GFR

This should be good. Right?

Increased albuminuria
Increased in GFR

This should be good. Right?

Increased albuminuria

That can’t be good. Right?
Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes (BEACON)

This study is currently recruiting participants.
Verified on November 2011 by Reata Pharmaceuticals, Inc.
First Received on December 3, 2010. Last Updated on November 10, 2011

Sponsor: Reata Pharmaceuticals, Inc.
Information provided by (Responsible Party): Reata Pharmaceuticals, Inc.
ClinicalTrials.gov identifier: NCT01351675

Purpose

This study assesses the efficacy of bardoxolone methyl relative to placebo in delaying progression to end-stage renal disease (ESRD) and cardiovascular deaths in patients with Stage 4 Chronic Kidney Disease (CKD) and type 2 diabetes receiving standard of care.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Renal Insufficiency, Chronic Diabetes Mellitus, Typo 2</td>
<td>Drug: Placebo Drug: Bardoxolone Methyl: 20 mg</td>
<td>Phase III</td>
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</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
 Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes: the Occurrence of Renal Events (BEACON)

Resource links provided by NLM:
- Genetics Home Reference related topics: 6q24-related transient neonatal diabetes mellitus
- MedlinePlus related topics: Diabetes Kidney Failure
- U.S. FDA Resources

Further study details are provided by Reata Pharmaceuticals, Inc.
BEACON phase III

- June 2011-June 2013
- Randomized, controlled, placebo-controlled trial
  - Placebo
  - 20 mg
- Primary end-point
  - Dialysis
  - Cardiovascular death
- 2750 patients
Judah is going to cure cancer in two years.

Dr. James D. Watson
Judah is going to cure cancer in two years.

Dr. James D. Watson, 1998
Company Statement: Termination of the BEACON Trial

Reata, in consultation with the BEACON Steering Committee, has decided to terminate the Phase 3 BEACON trial of bardoxolone methyl in patients with stage 4 chronic kidney disease and type 2 diabetes. This decision was made based upon a recommendation of the Independent Data Monitoring Committee (IDMC) to stop the trial "for safety concerns due to excess serious adverse events and mortality in the bardoxolone methyl arm."

Clinical trial sites have been notified, and patient participants are being instructed to stop taking study drug and return to the clinic for a final visit. In addition, Reata and Abbott have notified the FDA and other regulatory agencies of the decision to stop the clinical trial and all ongoing clinical trials with bardoxolone methyl in CKD.

We will continue our commitment to patient safety and developing medicines for intractable diseases by closely examining the data from this trial to determine if there is an appropriate path forward for the development of bardoxolone methyl in chronic kidney disease or other indications and for our other AIM compounds.
October 18, 2012
upon the recommendation of the
Independent Data Monitoring Committee
(IDMC) to stop the trial "for safety
concerns due to excess serious adverse
events and mortality in the bardoxolone
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Diabetic Nephropathy
New hope, or hope denied?

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<td>Year</td>
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Etiologies of ESRD

- Diabetes
- Hypertension
- Glomeruloneph
- Cystic kidney
Etiologies of ESRD

- Diabetes
- Hypertension
- Glomerulonephritis
- Cystic kidney
The incidence of developing ESRD with diabetes has decreased 35%, from 305/100,000 in 1996 to 199/100,000 in 2006.

Etiologies of ESRD

Cases per million

Diabetes
Hypertension
Glomeruloneph
Cystic kidney
Etiologies of ESRD

Cases per million

Diabetes
Hypertension
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Etiologies of ESRD

Cases per million


Diabetes
Hypertension
Glomeruloneph
Cystic kidney

IDNT Lewis et al
RENAAL Brenner et al
Etiologies of ESRD

Cases per million

- Diabetes
- Hypertension
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Diabetes

Hypertension

Glomeruloneph

Cystic kidney

1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008

120.0
140.0
160.0
180.0
200.0

DCCT
CCT

IDNT Lewis et al
RENAAL Brenner et al

The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy
Edmund J. Lewis, Lawrence G. Huesticker, Raymond P. Bux, Richard D. Bilode, for The Collaborative Study Group

ABSTRACT
Background Renal function declines progressively in patients who have diabetic nephropathy, and the decline may be slowed by antihypertensive drugs. The purpose of this study was to determine whether captopril has kidney-protecting properties independent of its effect on blood pressure in diabetic nephropathy.

Methods We performed a randomized, controlled trial comparing captopril with placebo in patients with insulin-dependent diabetes mellitus in whom urinary protein excretion was > 0 mg per day and the serum creatinine concentration was 2.5 mg per deciliter (221 mmol per liter). Blood-pressure goals were defined

The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus
The Diabetes Control and Complications Trial Research Group

ABSTRACT
Background Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods A total of 1441 patients with IDDM—726 with no retinopathy at baseline (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections.
type 1 diabetes
Type 1 diabetes with macroalbuminuria

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subcohort</th>
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<tbody>
<tr>
<td></td>
<td>1991 to 1995 (n = 113)</td>
<td>1996 to 2000 (n = 112)</td>
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<tr>
<td>Men (%)</td>
<td>53.1</td>
<td>53.6</td>
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<tr>
<td>Age (years)</td>
<td>34.1 ± 5.7</td>
<td>37.6 ± 7.2</td>
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<tr>
<td>Age at T1D diagnosis (years)</td>
<td>11.5 ± 6.7</td>
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<td>T1D duration (years)</td>
<td>22.6 ± 6.7</td>
<td>26.0 ± 8.2</td>
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<td>Duration of care at Joslin (years)</td>
<td>17.4 ± 8.8</td>
<td>21.2 ± 10.7</td>
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<td>HbA1c (%)</td>
<td>9.1 ± 1.6</td>
<td>9.4 ± 1.9</td>
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<td>Body mass index (kg/m²)</td>
<td>25.1 ± 4.3</td>
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<tr>
<td>Patients using lipid-lowering drugs (%)</td>
<td>8.0</td>
<td>10.7</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
<td>228 ± 64</td>
<td>212 ± 51</td>
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<tr>
<td>Current smokers (%)</td>
<td>28.1</td>
<td>26.4</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>137 ± 20</td>
<td>134 ± 18</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81 ± 10</td>
<td>80 ± 9</td>
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<td>Patients using ACE-I or ARB (%)</td>
<td>55.8</td>
<td>62.5</td>
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<tr>
<td>ACR (mg/g)</td>
<td>967 (526 to 1667)</td>
<td>736 (442 to 1310)</td>
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<td>eGFR (ml/min)</td>
<td>70 ± 35</td>
<td>73 ± 37</td>
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<td>Hgb A1c</td>
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<tr>
<td>Statins</td>
<td>8.0%</td>
<td>10.7%</td>
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6 years follow up: ESRD per 100 patient years
<table>
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<th>Year Range</th>
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<th>Full Follow Up: ESRD per 100 Patient Years</th>
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*6 years follow up: ESRD per 100 patient years*

*Full follow up: ESRD per 100 patient years*
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no difference in incidence of ESRD
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<td>pre-ESRD mortality per 100 patient years</td>
<td>0.8</td>
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**no difference in incidence of ESRD**

**no difference in mortality**
The incidence of developing ESRD with diabetes has decreased 35%, from 305/100,000 in 1996 to 199/100,000 in 2006.

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<tr>
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  - 11% decline with ACEi
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  - -6 mL/yr in control
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How do I get outcomes like this?

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  - -0.6 mL/yr control

Presumably better blood pressure and glycemic control.
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ABSTRACT

BACKGROUND
There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.

METHODS
A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

RESULTS
After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of
### ACCORD Double 2 x 2 Factorial Design

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<th>BP</th>
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<td>Placebo</td>
<td>Fibrate</td>
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<td>Intensive Glycemic</td>
<td>1383</td>
<td>1374</td>
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<tr>
<td>Control</td>
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<td>1391</td>
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<tr>
<td>Standard Glycemic</td>
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<td>2765</td>
</tr>
<tr>
<td></td>
<td>5518</td>
<td></td>
</tr>
</tbody>
</table>

* 94% power for 20% reduction in event rate, assuming standard group rate of 4% / yr and 5.6 yrs follow-up
Systolic Pressures (mean ± 95% CI)

Mean # Meds
- Intensive: 3.2, 3.4, 3.5, 3.4
- Standard: 1.9, 2.1, 2.2, 2.3
Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death

HR = 0.88
95% CI (0.73-1.06)
Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death

HR = 0.88
95% CI (0.73-1.06)

No reduction in primary outcome
<table>
<thead>
<tr>
<th>Serious adverse events — no. (%)†</th>
<th>intensive</th>
<th>usual care</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event attributed to blood-pressure medications</td>
<td>77 (3.3)</td>
<td>30 (1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.001</td>
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<tr>
<td>Syncope</td>
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<td>End-stage renal disease or need for dialysis</td>
<td>59 (2.5)</td>
<td>58 (2.4)</td>
<td>0.93</td>
</tr>
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<th>Adverse laboratory measures — no. (%)</th>
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</tr>
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<tr>
<td>Potassium &lt;3.2 mmol/liter</td>
<td>49 (2.1)</td>
<td>27 (1.1)</td>
<td>0.01</td>
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<tr>
<th>Clinical measures‡</th>
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<tbody>
<tr>
<td>Serum creatinine — mg/dl</td>
<td>1.1±0.4</td>
<td>1.0±0.5</td>
<td>&lt;0.001</td>
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<td>Estimated GFR — ml/min/1.73 m²</td>
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<tr>
<td>Microalbuminuria — no./total no. (%)</td>
<td>656/2174 (30.2)</td>
<td>712/2205 (32.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Macroalbuminuria — no. /total no. (%)</td>
<td>143/2174 (6.6)</td>
<td>192/2205 (8.7)</td>
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<tr>
<td>Serious adverse events — no. (%)</td>
<td>intensive</td>
<td>usual care</td>
<td>p value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------</td>
<td>------------</td>
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<td>Event attributed to blood-pressure medications</td>
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<td>Particulars</td>
<td>Rs.</td>
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<td>----------------------</td>
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<tr>
<td>1</td>
<td>Cho. Plate</td>
<td>40</td>
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<tr>
<td></td>
<td>Water</td>
<td>20</td>
</tr>
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<td></td>
<td>Ch. Masala</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Poda &amp; Jw Rice</td>
<td>80</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>230</strong></td>
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Manager
You pay for controlling the blood pressure with acute renal failure, hypotension and potassium abnormalities.
Acute Kidney Injury Episodes and Chronic Kidney Disease Risk in Diabetes Mellitus

Charuhas V. Thakar,* Annette Christianson,* Jonathan Himmelfarb,§ and Anthony C. Leonard†

Summary

Background and objectives Prior studies have examined long-term outcomes of a single acute kidney injury (AKI) event in hospitalized patients. We examined the effects of AKI episodes during multiple hospitalizations on the risk of chronic kidney disease (CKD) in a cohort with diabetes mellitus (DM).

Design, setting, participants, & measurements A total of 4082 diabetics were followed from January 1999 until December 2008. The primary outcome was reaching stage 4 CKD (GFR of <30 ml/min per 1.73 m²). AKI during hospitalization was defined as >0.3 mg/dl or a 1.5-fold increase in creatinine relative to admission. Cox survival models examined the effect of first AKI episode and up to three episodes as time-dependent covariates, on the risk of stage 4 CKD. Covariates included demographic variables, baseline creatinine, and diagnoses of comorbidities including proteinuria.

Results Of the 3679 patients who met eligibility criteria (mean age = 61.7 years [SD, 11.2]; mean baseline creatinine = 1.10 mg/dl [SD, 0.3]), 1822 required at least one hospitalization during the time under observation (mean = 61.2 months [SD, 25]). Five hundred thirty of 1822 patients experienced one AKI episode; 157 of 530 experienced ≥2 AKI episodes. In multivariable Cox proportional hazards models, any AKI versus no AKI was a risk factor for stage 4 CKD (hazard ratio [HR], 3.56; 95% confidence interval [CI], 2.76, 4.61); each AKI episode doubled that risk (HR, 2.02; 95% CI, 1.78, 2.30).

Conclusions AKI episodes are associated with a cumulative risk for developing advanced CKD in diabetes mellitus, independent of other major risk factors of progression.


*Cincinnati Veterans Affairs Medical Center; †Department of Internal Medicine and Department of Public Health, University of Cincinnati, OH; §Kidney Research Institute, University of Washington, Seattle, WA

Correspondence: Dr. Charuhas V. Thakar, University of Cincinnati, Renal Section, Cincinnati VA Medical Center, 3200 Vine Street, Cincinnati, OH 45220. Phone: 513-475-6356; Fax: 513-558-4309; E-mail: charuhas.thakar@va.gov or charuhas.thakar@uc.
- 3,679 diabetic veterans
- baseline creatinine 1.1
- followed from 1999-2008
- primary outcome: development of CKD 4
- secondary outcome: all-cause mortality
  - 1,822 hospitalized
  - 530 developed AKI at least once
    - 88% creatinine rise of 50-100% (AKIN 1)
    - 12% More than that (AKIN 2,3)
% Stage IV CKD

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>Hospitalized and AKI</td>
<td>23.4</td>
<td>530</td>
</tr>
<tr>
<td>Hospitalized no AKI</td>
<td>10.4</td>
<td>1,292</td>
</tr>
<tr>
<td>Not Hospitalized</td>
<td>13.19</td>
<td>1,857</td>
</tr>
<tr>
<td>Overall</td>
<td>13.67</td>
<td>3,679</td>
</tr>
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(*Chl-square p < 0.0001)
used to be...
No dialysis.
No foul.
Acute renal failure is a risk factor for progression of CKD
The other lesson of 1993 is ACEi are good

The lesson of 2001 was ARB are good
The other lesson of 1993 is ACEi are good

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What about both together?
The other lesson of 1993 is ACE inhibitors are good. What about both together?

The lesson of 2001 was ARBs are good.
VA NEPHRON-D: Diabetes in Nephropathy Study

This study is ongoing, but not recruiting participants.

Sponsor:
Department of Veterans Affairs

Information provided by (Responsible Party):
Department of Veterans Affairs

ClinicalTrials.gov Identifier:
NCT00555217

First received: November 7, 2007
Last updated: October 4, 2012
Last verified: October 2012

Purpose

Diabetes is the leading cause of end-stage renal disease (ESRD) in the United States. The overall rate of ESRD secondary to diabetes has risen 68% since 1992. Medications that block the renin angiotensin system have been shown to decrease the progression of diabetic nephropathy. The use of an angiotensin receptor blocker (ARB) has been shown to decrease the risk of progression of kidney disease in two studies of individuals with Type 2 diabetes and proteinuria. Despite the use of an ARB, the incidence of renal failure remained high in the treated group in both studies. The combination of an angiotensin converting enzyme inhibitor (ACEI) and ARB can lead to more complete blockade of the renin angiotensin system. In diabetic kidney disease, combination therapy has been shown to decrease proteinuria in short-term studies. Although there are encouraging results for improvement in proteinuria there are no data on progression of kidney disease for the use of combination of ACEI and ARB therapy in patients with diabetes. In addition, there could be an increased risk of serious hyperkalemia in individuals with diabetes who receive combination ACEI and ARB. The investigators therefore propose a randomized double blind multi-center clinical trial to assess the effect of combination of ACEI and ARB in patients with diabetes and proteinuria on progression of kidney disease.
On Target

- Telmisartan + ramipril vs ramipril vs telmisartan
- Outcome: CV death, MI, CVA, hospitalization for CHF
- 25,620 patients were randomized
- Study population: age >55, coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage

- 37% had diabetes
- 13% had microalbuminuria
- 50% had prior MI
- 22% had prior CABG
- 68% had history of hypertension

- 56 months of follow-up

Primary outcome

Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.
Renal outcomes

- Renal impairment:
  - 13.5% with combo tx
  - 10.2% ramipril
  - 10.6% telmisartan
  - RR 1.33 for combination tx (p=<0.001)

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- Initiation of dialysis
  - 0.8% with combination therapy
  - 0.6% with monotherapy
  - RR 1.37 (p=0.1)

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<tr>
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<th>Ramipril n (%)</th>
<th>Telmisartan n (%)</th>
<th>Ramipril+telmisartan n (%)</th>
<th>Telmisartan vs ramipril HR (95% CI)</th>
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<td>1150 (13.4)</td>
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<td>174 (2.03)</td>
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<td>All dialysis</td>
<td>48 (0.56)</td>
<td>51 (0.60)</td>
<td>63 (0.74)</td>
<td>1.07 (0.72–1.58)</td>
<td>0.747</td>
<td>1.33 (0.92–1.94)</td>
<td>0.133</td>
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<tr>
<td>All death</td>
<td>1014 (11.8)</td>
<td>989 (11.6)</td>
<td>1065 (12.5)</td>
<td>0.98 (0.90–1.07)</td>
<td>0.641</td>
<td>1.07 (0.98–1.15)</td>
<td>0.144</td>
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<tr>
<td>Doubling</td>
<td>140 (1.63)</td>
<td>155 (1.81)</td>
<td>166 (1.95)</td>
<td>1.11 (0.88–1.39)</td>
<td>0.378</td>
<td>1.20 (0.96–1.50)</td>
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<td>Acute dialysis</td>
<td>13 (0.15)</td>
<td>20 (0.23)</td>
<td>28 (0.33)</td>
<td>1.55 (0.77–3.11)</td>
<td>0.221</td>
<td>2.19 (1.13–4.22)</td>
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<td>Chronic dialysis</td>
<td>33 (0.39)</td>
<td>31 (0.36)</td>
<td>34 (0.40)</td>
<td>0.94 (0.58–1.54)</td>
<td>0.817</td>
<td>1.05 (0.65–1.69)</td>
<td>0.854</td>
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Dialysis=at least one dialysis. Chronic dialysis=more than 2 months. Acute dialysis=2 months or less. Doubling=doubling of serum creatinine from baseline values. HR=hazard ratio. Reasons for acute dialysis were reported as severe infection (n=22), volume depletion (n=9), post-surgery (n=7), drugs (n=5), specific renal diseases (n=5), and other reasons (n=23). In three of 165 originally reported cases of dialysis, a detailed analysis revealed that no dialysis took place. In three of the 162 cases of dialysis, we got no information on duration of dialysis. Investigators could report several reasons for acute dialysis.

**Table 2: Incidence of primary and secondary renal outcomes and of its components**
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Table 2: Incidence of primary and secondary renal outcomes and of its components
poor renal outcomes despite decreased proteinuria
- Blood pressure control is good
  - intensive blood pressure control (<120 systolic) reduced albuminuria but increased ARF, hypotension and abnormal potassium (up and down)
- ACEi or ARBs are good
  - combination may not be good
- Episodes of acute kidney injury may cause problems down the line
- Reductions in albuminuria may not translate to improved renal outcomes
Temporal Trends in the Prevalence of Diabetic Kidney Disease in the United States

Ian H. de Boer, MD, MS
Tessa C. Rue, MS
Yoshio N. Hall, MD
Patrick J. Heagerty, PhD
Noel S. Weiss, MD, DrPH
Jonathan Himmelfarb, MD

Diabetic kidney disease (DKD) is a common and morbid complication of diabetes and the leading cause of chronic kidney disease in the developed world. Approximately 40% of persons with diabetes develop DKD, manifested as albuminuria, impaired glomerular filtration rate (GFR), or both. Even mild degrees of albuminuria and decrease in GFR are associated with increased risk of cardiovascular disease and death. Over time, the prevalence of diabetic kidney disease (DKD) may increase due to the expanding size of the diabetes population or decrease due to the implementation of diabetes therapies.

Context Diabetes is the leading cause of kidney disease in the developed world. Over time, the prevalence of diabetic kidney disease (DKD) may increase due to the expanding size of the diabetes population or decrease due to the implementation of diabetes therapies.

Objective To define temporal changes in DKD prevalence in the United States.

Design, Setting, and Participants Cross-sectional analyses of the Third National Health and Nutrition Examination Survey (NHANES III) from 1988-1994 (N=15,073), NHANES 1999-2004 (N=13,045), and NHANES 2005-2008 (N=9,588). Participants with diabetes were defined by levels of hemoglobin A1c of 6.5% or greater, use of glucose-lowering medications, or both (n=1,431 in NHANES III; n=1,443 in NHANES 1999-2004; n=1,280 in NHANES 2005-2008).

Main Outcome Measures Diabetic kidney disease was defined as diabetes with albuminuria (ratio of urine albumin to creatinine ≥30 mg/g), impaired glomerular filtration rate (<60 mL/min/1.73 m² estimated using the Chronic Kidney Disease Epidemiology Collaboration formula), or both. Prevalence of albuminuria was adjusted to estimate persistent albuminuria.

Results The prevalence of DKD in the US population was 2.2% (95% confidence interval [CI], 1.8%-2.6%) in NHANES III, 2.8% (95% CI, 2.4%-3.1%) in NHANES 1999-2004, and 3.3% (95% CI, 2.8%-3.7%) in NHANES 2005-2008 (P<.001 for...
% U.S. Population with diabetes  % U.S. Diabetics with kidney disease

<table>
<thead>
<tr>
<th>Year</th>
<th>% Diabetes</th>
<th>% Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1994</td>
<td>36.4%</td>
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</tr>
<tr>
<td>1999-2004</td>
<td>34.5%</td>
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</tr>
<tr>
<td>2005-2008</td>
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<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18%</td>
</tr>
</tbody>
</table>
We are reducing albuminuria but not reducing diabetic kidney disease.
We are reducing albuminuria but not reducing diabetic kidney disease. The surrogate end point of proteinuria may not be valid.
5...10...20...years?
Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes

The DCCT/EDIC Research Group*
Risk reduction with intensive therapy: 50% (95% CI, 18–69)
P = 0.006

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Cumulative Incidence of Impaired GFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>No. at Risk</th>
<th>Intensive therapy</th>
<th>Conventional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>711 704 684 672 619 108</td>
<td>730 719 697 657 594  90</td>
</tr>
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</table>
Surrogate must predict the end-point
Effects on the surrogate must effect changes in the end-point
The Surrogate must predict the End-point. Effects on the surrogate must effect changes in the end-point.
disease intervention

Surrogate must predict the end-point

Effects on the surrogate must effect changes in the end-point
disease intervention Surrogate endpoint

Surrogate must predict the end-point
Effects on the surrogate must effect changes in the end-point
Tight glycemic control
ACEi

Tight glycemic control
Tight glycemic control

ACEi

ARB
Tight glycemic control
ACEi
ARB
Endothelin antagonists
Tight glycemic control
ACEi
ARB
Endothelin antagonists
ACEi + ARB
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ACEi
ARB
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ACEi
ARB
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ACEi + ARB
Very tight glycemic control
SBP < 120
Tight glycemic control
ACEi
ARB
Endothelin antagonists
ACEi + ARB
Very tight glycemic control
SBP < 120
Bardoxolone
Mechanisms of injury

disease

Out-come
Mechanisms of injury

- Disease
- Surrogate end-point
- Out-come
Mechanisms of injury

disease

Surrogate end-point

Outcome
Since the precise mechanisms of GFR loss and proteinuria are unknown, the finding that they become uncoupled should not be surprising.
In macroalbuminuria, reductions result in reduced progression of GFR

Overall % Δ GFR/year

$r = -0.57$, $p = 0.02$
In macroalbuminuria, reductions result in reduced progression of GFR
IDNT
1715 type II DM with nephropathy
Cr 1.9
Randomized to placebo, amlodipine or losartan
Primary outcome: composite of doubling serum Cr, ESRD, or death

Relative RR 20%
Absolute RR 6.4%
Number needed to treat 16

Lewis EJ, Et al. NEJM 2001; 343: 851-60.
RENAAL Trial
1513 type II DM with nephropathy
Cr 1.9
Randomized to placebo or losartan
Primary outcome: composite of doubling serum Cr, ESRD, or death

Relative RR 16 (22)%
Absolute RR 3.6%
Number needed to treat 27
RENAAL Trial
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Randomized to placebo or losartan
Primary outcome: composite of
doubling serum Cr, ESRD, or death

Relative RR 16 (22)%
Absolute RR 3.6%
Number needed to treat 27
ASCEND Trial
1392 type II DM with nephropathy
eGFR 33
Randomized to placebo, 25, or 50 mg of avosentan
Primary outcome: composite of doubling serum Cr, ESRD, or death


Stopped early (mean 4 mo)
Excess CV events (CHF, fluid overload)

Loss of GFR: avosentan worse than placebo (P=0.030)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Albuminuria reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9.7%</td>
</tr>
<tr>
<td>25 mg</td>
<td>44.3%</td>
</tr>
<tr>
<td>50 mg</td>
<td>49.3%</td>
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</table>

![Graph showing albuminuria reduction over time and survival estimates]
Reduction in proteinuria from the macroalbuminuric range cannot be considered a valid surrogate outcome unless it is associated with a specific, validated intervention i.e. RAAS blockade.
Glomerular filtration rate (GFR) [mL/min]

Years

<table>
<thead>
<tr>
<th>Pre</th>
<th>Incipient diabetic nephropathy</th>
<th>Overt diabetic nephropathy</th>
<th>End-stage renal disease</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>3</td>
<td>4</td>
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GFR ↑ (90% - 95%)

Microalbuminuria, hypertension

Proteinuria, nephrotic syndrome, GFR ↓

Urinary protein excretion [mg/d]

0

20

100

1000

5000

Years

Functional

Structural

Renal hypertrophy

Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis

Mesangial nodules (Kimmelstiel-Wilson lesions) Tubular-interstitial fibrosis

Accord BP trial

- Type II diabetics
- Study looked at two glycemic targets and two blood pressure targets
No albuminuria 
N=2,943 (68.6%)

Microalbuminuria 
N=1,110 (25.9%)

Macroalbuminuria 
N=239 (5.6%)
No albuminuria  
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No albuminuria  
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Microalbuminuria  
N=444 (15%)

Macroalbuminuria  
N=44 (1.5%)
Microalbuminuria: N=1,110 (25.9%)

Macroalbuminuria: N=239 (5.6%)

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Renal Failure: ESRD, dialysis, Cr >3.3
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Macroalbuminuria
N=150 (14%)

Microalbuminuria
N=444 (15%)

No albuminuria
N=2459 (83%)

Macroalbuminuria
N=44 (1.5%)

Microalbuminuria
N=239 (5.6%)

No albuminuria
N=233 (1.3)

Macroalbuminuria
N=138 (14%)

Microalbuminuria
N=79 (33%)

No albuminuria
N=22 (34%)

Macroalbuminuria
N=150 (14%)

Microalbuminuria
N=581 (52%)

No albuminuria
N=33 (1.3)

Macroalbuminuria
N=150 (14%)

Microalbuminuria
N=444 (15%)

No albuminuria
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Macroalbuminuria
N=150 (14%)

Microalbuminuria
N=581 (52%)

No albuminuria
N=33 (1.3)
Macroalbuminuria
N=239 (5.6%)

Microalbuminuria
N=44 (1.5%)

No albuminuria
N=2,943 (68.6%)

No albuminuria
N=379 (34%)

Microalbuminuria
N=581 (52%)

Macroalbuminuria
N=150 (14%)

No albuminuria
N=33 (1.3)

Microalbuminuria
N=79 (33%)

Macroalbuminuria
N=138 (14%)

Microalbuminuria
N=1,110 (25.9%)

No albuminuria
N=2,943 (68.6%)

Microalbuminuria
N=581 (52%)

Macroalbuminuria
N=150 (14%)

No albuminuria
N=0 (0.0)

Microalbuminuria
N=79 (33%)

Macroalbuminuria
N=138 (14%)

No albuminuria
N=22 (34%)

Microalbuminuria
N=444 (15%)

No albuminuria
N=2,459 (83%)

Microalbuminuria
N=444 (15%)

Macroalbuminuria
N=44 (1.5%)

No albuminuria
N=33 (1.3)

Microalbuminuria
N=2 (0.5)

Macroalbuminuria
N=1 (2.3)

Microalbuminuria
N=1,110 (25.9%)

No albuminuria
N=2,943 (68.6%)

Macroalbuminuria
N=138 (14%)

No albuminuria
N=12 (8.7)
Macroalbuminuria
N=239 (5.6%)

Microalbuminuria
N=444 (15%)

No albuminuria
N=2,943 (68.6%)

Macroalbuminuria
N=3 (0.8)

Microalbuminuria
N=17 (2.9)

No albuminuria
N=33 (1.3)

Microalbuminuria
N=2 (0.5)

No albuminuria
N=0 (0.0)

Microalbuminuria
N=2 (2.5)

No albuminuria
N=12 (8.7)

Macroalbuminuria
N=1 (2.3)

Microalbuminuria
N=2 (0.5)

No albuminuria
N=0 (0.0)
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<tr>
<td>N, %</td>
<td>N=2,943 (68.6%)</td>
<td>N=1,110 (25.9%)</td>
<td>N=239 (5.6%)</td>
</tr>
<tr>
<td>Final proteinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No albuminuria</td>
<td>N=33 (1.3)</td>
<td>N=3 (0.8)</td>
<td>N=0 (0.0)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>N=2 (0.5)</td>
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</tr>
<tr>
<td>Macroalbuminuria</td>
<td>N=1 (2.3)</td>
<td>N=2 (1.3)</td>
<td>N=12 (8.7)</td>
</tr>
</tbody>
</table>
Only 18 patients developed ESRD and at one time had macroalbuminuria.
Only 18 patients developed ESRD and at one time had macroalbuminuria. 55 patients developed ESRD and never had macroalbuminuria.
<table>
<thead>
<tr>
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<tr>
<td>Macro-albuminuria</td>
<td>18</td>
<td>415</td>
</tr>
<tr>
<td>No Macro-Albuminuria</td>
<td>55</td>
<td>3803</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>4218</td>
</tr>
</tbody>
</table>

Sensitivity: $\frac{18}{73} = 24\%$

Specificity: $\frac{3803}{4218} = 90\%$
<table>
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</tr>
<tr>
<td>No Macro-Albuminuria</td>
<td>56</td>
<td>3803</td>
</tr>
</tbody>
</table>

Pos pred value: 18/433 4%

Neg pred value: 3803/3859 90%
<table>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Macro-albuminuria</td>
<td>18</td>
<td>415</td>
<td>433</td>
</tr>
<tr>
<td>No Macro-albuminuria</td>
<td>56</td>
<td>3803</td>
<td>3859</td>
</tr>
</tbody>
</table>

Pos pred value: 18/433 = 4%
Neg pred value: 3803/3859 = 90%
Macroalbuminuria  
N=239 (5.6%)  

Microalbuminuria  
N=1,110 (25.9%)  

No albuminuria  
N=2,943 (68.6%)  

Final proteinuria

No albuminuria
N=33 (1.3)

Microalbuminuria
N=2 (0.5)

Macroalbuminuria
N=1 (2.3)

Initial proteinuria

No albuminuria
N=3 (0.8)

Microalbuminuria
N=17 (2.9)

Macroalbuminuria
N=12 (8.7)
Macroalbuminuria
N=239 (5.6%)

Microalbuminuria
N=1,110 (25.9%)

No albuminuria
N=2,943 (68.6%)

Initial proteinuria

Final proteinuria
No albuminuria
N=33 (1.3)

Microalbuminuria
N=2 (0.5)
N=17 (2.9)
N=2 (2.5)

Macroalbuminuria
N=1 (2.3)
N=2 (1.3)
N=12 (8.7)
41 patients developed ESRD and at one time had albuminuria.
41 patients developed ESRD and at one time had albuminuria. 33 patients developed ESRD and never had albuminuria.

33 patients developed ESRD and never had albuminuria. No albuminuria N=2,943 (68.6%) Microalbuminuria N=1,110 (25.9%) Macroalbuminuria N=239 (5.6%)

No albuminuria
N=33 (1.3)
Microalbuminuria
N=3 (0.8)
N=17 (2.9)
N=2 (2.5)
N=12 (8.7)
Macroalbuminuria
N=0 (0.0)
N=2 (0.5)
N=1 (2.3)
N=2 (1.3)
N=3 (0.8)

Initial proteinuria
Final proteinuria

33 patients developed ESRD and never had albuminuria.
<table>
<thead>
<tr>
<th>Microalbuminuria</th>
<th>ESRD</th>
<th>No ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>41</td>
<td>1792</td>
</tr>
<tr>
<td>No Microalbuminuria</td>
<td>33</td>
<td>2426</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>4218</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>No ESRD</td>
</tr>
<tr>
<td>----------------</td>
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<td>---------</td>
</tr>
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</tr>
<tr>
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<td>33</td>
<td>2426</td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>41/74</td>
<td>55%</td>
</tr>
<tr>
<td>Specificity:</td>
<td>2426/4218</td>
<td>58%</td>
</tr>
<tr>
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</tr>
<tr>
<td>--------------------------</td>
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<td>2426</td>
</tr>
</tbody>
</table>

Pos Pred Value: 18/433, 2.2%
Neg Pred Value: 3803/3859, 99%
<table>
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<td>2426</td>
</tr>
</tbody>
</table>

18/433 = 2.2%
3803/3859 = 99%
The graph illustrates the progression of diabetic nephropathy over time, with three stages:

1. **Pre-Stage**
   - GFR increase (90% - 95%)
   - Microalbuminuria, hypertension

2. **Incipient Diabetic Nephropathy**
   - GFR decrease
   - Proteinuria, microalbuminuria, hypertension

3. **Overt Diabetic Nephropathy**
   - GFR decrease
   - Proteinuria, nephrotic syndrome, GFR decrease

4. **End-stage Renal Disease**
   - GFR decrease
   - Proteinuria, nephrotic syndrome

The graph shows the relationship between years and glomerular filtration rate (GFR) as well as urinary protein excretion.

Regression of Microalbuminuria in Type 1 Diabetes


ABSTRACT

BACKGROUND
In the present study, we aimed to determine the frequency of a significant reduction in urinary albumin excretion and factors affecting such reduction in patients with type 1 diabetes and microalbuminuria.

METHODS
The study included 386 patients with persistent microalbuminuria, indicated by repeated measurements of urinary albumin excretion (estimated on the basis of albumin to creatinine ratio) in the range of 30 to 300 mg/mmol during a 5-year period. From the Section on Genetics and Epidemiology, Joslin Diabetes Center (B.A.P., L.H.F., K.H.S., J.H.W., A.S.K.); the Department of Medicine, Harvard Medical School (B.A.P., D.M.F., A.S.K.); the Massachusetts General Hospital Biostatistics Center (D.M.F.); and the Harvard School of Public Health (D.M.F., J.H.W., A.S.K.) — all in Boston. Address reprint requests to Dr. Krolewski at the Section on
Regression of Microalbuminuria in Type 1 Diabetes


BACKGROUND
In the presence of microalbuminuria, the progression to diabetic nephropathy is difficult to prevent and is commonly associated with cardiovascular disease. In metabolic syndrome, microalbuminuria is present in 17%, and the majority of these patients are asymptomatic. The relationship between albuminuria and cardiovascular disease is still unclear.

METHODS
The study included 43 patients with diabetes mellitus and microalbuminuria. The patients were treated with insulin and were followed up for 3 years with annual urine albumin measurements. The study was performed in a hospital setting.

RESULTS
The study showed a significant regression of microalbuminuria in type 1 diabetes. The initial evaluation interval showed a decrease in albumin excretion rate, while the first follow-up interval showed a stabilization of the values. The second follow-up interval showed a further decrease in albumin excretion rate, and the third follow-up interval showed a stabilization of the values.

CONCLUSIONS
The regression of microalbuminuria in type 1 diabetes is associated with improved glycemic control and reduced albumin excretion rate. This finding suggests that early intervention may delay the progression of diabetic nephropathy.
- 386 patients with type 1 DM
- Patients had repeatedly positive microalbuminuria (30-299 mg/g Cr) over 2 years
- Over the subsequent 6 years 58% lost their microalbuminuria
- Not related to use of ACEi/ARB
Albuminuria
Albuminuria

Decreased GFR
Albuminuria

Decreased GFR

Decreased GFR

Albuminuria
Iron sucrose causes greater proteinuria than ferric gluconate in non-dialysis chronic kidney disease

R Agarwal1, A R Rizkala2, M O Kaskas3, R Mlnasian4 and J R Trout5

1Department of Medicine, Indiana University School of Medicine and the Richard L Roudebush VA Medical Center, Indianapolis, Indiana, USA
2Clinical Affairs, Watson Laboratories, Inc., Morristown, New Jersey, USA
3Northwest Louisiana Nephrology Associates, Shreveport, Louisiana, USA
4Glendale Kidney Center, Glendale, California, USA
5Rutgers University, New Brunswick, New Jersey, USA

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Received 28 February 2007; Revised 17 April 2007; Accepted 15 May 2007; Published online 11 July 2007.

ABSTRACT

Non-dextran intravenous (i.v.) iron preparations seem to differentially affect proteinuria in patients with chronic kidney disease. To study effects of ferric gluconate and iron sucrose on proteinuria, we conducted a crossover trial in 12 patients with stage 3–4 chronic kidney disease. These patients were randomized to receive the same dose of either drug 1 week apart. Urine samples were obtained immediately before and at frequent intervals after the drug administration. The 24-hour urinary protein excretion was significantly lower (p=0.03) in the patients treated with iron sucrose than in the ferric gluconate group.

Keywords: Iron, chronic kidney disease, proteinuria
Iron sucrose causes greater proteinuria than ferric gluconate in non-dialysis chronic kidney disease

R Agarwal¹, A R Rizkala², M O Kaskas³, R Minasian⁴ and J R Rieder⁵

¹Department of Medicine, Indiana University School of Medicine and the Richard L. Roudebush VA Medical Center, Indianapolis, Indiana, USA
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ABSTRACT

Non-dextran intravenous (i.v.) iron preparations seem to affect proteinuria in patients with chronic kidney disease (CKD) of ferric gluconate and iron sucrose on proteinuria, we conducted a crossover trial in 12 patients with stage 3–4 chronic kidney disease randomized to receive the same dose of either iron sucrose or ferric gluconate. Urine samples were obtained immediately before and after each infusion. Treatment with iron sucrose was followed by a significant decrease in proteinuria (P = 0.001). The decrease in proteinuria was greater with iron sucrose than with ferric gluconate (P = 0.02).

Clinical Nephrology – Epidemiology – Clinical Trials

Antiproteinuric effect of oral paricalcitol in chronic kidney disease

RAJIV AGARWAL, MURALIDHARACHARYA, JIN TIAN, RICHARD L HEBBENSTEEL, JOEL Z MELNICK, PING QIU, LAURA WILLIAMS and DANIEL BATTE

*Indiana University School of Medicine and Richard L. Roudebush VA Medical Center, Indianapolis, Indiana; Outcomes Research International, Inc., Hudson, Florida; Renal Global Project Team, GSK, Abbott Laboratories, Abbott Park, Illinois, and Division of Nephrology and Hypertension, The Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Correspondence: Rajiv Agarwal, M.D., YAMC, 111N 1481 West 10th Street, Indianapolis, IN 46202. E-mail: ragarwal@iupui.edu

Received 18 May 2005; Revised 13 June 2005; Accepted 8 July 2005

ABSTRACT

Antiproteinuric effect of oral paricalcitol in chronic kidney disease.

Background Proteinuria is a marker of cardiovascular and renal disease in patients with chronic kidney disease (CKD), and reduction in proteinuria has been associated with improved cardiovascular and renal outcomes. While active vitamin D and its analogs have been shown to have renal protective effects in animals, these hormones have not been shown to reduce proteinuria in CKD patients.
64 years old
Diabetes for 8 years
Hgb A1c fluctuates between 7 and 8
Blood pressure runs in the 130s but recently it has been going up
No signs of retinopathy per ophtho
Creatinine over the last year: 1.3 to 1.6 to 1.8
The U/A shows protein of 100, 4-6 RBC/hpf
Does he have diabetic nephropathy?
Does he need a biopsy?
diagnosis

- risk factors
  - long duration
  - poor glycemic control
  - hypertension
  - proteinuria

- gold standard is biopsy
  - though dx usually made on clinical grounds
Size Matters

Normal kidney weight is 150 g
Size Matters

Normal kidney weight is 150 g

Diseases with large kidneys:
- Multiple Myeloma
- Amyloidosis
- ADPKD/ARPKD
- Hydronephrosis
- Renal Cell Cancer
- HIVAN
Retinopathy is supportive but not necessary for the diagnosis

26% of T1DM with CKD
9% with retinopathy

30% of T2DM with CKD will have no retinopathy or albuminuria

when not to think diabetes

- rapid loss of kidney function
- rapid increase in proteinuria
- active sediment
- refractory hypertension
- large reduction of GFR with ACEi
Diabetic Nephropathy
Non-diabetic
Mixed picture

role of biopsy

- acute interstitial nephritis
- glomerulonephritis
- hypertension
- acute tubular necrosis

19%
18%
63%
hematuria

- Found in 62% of cases of diabetic nephropathy
- Dysmorphic RBC found in only 4% of diabetic nephropathy
hematuria

- Found in 62% of cases of diabetic nephropathy
- Dysmorphic RBC found in only 4% of diabetic nephropathy
glycemic control
metabolic memory
Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes

The DCCT/EDIC Research Group*
Risk reduction with intensive therapy: 50% (95% CI, 18–69)  
P=0.006
Risk reduction with intensive therapy: 50% (95% CI, 18–69)  
P = 0.006

Cumulative Incidence of Impaired GFR (%)

Years since Randomization

<table>
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<tr>
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<th>No. at Risk</th>
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<tr>
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<tr>
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<td>20</td>
<td>619</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

6.5 yrs  22 yrs
The mean glycated hemoglobin level during the DCCT was 7.3% in the intensive-therapy group and 9.1% in the conventional-therapy group. During the EDIC study the time-averaged mean glycated hemoglobin level in participants who had been in the DCCT intensive-therapy group was similar to the level in participants who had been in the DCCT conventional-therapy group.
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The relative risk of reduced renal function was reduced by 50%.
6.5 years in the experimental group of the DCCT resulted in decreased:

- nephropathy
- CKD
- Retinopathy
- CVD
- Neuropathy

15 years after the intervention
Accord

- intensive glycemic control
  - Hgb A1c <6% versus 7-7.9%
  - Stopped early due to excess mortality with intensive glycemic control
  - Patients were all transitioned to conventional glycemic control until the study ended
The diagram shows the Hgb A1c levels for standard and intensive treatments at three stages:

- **Baseline**: Standard 8.1, Intensive 8.1
- **Transition**: Standard 7.6, Intensive 6.3
- **Study End**: Standard 7.6, Intensive 7.2
Results – Nephropathy Outcome #1

Development of microalbuminuria
(urine albumin:creatinine ratio ≥ 30 mg/g)

Until Transition

**HR (95% CI):** 0.79 (0.69, 0.90) P= 0.0005

Through End of Study

**HR (95% CI):** 0.85 (0.77, 0.94) P=0.0012
Results – Nephropathy Outcome #2
Development of macroalbuminuria
(urine albumin:creatinine ratio \( \geq 300 \) mg/g)

Until Transition

HR (95% CI):
\[ 0.68 \( (0.54, 0.86) \) \]
P = 0.0013

Through End of Study

HR (95% CI):
\[ 0.71 \( (0.59, 0.86) \) \]
P = 0.0003
Results – Nephropathy Outcome #3

Development of renal failure: initiation of dialysis or ESRD, or renal transplant, or a rise of serum creatinine above 3.3 mg/dL

Until Transition

HR (95% CI): 0.95 (0.73, 1.24)  
P = 0.71

Through End of Study

HR (95% CI): 0.92 (0.73, 1.16)  
P = 0.49
Results – Nephropathy Outcome #4

Development of any of the following nephropathy outcomes:
- Doubling of serum creatinine or more than 20 mL/min/1.73 m$^2$ decrease in estimated GFR or development of macroalbuminuria, or development of renal failure)

Until Transition

HR (95% CI): 1.04 (0.99, 1.10)  
P = 0.11

Through End of Study

HR (95% CI): 1.07 (1.02, 1.13)  
P = 0.0160
Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

William Duckworth, M.D., Carlos Abraira, M.D., Thomas Moritz, M.S.,
Domenic Reda, Ph.D., Nicholas Emanuele, M.D., Peter D. Reaven, M.D.,
Franklin J. Zieve, M.D., Ph.D., Jennifer Marks, M.D., Stephen N. Davis, M.D.,
Rodney Hayward, M.D., Stuart R. Warren, J.D., Pharm.D., Steven Goldman, M.D.,
Madeline McCarren, Ph.D., M.P.H., Mary Ellen Vitek, William G. Henderson, Ph.D.,
and Grant D. Huang, M.P.H., Ph.D., for the VADT Investigators*

ABSTRACT

BACKGROUND
The effects of intensive glucose control on cardiovascular events in patients with longstanding type 2 diabetes mellitus remain uncertain.

METHODS
We randomly assigned 1791 military veterans (mean age, 60.4 years) who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. Other cardiovascular risk factors were treated uniformly. The mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time...
ABSTRACT

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The effects of intensive glucose control on cardiovascular events in patients with longstanding type 2 diabetes mellitus remain uncertain.

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We randomly assigned 1791 military veterans (mean age, 60.4 years) who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. Other cardiovascular risk factors were treated uniformly. The mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time
BACKGROUND
The effects of intensive glucose control in patients with longstanding type 2 diabetes remain uncertain.

METHODS
We randomly assigned 1791 patients with type 2 diabetes and a mean baseline hemoglobin A1c level of 8.6% to receive either intensive or standard glucose control. Other cardiovascular risk factors were treated uniformly. The mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time to the first major cardiovascular event or death from cardiovascular disease.

A Primary Outcome

![Graph showing the primary outcome](image)

- Intensive therapy
- Standard therapy

Probability of Survival

- Intensive therapy
- Standard therapy

$P = 0.14$
BACKGROUND
The effects of intensive glycemic control in patients with type 2 diabetes and mild hyperglycemia have been studied. The primary outcome was the time to the first cardiovascular event, defined as death from any cause, myocardial infarction, or stroke. The goal of the intensive-therapy group was to achieve a glycated hemoglobin level of less than 7.0%, while the standard-therapy group was to achieve a level of less than 7.5%.

METHODS
We randomly assigned 1797 patients to the intensive-therapy group and 1838 to the standard-therapy group. The mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The mean number of years since the diagnosis was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time to the first cardiovascular event, defined as death from any cause, myocardial infarction, or stroke.
Any worsening of albumin excretion was greater in the standard-therapy group ($P = 0.01$); progression to macroalbuminuria was also significant ($P=0.04$).
Tips for diabetic management in CKD

- A third of insulin metabolism occurs in the kidney
- In CKD,
  - less gluconeogenesis
  - less insulin metabolism
  - reduced insulin requirements
- burnt out diabetes
- hypoglycemia
diabetic management in CKD

- first generation sulfonylureas
  - chlorpropamide
  - tolazamide
  - tolbutamide
- Active metabolites that are excreted by the kidney
- Avoid as GFR falls below 60 mL/min
- Glipizide is metabolized in the liver
diabetic management in CKD

- Metformin
- cleared by the kidney
- FDA says do not use if creatinine
  - ≥1.5 in men
  - ≥1.4 in women
- British National formulary
  - re-evaluate when eGFR <45
  - Stop when eGFR <30
fin