New therapeutic interventions in the management of DN
Christoph Wanner MD
Mandaluyong City
April 25 2014
Disappointment & Hope

Because......

All recent trials failed to improve CV and renal outcomes in patients with type 2 diabetes mellitus

But .......

More than 50,000 patients are currently in clinical trials that will report renal outcome data from 2015 onwards.
Diabetic Kidney Disease – A clinical update from KDIGO

Mark E. Molitch¹, Amanda I. Adler², Dick de Zeeuw³, Allan Flyvbjerg⁴, Robert G. Nelson⁵, Wing-Yee So⁶, Christoph Wanner⁷, Bertram L. Kasiske⁸,⁹, David C. Wheeler¹⁰, and Carl E. Mogensen¹¹

Kidney International 2014 in press
Objectives

Global picture
Diabetes complication
Recent advances in treatment
  Established Strategies
  New Treatments
Potential future Interventions
Global picture and the Asian-Pacific region
The diabetes epidemic: global projections for 2013–2035

2011: 382 million
2035: 592 million

↑ 55%

The Diabetes Atlas, 6th ed. IDF 2013
Estimated national prevalence of diabetes mellitus in selected Asia-Pacific region countries

<table>
<thead>
<tr>
<th>Country</th>
<th>2013</th>
<th>2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>9.6</td>
<td>13</td>
</tr>
<tr>
<td>Japan</td>
<td>7.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Australia</td>
<td>10</td>
<td>11.3</td>
</tr>
<tr>
<td>South Korea</td>
<td>11.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Indonesia</td>
<td>5.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Taiwan</td>
<td>6.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Thailand</td>
<td>8.3</td>
<td>10.1</td>
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<tr>
<td>Malaysia</td>
<td>12.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Singapore</td>
<td>15.3</td>
<td></td>
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</tbody>
</table>

Source: www.idf.org/atlasmap/atlasmap
Diabetes complications
Cardiovascular risk is greatest when both diabetes and CKD are present

Among patients with diabetes and CKD, the rate of cardiovascular events is more than twice that among patients with diabetes only.
Impact of nephropathy on risk of death

- No nephropathy: 1%
- Microalbuminurias: 3%
- Macroalbuminurias: 5%
- ESRD: 19%
Diabetic nephropathy

- Leading cause of ESRD
  ~ 30-50% of new cases
- Increasing prevalence globally
- Approximately one-third of all patients
- More common in Hispanics, Blacks and Native Americans
- High cardiovascular morbidity and mortality
- Cause incompletely understood and.... No cure
## New therapeutic interventions in the management of DN

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Approaches to improving outcomes related to DKD

Prevention of Obesity

Screening & Prevention of Diabetes

Diabetes

Diabetic Kidney Disease

Glycemic Control

Blood Pressure Control

RAAS Inhibition

Lipid Management

ESRD

CVD

Kidney Disease: Improving Global Outcomes
Kidney International 2014 in press
ACE inhibitors and angiotensin receptor blockers slow progression of kidney disease in hypertensive type 2 diabetics.
Glycemic control in diabetes: a brief history of intervention trials

1960
UGDP

1970
Oxford
Steno
Kroc
Dallas
Oslo

1980
UKPDS

1990
DCCT
EDIC

2000

2010

ADA Standards of Care
1989

VADT
ADVANCE
ACCORD
PROactive
RECORD
BARI-2D
Kumamoto
VACS

Kidney Disease: Improving Global Outcomes
Cumulative incidence of macroalbuminuria by diabetes duration – Typ 1 DM

Cumulative incidence at 25 yrs’ duration of diabetes:
- Conv 17%
- Int 6%
Oral Antidiabetics and Kidney Function

- Metformin
- Pioglitazon
- Acarbose
- Repaglinid
- Gliclazid
- Gliquidon
- Pioglitazon

Dose reduction

- Ordi
- Hemodialysis

Kidney Disease: Improving Global Outcomes

Avogaro & Schernthaner Acta Diab 2013
The use of Metformin

A Cochrane review (347 trials & cohort studies) found no cases of lactic acidosis; half of the studies included CKD patients.

Metformin use should be re-evaluated when GFR <45 ml/min/1.73m² (max 1000 mg) and stopped when <30 ml/min/1.73m².

The major precipitating factor is an abrupt loss of tubular secretion. Such a loss does not occur in stable CKD, but in AKI or rapid volume depletion associated with an intercurrent illness. Patients with CKD should be alerted to withhold metformin if they experience intercurrent illness that could lead to rapid volume depletion.

Salpeter et al. Cochrane Database Syst Rev 2010: CD002967
KDIGO: Kidney International 2014
Potential clinical signals of concern with therapies for T2DM? Another dimension in the complexity (cardiotoxicity)?

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Therapy</th>
<th>Outcome</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>UGDP</td>
<td>1969</td>
<td>Tolbutamide</td>
<td>CV death</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Meta analysis</td>
<td>2005</td>
<td>Muraglitazar</td>
<td>CVD</td>
<td>&lt;0.03</td>
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<tr>
<td>Meta analysis</td>
<td>2007</td>
<td>Rosiglitazone</td>
<td>CVD</td>
<td>&lt;0.043</td>
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<tr>
<td>ACCORD</td>
<td>2008</td>
<td>Intensive control</td>
<td>Death</td>
<td>&lt;0.04</td>
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All failed!
Recent advances in treatment

**The NEW ENGLAND JOURNAL of MEDICINE**

**EDITORIAL**

**New Therapies for Diabetic Kidney Disease**
Jonathan Himmelfarb, M.D., and Katherine R. Tuttle, M.D.

Kidney Disease: Improving Global Outcomes
Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease

Dick de Zeeuw, M.D., Ph.D., Tadao Akizawa, M.D., Ph.D., Paul Audhya, M.D., M.B.A., George L. Bakris, M.D., Melanie Chin, Ph.D., Heidi Christ-Schmidt, M.S.E., Angie Goldsberry, M.S., Mark Houser, M.D., Melissa Krauth, M.B.A., Hiddo J. Lambers Heerspink, Pharm.D., Ph.D., John J. McMurray, M.D., Colin J. Meyer, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Robert D. Toto, M.D., Nosratola D. Vaziri, M.D., Christoph Wanner, M.D., Janet Wittes, Ph.D., Danielle Wrolstad, M.S., and Glenn M. Chertow, M.D., M.P.H., for the BEACON Trial Investigators*
Kidney Disease:
Improving Global Outcomes

Heart failure and death

Hazard ratio, 1.83 (95% CI, 1.32–2.55)
P<0.001

This portion of the figure based on <20% of patients

Weeks since Randomization

<table>
<thead>
<tr>
<th>weeks</th>
<th>Patients</th>
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<tr>
<td>0</td>
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<td>4</td>
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<td>40</td>
<td>15</td>
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<tr>
<td>44</td>
<td>0</td>
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Bardoxolone methyl

Placebo
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O’Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., Stuart R. Warren, J.D., Pharm.D., Suzanne Watnick, M.D., Peter Peduzzi, Ph.D., and Peter Guarino, M.P.H., Ph.D., for the VA NEPHRON-D Investigators*
The End of Dual Therapy with Renin–Angiotensin–Aldosterone System Blockade?

Dick de Zeeuw, M.D., Ph.D.
Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus

The AleCardio Randomized Clinical Trial

JAMA. doi:10.1001/jama.2014.3321
Published online March 30, 2014.
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<td>CCRX Inhibition (Spiegelmer)</td>
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A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy

SONAR: Study of Diabetic Nephropathy with Atrasentan
Each of these trials was controversial in some respects.
SAVOR-TIMI 53: study design

Documented Type 2 Diabetes

N ~ 16,500

Established CV disease or Multiple Risk Factors

RANDOMIZE 1:1 DOUBLE BLIND

Dosing based on eGFR

All other diabetes therapy per treating doctors

SAXAGLIPTIN
2.5 or 5 mg/d

PLACEBO

Follow up Visits Q6 months

Final Visit

Primary Endpoint
CV Death, non-fatal MI, non-fatal ischemic stroke

Duration
Event driven (n=1040)
Median duration: 2.1 yr
LFU 0.2%
W/C 2.4%

Major Secondary Endpoints: CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure, unstable angina pectoris, or coronary revascularization
The primary endpoint (CV death, nonfatal MI, nonfatal stroke)

The upper limit of the 95% CI was <1.3 but not <1.0. Therefore, saxagliptin met the non-inferiority criterion (did not increase the risk of CV events versus placebo) but did not demonstrate superiority (did not reduce the risk for CV events versus placebo).

NEJM 2013;369:1317-2
Alogliptin versus placebo, in addition to standard of care, in subjects with type 2 diabetes mellitus, HbA1c 6.5–11.0%, and acute coronary syndrome (within 15-90 days prior to randomization)
EXAMINE: primary endpoint

The upper limit of the HR was <1.3, which was the pre-specified safety boundary based on the FDA’s 2008 guidance for evaluating CV safety of new antidiabetes drugs. Therefore, alogliptin met the non-inferiority criterion (did not increase the risk of CV events versus placebo). However, as the limit was not <1.0, alogliptin did not demonstrate superiority (did not reduce the risk for CV events versus placebo).

The primary endpoint (CV death, nonfatal MI, nonfatal stroke) occurred in 11.3% of alogliptin patients and 11.8% of placebo patients; hazard ratio=0.96 (one-sided repeated CI bound, 1.16).

Each of these trials was controversial in some respects.
New therapeutic interventions in the management of DN

Established Strategies

- Prevention of obesity
- Glycemic control
- BP control
- RAAS blockade/inhibition
- Low salt

New Treatments

- Bardoxolone
- Aleglitazar
- Double RAAS-B
- ONTARGET ALTITUDE
- VA-NephronD

Future potential Interventions

- Atrasentan
- DPP4 Inhibitors
- SGLT2 Inhibitors
- CCRX Inhibition (Spiegelmer)
Summary

- Worldwide epidemic of type 2 diabetes
- Aggressive multi-risk factor intervention including tight glycemic control improves outcomes
  - Microvascular
  - Macrovascular (not so much)
- Guidelines recommend tighter control of glycemia, but ...
- Renal endpoints critically important for newer therapies
- Regulatory agencies establish guidance for safety
Thank you

April 23-26, 2014 | Manila, Philippines
PSN 34th Annual Convention

Kidney Disease: Improving Global Outcomes