Ο έλεγχος της πρωτεϊνουρίας για επιβράδυνση της εξέλιξης της Διαβητικής Νεφροπάθειας

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Disclosure Statement of Financial Interests

Nothing to declare concerning this presentation
The spectrum of Albuminuria

Diabetic nephropathy progression

Pathophysiologic mechanism

Strict glycemic control

Reduction of the intraglomerular pressure

RAAS inhibition for primary prevention-agents

Blood Pressure levels & diabetic nephropathy progression

Conclusions
The spectrum of Albuminuria
Screening for albuminuria
The past (1892)

Potential presence of albuminuria even in perfectly (or at least seemingly) healthy individuals

Hermann Senator (1834–1911)

A forgotten pioneer

Gansevoort and Ritz, Nephrol Dial Transplant 2008
24-hour urine collection is the gold standard

A variety of **semi quantitative** dipsticks

- Clinitek Microalbumin Dipsticks
- Micral-Test II test strips
- DC 2000 (*Nyocard U-Albumin test*)
  
  *(HemoCue Urine Albumin)*
Proteinuria

- Ποσοτικός προσδιορισμός
  - 24ωρη συλλογή ούρων
  - Δείγμα ούρων: πρωτεϊνή/κρεατινίνη
The long-term intra-individual coefficient of variation of AER is high, implying that more than three AER measurements may be necessary to accurately categorize albuminuria.
Changes in Albuminuria/Proteinuria—
A Prognostic Marker of Kidney Disease Progression

Rigas G Kalaitzidis, MD, Madhav Rao, MD and George L Bakris, MD

Table 2: Methods of Albuminuria Measurement with Normal and Abnormal Ranges

<table>
<thead>
<tr>
<th></th>
<th>24-hour Urine Albumin (mg/24hr)</th>
<th>Overnight Urine Albumin (μg/min)</th>
<th>Spot Urine</th>
<th>Gender</th>
<th>Albumin/Creatinine Ratio (mg/mmol)</th>
<th>Albumin/Creatinine Ratio (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;15</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>M</td>
<td>&lt;1.25</td>
<td>&lt;10</td>
</tr>
<tr>
<td>High/normal</td>
<td>15 to &lt;30</td>
<td>10 to &lt;20</td>
<td>10 to &lt;20</td>
<td>F</td>
<td>1.75 to 2.5</td>
<td>15 to &lt;30</td>
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<tr>
<td>Microalbuminuria</td>
<td>30 to &lt;300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Macroalbuminuria</td>
<td>&gt;300</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Moderately increased albuminuria-Μέτρια αύξηση**

**Severely increased albuminuria-σημαντική αύξηση**
The Spectrum of Albuminuria

- Microalbuminuria
- Albuminuria (Proteinuria)

↑CV Risk and Presence of Vascular Dysfunction and Renal Dysfunction

Normal
Is albuminuria a myocardial infarction risk equivalent for atherothrombotic events?

Event-free survival with respect to albuminuria and prior MI. Event-free survival in normoalbuminuric patients with no history of prior MI (green line), in patients with albuminuria without prior MI (orange line), in normoalbuminuric patients with a history of prior MI (blue line), and in patients with both, albuminuria and prior MI (red line).

Albuminuria emerges as a CAD risk equivalent: The event rate of patients with albuminuria but no prior MI was almost equal to that of normoalbuminuric patients with prior MI.

Albuminuria is a CAD risk equivalent. Thus, cardiovascular risk factors in albuminuric patients should be treated as aggressively as in patients with prior MI.

Atherosclerosis 240 (2015) 21e25
Ultra filtered proteins in excess are toxic to the tubular cells, resulting in tubular damage and interstitial inflammation in the kidney.

Regardless of the origin of albumin leakage emerging data show that albuminuria also has a direct toxic effect on renal tissue leading to progressive function loss.

Φυσική εξέλιξη της διαβητικής νεφροπάθειας τύπου 2

- Κλινικός διαβήτης τύπου 2
- Λειτουργικές μεταβολές*
- Δομικές μεταβολές†
- Αύξηση της αρτηριακής πίεσης
- Μικρολευκωματινουρία
- Πρωτεϊνουρία
- Νεφρική νόσος τελικού σταδίου
- Πρωτεϊνουρία
- Αύξηση επιπέδων κρεατίνης ορού
- Αύξηση επιπέδων κρεατίνης ορού
- Καρδιαγγειακός θάνατος

* Μέγεθος νεφρών ↑, βραχυχρόνια GFR ↑, μακροχρόνια GFR ↓.
† Πάχυνση GBM ↑, Διόγκωση του μέσου πετάλου του έλυτρου Bowmann ↑, μικροαγγειακές μεταβολές +/-.
Diabetic nephropathy, is most likely to occur in patients who have:

- Worse glycemic control
- Hypertension
- Glomerular hyperfiltration
- Genetic predisposition

Light micrograph showing diffuse and nodular (IV) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis.

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).
The degree of albuminuria is not necessarily linked to disease progression in patients with diabetic nephropathy associated with either type 1 or type 2 diabetes.

Patients who progressed to severely increased albuminuria had the highest rate of loss of GFR.
Proteinuria as a Risk Factor for Mortality in Type 2 Diabetes

P<0.01 normoalbuminuria vs. microalbuminuria
P<0.001 normoalbuminuria vs. macroalbuminuria
P<0.05 microalbuminuria vs. macroalbuminuria

Factor(s) responsible for progressive GFR decline in nonalbuminuric diabetic nephropathy

Intrarenal vascular disease.
Pathophysiological mechanism
There are four major histologic changes in the glomeruli in diabetic nephropathy:

- Mesangial expansion;
- Glomerular basement membrane thickening;
- Podocyte injury;
- Glomerular sclerosis
Diabetic nephropathy

- Glomerular hyperfiltration
- Hyperglycemia and AGEs
- Nephrin expression
- Cytokines
- Impaired podocyte-specific insulin signaling
Increased Proteinuria

Increased Glomerular Pressure

Afferent Arteriolar Dilatation

Efferent Arteriole Constriction

Blood Flow

Angiotensin II

Blood Flow
Мηχανισμοί Νεφρικής βλάβης στην ΥΠ

- Ενδοσπειραματική Υπέρταση
  - Υπερδιήθηση
- Δυσλειτουργία του σπειραματικού φραγμού
  - Πρωτεϊνουρία
- Υπερπλασία μεσαγγειακών κυττάρων
- Ενδονεφρική φλεγμονώδης διαδικασία
- Ενδοθηλιακή δυσλειτουργία
- VSMC υπερπλασία

Αρτηριακή πίεση
Renal injury
↓ Nephron mass

Glomerular hypertension

Progressive Loss of Filtration Surface Area

Renal microvascular injury

Renal scarring

Transdifferentiation of renal cells to fibroblast phenotype

Influx of monocytes and macrophages

Fibrogenesis

Renal growth factor & cytokine activation

Hyperlipidemia

Filtration of plasma proteins (Proteinuria)

Proximal tubule protein uptake

Systemic hypertension

GFR

Equivalent renal risk in type 1 and 2 diabetes

**TYPE 1:** The incidence of overt nephropathy was 25 to 45 percent, and the incidence of ESRD was 4 to 17 percent at 20 years and 16 percent at 30 years of being diagnosed with diabetes.

**TYPE 2:** The incidence of diabetic ESRD was noted to have declined significantly from the period 1991-1994 to the period 1999-2002 (32 to 15 cases per 1000 patient-years, respectively)

Data suggest that **the renal risk is currently equivalent** in the two types of diabetes
Incident counts & adjusted rates of ESRD by primary diagnosis

USRDS 2008, Figure 2.8 (Volume 2)
Βασική αιτία ΧΝΝ τελικού σταδίου ασθενών που εντάσσονται σε πρόγραμμα υποκατάστασης της νεφρικής λειτουργίας

Albuminuria as a Appropriate Therapeutic Target in diabetic nephropathy
There is now consensus that a decrease in protein excretion has predictive importance for improved renal outcomes.
Παρεμβάσεις για την πρόληψη της εξέλιξης της νεφρικής νόσου σε διαβητικούς ασθενείς

Αυστηρός γλυκαιμικός έλεγχος
Αυστηρός έλεγχος υπέρτασης, Χορήγηση ACEi-ARB,
Statins, Salt, Obesity ,Diet
The importance of glycemic control
Cumulative incidence of moderately increased albuminuria () in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years. There was an increasing benefit of intensive therapy over time (p<0.04)

Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus

Reducing the intraglomerular pressure
AND/OR
Prevention of intraglomerular hypertension
Rhythm of glucose is superior to rhythm of AP in the onset of cardiovascular epiplokov in patients with Type 2 DM.

- **Stroke**: 5% reduction in relative risk with tight glucose control compared to tight BP control.
- **Any Diabetic Endpoint**: 12% reduction in relative risk with tight glucose control.
- **DM Deaths**: 10% reduction in relative risk with tight glucose control.
- **Microvascular Complications**: 32% reduction in relative risk with tight glucose control.

*P <0.05 compared to tight glucose control*

Tight Glucose Control (Goal <6.0 mmol/l or 108 mg/dL)

Tight BP Control (Average 144/82 mmHg)

Reducing the intraglomerular pressure with dietary protein restriction or antihypertensive therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or the prevention of intraglomerular hypertension because of concurrent renal artery stenosis can minimize progression of or even prevent glomerular disease in the absence of glycemic control.
Antihypertensive therapy with emphasis on the use of ACE inhibitors or ARBs
Mechanistic rationale for ACE inhibitors and ARBs in diabetes

Dilation of Efferent Arteriole Only

Glomerulus

Bowman’s capsule

Afferent arteriole

Efferent arteriole

↓ Glomerular pressure
↓ Albumin excretion rate

Intratubular Renin-Angiotensin System in Hypertension

L. Gabriel Navar, Hiroyuki Kobori, Minolfa C. Prieto, Romer A. Gonzalez-Villalobos
Αναστολή της εξέλιξης της διαβητικής νεφροπάθειας μέσω του αποκλεισμού του RAS

**ARB**

- Τύπου II Σ. Διαβήτης Υπέρταση
- Ενδοθηλιακή δυσλειτουργία
- Μίκρο-αλβουμινουρία
- Αλβουμινουρία
- Νεφρική Ανεπάρκεια
- ESRD

**α-MEA**

- Τύπου II Σ. Διαβήτης Υπέρταση
- Ενδοθηλιακή δυσλειτουργία
- Μίκρο-αλβουμινουρία
- Αλβουμινουρία
- Νεφρική Ανεπάρκεια
- ESRD

Schmieder RE. J Hypertens.Suppl 2006;24:S31–S35
Type 1 diabetes

Renal protection with ACEIs
Efficacy of antihypertensive therapy in diabetic rats in reducing the number of sclerotic glomeruli at 70 weeks. Triple therapy with hydrochlorothiazide, hydralazine, and reserpine was partially protective, but captopril was completely protective, with the degree of glomerulosclerosis being less than that in control (normal) rats (left column). Captopril also normalized the intraglomerular pressure (46 mmHg) versus 64 mmHg in untreated diabetic animals and 56 mmHg with triple therapy.

The effect of the administration of placebo or captopril to patients with type 1 diabetes with overt proteinuria and a Pcr equal to or greater than 1.5 mg/dL (132 μmol/L). The likelihood of a doubling of the Pcr was reduced by more than 50 percent in the captopril group.

Copyright © 1993 Massachusetts Medical Society. Adapted with permission.
ACE inhibitors — The benefit of antihypertensive therapy with an ACE inhibitor in type 1 diabetes

Captopril delays progression of moderately increased albuminuria (formerly called microalbuminuria) in diabetes

MICRO-HOPE Events Per Patient Group for Secondary Endpoints

- Total mortality
- Revascularization
- Overt nephropathy
- Heart failure†
- Unstable angina†

RR=Relative risk reduction
P=Probability
NS=Not significant

- RR=24% P=0.03
- RR=17% P=0.004
- RR=24% P=0.03
- RR=24% P=0.004
- RR=NS P=0.05

Based on positive 24h urine collection or albumin/creatinine ratio ≥36 mg/mmol
Requiring hospital admission


↓ κατά 24% του σχετικού κινδύνου εμφάνισης μακροαλβουμινουρίας στην ομάδα της ραμιπρίλης vs placebo
Type 2 diabetes

Renal protection with ARBs
Irbesartan slows progression of nephropathy in type 2 diabetes

A dose-response relationship, with a greater reduction in proteinuria associated with greater reduction in risk of renal failure.
MARVAL: Valsartan Significantly Lowers Urinary Albumin Excretion Rate

Valsartan Significantly Lowers Urinary Albumin Excretion Rate

*P <0.001 vs amlodipine.
RENAAL: Losartan reduced the incidence of a doubling of the plasma Creatinine by 25% & ESRD by 28 percent;

Every 50% reduction in albuminuria in the first 6 mo produced a reduction of 36% in the primary endpoint and a reduction of 45% in (ESRD) at the end of study.
RENAAL: Albuminuria at Baseline Predicts ESRD in Type 2 Diabetics With Nephropathy (N=1513)

RENAAL: Dominant Role of Altered Proteinuria in Reducing Risk of ESRD

Increase in albuminuria constitutes higher risk for ESRD than increase in BP

DETAIL was a randomized controlled trial that compared enalapril to the ARB telmisartan.

ACEI or ARB?

**ACE inhibitors are at least as effective as ARBs in diabetic patients with moderately increased albuminuria.**

Additive Effect of ACE Inhibition and Angiotensin II Receptor Blockade in Type I Diabetic Patients with Diabetic Nephropathy

20 patients, 8 weeks
Benazepril 20 mg
Valsartan 80 mg
Dual

SBP: -6, -7 mmHg
DBP: -7 mmHg

Additional -43%

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

A. Acute Kidney Injury

Percent of Patients (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan + Placebo</td>
<td>5.2</td>
<td>(3.8–7.2)</td>
</tr>
<tr>
<td>Losartan + Lisinopril</td>
<td>9.2</td>
<td>(7.3–11.7)</td>
</tr>
<tr>
<td>Losartan + Placebo</td>
<td>11.2</td>
<td>(8.8–14.1)</td>
</tr>
<tr>
<td>Losartan + Lisinopril</td>
<td>15.4</td>
<td>(12.4–19.1)</td>
</tr>
<tr>
<td>Losartan + Placebo</td>
<td>18.3</td>
<td>(14.2–23.3)</td>
</tr>
<tr>
<td>Losartan + Lisinopril</td>
<td>23.7</td>
<td>(20.0–28.0)</td>
</tr>
<tr>
<td>Losartan + Placebo</td>
<td>30.5</td>
<td>(28.2–56.4)</td>
</tr>
</tbody>
</table>

P < 0.001

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan + Placebo</td>
<td>724</td>
</tr>
<tr>
<td>Losartan + Lisinopril</td>
<td>724</td>
</tr>
</tbody>
</table>

No. Lost

<table>
<thead>
<tr>
<th>Group</th>
<th>No. Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan + Placebo</td>
<td>641</td>
</tr>
<tr>
<td>Losartan + Lisinopril</td>
<td>631</td>
</tr>
</tbody>
</table>
Other antihypertensive drugs and combinations
Protein excretion at baseline (black columns) and after one year of antihypertensive therapy (hatched columns) in patients with type 2 diabetes treated with lisinopril (mean dose 29 mg/day), verapamil (mean dose 360 mg/day), half-dose lisinopril plus verapamil, or hydrochlorothiazide plus guanfacine.

Diltiazem and verapamil appear to be as consistently effective as an ACE inhibitor or ARB in lowering protein excretion in diabetic patients.
The percentage change in proteinuria among patients treated with dihydropiridine CAs or nondihydropiridine CAs adjusted for change in SBP and DBP

ACE-I + Verapamil: Additive Reduction of Proteinuria in Type 2 Diabetes at 1 Year

(5.5 mg/d)  (315 mg/d)  + Verapamil (219 mg/d)

MAP  Proteinuria
Dihydropyridine CCBs only when used in combination with a RAAS blocker

Can reduce proteinuria among patients with advanced proteinuric nephropathy

The mechanism of protection appeared to be different: enalapril lowered the glomerular capillary pressure (PGC), while nifedipine minimized glomerular hypertrophy as manifested by a reduction in glomerular volume.

Mineralocorticoid receptor antagonists
Aldosterone Blockade in Diabetic Nephropathy with Proteinuria

A dose-dependent effect was observed, with albuminuria reductions ranging from 21 to 38 percent with doses ranging from 7.5 mg/day to 20 mg/day.

Bakris GL JAMA. 2015 Sep;314(9):884-94.
Sodium-glucose cotransporter 2 inhibitors
Sodium-glucose cotransporter 2 inhibitors

The use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, such as canagliflozin and empagliflozin in patients with type 2 diabetes

Reduced the risk of kidney disease progression and of renal endpoints in some trials

Canagliflozin 100 or 300 mg/d, compared with glimepiride, slowed the progression of renal disease over 2 years in patients with type 2 diabetes. Changes in UACR in a subgroup of patients with UACR $\geq 30$ mg/g at baseline, and canagliflozin may confer renoprotective effects independently of its glycemic effects.

Am Soc Nephrol 28: 368–375, 2017
In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events

### Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Renal Outcome Measure</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or cardiovascular death</td>
<td>675/4170 (16.2)</td>
<td>497/2302 (23.6)</td>
<td>0.61 (0.55–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124 (12.7)</td>
<td>388/2061 (18.8)</td>
<td>0.61 (0.53–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>459/4091 (11.2)</td>
<td>330/2033 (16.2)</td>
<td>0.62 (0.54–0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²</td>
<td>70/4645 (1.5)</td>
<td>60/2323 (2.8)</td>
<td>0.56 (0.39–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal-replacement therapy</td>
<td>13/4687 (0.3)</td>
<td>14/2333 (0.6)</td>
<td>0.45 (0.21–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease</td>
<td>81/4645 (1.7)</td>
<td>71/2323 (3.1)</td>
<td>0.54 (0.40–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria in patients with a normal albumin in level at baseline</td>
<td>1430/2779 (51.5)</td>
<td>703/1374 (51.2)</td>
<td>0.95 (0.87–1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Risk Comparison for Seven Renal Outcomes

Putative mechanism for sodium-mediated changes in adenosine bioactivity at the afferent arteriole. During normal conditions (A), sodium-glucose cotransport leads to minimal glycosuria.
Effects of SGLT2 inhibitors on GFR. The effects of canagliflozin (100 mg daily, square s; 300 mg daily, circles) versus glimepiride (triangles) in patients with preserved renal function (A) (Reproduced from Cefalu et al17 with permission of the publisher.


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SGLT2 inhibitors, does not lower albuminuria in patients who are non-responsive to RAAS intervention. This suggests that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapagliflozin on albuminuria is through the RAAS.

Individual therapy resistance to RAASi cannot be overcome with the addition of a completely different class of drugs, SGLT2 inhibitors. These data suggest that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapagliflozin on albuminuria is through the RAAS.
Does SGLT2 inhibition with dapagliflozin overcome individual therapy resistance to RAAS inhibition?

The albuminuria response to RAASi significantly correlated with response to dapagliflozin

Individual therapy resistance to RAASi cannot be overcome with the addition of a completely different class of drugs, SGLT2 inhibitors. These data suggest that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapagliflozin on albuminuria is through the RAAS.

\[
\begin{align*}
\text{Albuminuria response (\%)} & \quad \text{during dapagliflozin} \\
\text{Albuminuria response (\%)} & \quad \text{during RAAS inhibition} \\
\end{align*}
\]

\[r=0.635, \quad R^2=0.40\]

\[
\begin{align*}
\text{24hr Albuminuria change (\%)} & \quad \text{Placebo} \\
\text{24hr Albuminuria change (\%)} & \quad \text{Dapa} \\
\end{align*}
\]

10.4\% (-7.2, 31.4) \\
-29.6\% (-40.9, -16.1)
Glucagon-like peptide-1 receptor agonists

The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in a large trial of patients with type 2 diabetes

Reduced the incidence of a composite renal endpoint (consisting of new onset of albuminuria $>300$ mg/day, doubling of serum creatinine, end-stage renal disease, or renal death)

_N Engl J Med. 2017;377(9):839._
When added to usual care, liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo.
Changes in urinary albumin excretion rate. Change in urinary albumin excretion rate (UAER) from baseline to end of treatment. UAER was reduced by 26 (95% CI: 5; 43)% during liraglutide treatment and increased by 9 (95% CI: −6; 22)% during placebo treatment.
GLP-1Rs are associated with direct GLP-1R-mediated and, at least in part, nitric oxide-dependent vasodilation of the afferent renal arteriole, as well as indirect inhibition of vascular and tubular factors that are putative mediators of glomerular hyperfiltration in diabetes. The integrated effect of incretin-based therapy on renal haemodynamics seems to be the result of direct vasodilative actions and inhibition of pathways of glomerular hyperfiltration.

Data from clinical trials suggest that GLP-1R agonists and, to a lesser extent, DPP-4 inhibitors marginally improve surrogate renal end points, plausibly beyond the effects of improved glycaemic control.

Salt intake and proteinuria
Salt intake and proteinuria

Figure 3 Relationship between dietary salt intake and albuminuria in normal (control) rats and uninephrectomized Lewis rats

- Uninephrectomy: $y = -6.62 + 0.03x$, $R = 0.834$
- Control: $y = -1.48 + 0.006x$, $R = 0.723$

A direct correlation between degree of salt intake and albumin excretion rate was identified in both groups, although the slope of the line was increased in those rats that had undergone unilateral nephrectomy. Data were obtained from Sanders et al. [41].
A Low-Sodium Diet Potentiates the Effects of Losartan in Type 2 Diabetes

Salt restriction and/or diuretics enhance the effect of renin-angiotensin blockade on proteinuria in these patients.
Protein restriction for diabetic renal disease (Review)

- **12 μελέτες** (9 RCT, 3 before and after)
- **Σκοπός:** πιθανή επίδραση του περιορισμού της πρωτεϊνικής πρόσληψης (0.7-1.1g/kg/d) στη νεφρική λειτουργία ασθενών με ΣΔ τύπου I & II
- **ΣΔ I:** μεταβολή του GFR κατά 0.1ml/min/m (μη σημαντική)
- **ΣΔ II:** παρόμοια – μη σημαντική μεταβολή του GFR

Η μειωμένη πρωτεϊνική πρόσληψη επιβραδύνει ελάχιστα και μη στατιστικά σημαντικά την εξέλιξη της διαβητικής ΧΝΝ

- Προτεινόμενη ημερήσια πρόσληψη πρωτεϊνής: 0.8-1 g/kg
Marked decreases in proteinuria may be observed in obese diabetics who lose weight.

The effects of weight loss on renal function in patients with severe obesity

Chagnac A, JASN 2003
Lipid lowering (at least with statins) may slow the rate of progression of chronic kidney disease, including diabetic nephropathy.
### The Role of Statins in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Table 1. Statins and CKD progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>HPS [36]</td>
</tr>
<tr>
<td>GREACE [32]</td>
</tr>
<tr>
<td>ALLIANCE [54]</td>
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<tr>
<td>CARE [33]</td>
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<td>CARE [35]</td>
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<td>TNT [55]</td>
</tr>
<tr>
<td>PREVEND-IT [26]</td>
</tr>
</tbody>
</table>

Kalaitzidis R et al AJ Nephrology 2011
Βελτίωση λευκωματουρίας με την χορήγηση στατινών

(A) Change in urinary protein excretion (g/24 h)
(B) for statins versus controls, expressed as
(C) weighted mean difference (WMD).
(D) (B) Change in urinary protein excretion
(E) for statins versus controls, expressed as
(F) standardized mean difference (SMD).
(G) Negative differences in changes from
(H) baseline indicate greater decreases in
(I) proteinuria or albuminuria in the statin
(J) group as compared with the placebo group.
Διάρκεια του ΣΔ ως την ουραιμία σε 33 ασθενείς σε σχέση με την ολική ποσότητα του καπνίσματος
Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection
Statistically significant association between drug effects on albuminuria and ESRD. The associations appear to be consistent across a range of drug classes used in the included studies and various patient characteristics.
Treatment effects on change in proteinuria and on the clinical outcome. Shown are geometric mean ratios and 95% confidence intervals comparing early change in proteinuria between treatment groups (left), and hazard ratios and 95% confidence intervals relating the clinical outcome (time to doubling of serum creatinine level, end-stage renal disease, or death)
Multiple Risk Factors Intervention In diabetic nephropathy
Steno-2: Multiple Risk Factor Intervention Improves Outcomes in Type 2 Diabetics With Microalbuminurina

- Randomized, open-label, target-driven, long-term intensified intervention trial aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - BP <130/80 mm Hg, (all treated with an ACEI or ARB)
  - A1c <6.5%
  - Total cholesterol <175 mg/dL
  - Total triglyceride 150 mg/dL
- Significant reductions in
  - Primary outcome by 53%
  - Nephropathy 61%
  - Retinopathy 58%

Risk factor control in the intensive treatment group of the Steno-2 trial in patients with type 2 diabetes mellitus and microalbuminuria

Intensive Multiple Risk Factor Intervention Improves Outcomes in Type 2 Diabetes

Composite outcome: CV death, MI, coronary or peripheral revascularization, CVA, amputation

$P = 0.007$

## Άμεση συσχέτιση μεταξύ του βαθμού της πρωτεϊνουρίας και εξέλιξης σε τελικό στάδιο ΧΝΝ

Μείωση της πρωτεϊνουρίας >30%, μείωση του κινδύνου για ΑΜΚ κατά 39-72% (3-5έτη)

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Groups</th>
<th>Follow up (Mean in Years)</th>
<th>Achieved BP (mm Hg)</th>
<th>Change in Proteinuria</th>
<th>Relevant Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril trial</td>
<td>Captopril or placebo</td>
<td>3 (median)</td>
<td>MAP 96 MAP 100</td>
<td>−30%</td>
<td>Captopril delays the progression of diabetic nephropathy</td>
</tr>
<tr>
<td>AASK*</td>
<td>Metoprolol, ramipril, or amlodipine and conventional or intensive blood pressure targets</td>
<td>4</td>
<td>128/78 for lower group 141/85 for usual group</td>
<td>−14% for metoprolol −20% for ramipril +58% for amlodipine at 5 months</td>
<td>Ramipril slowed the progression of renal disease when compared with the other groups</td>
</tr>
<tr>
<td>RENAAL*</td>
<td>Losartan or placebo</td>
<td>3.4</td>
<td>140/74 142/74</td>
<td>−35%</td>
<td>Losartan delayed the need for dialysis by 2 years when compared with placebo</td>
</tr>
<tr>
<td>IDNT*</td>
<td>Irbesartan or amlodipine or placebo</td>
<td>2.6</td>
<td>140/77 141/77 144/80</td>
<td>−33% −6% −10%</td>
<td>Irbesartan reduced proteinuria to a greater extent and lead to slower progression of renal disease when compared with the other groups</td>
</tr>
</tbody>
</table>
Επίπεδα ΑΠ & εξέλιξη διαβητικής Νεφροπάθειας
Relationship between BP and progression of diabetic nephropathy.

BP, albumin excretion rate, and GFR in patients with type 1 DMs randomly assigned to a reduction in MAP of 10 mm Hg using metoprolol at 100 to 400 mg/d, hydralazine at 50 to 200 mg/d, and furosemide at 80 to 500 mg/d versus no antihypertensive therapy. Solid circles represent the treated group. Open circles represent the control group. Vertical lines represent standard error. Study was stopped earlier in the control group because of faster decline in GFR. Reprinted with permission.253
Optimizing Blood Pressure and Reducing Proteinuria

Rigas Kalaitzidis and George L. Bakris

**Graph:**
- **GFR (mL/min/year)** vs. **SBP (mm Hg)**
- **Δ = 10 mmHg**
- **r = 0.43; P < 0.05**
- Untreated HTN
### Major Recommendations of Treatment Guidelines Related to Management of Hypertension in Patients with CKD and Albuminuria

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminuria ≥300 mg/d or ≥300 mg/g creatinine</td>
<td>Overt proteinuria</td>
<td>Urinary albumin-to-creatinine ratio ≥300 mg/g creatinine or 30–299 mg/g creatinine</td>
<td>Urine albumin excretion of 30 to 300 mg or &gt;300 mg per 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

### Recommended BP target (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowering &lt;130/80</td>
<td>Lowering SBP to &lt;140 Lowering &lt;130/80 mmHg in individuals with overt proteinuria</td>
<td>Lowering &lt;140/90 Lowering &lt;130/80 mmHg, for individuals at high risk of cardiovascular disease</td>
<td>Lowering ≤130/80</td>
</tr>
</tbody>
</table>

### Recommended initial antihypertensive treatment

<table>
<thead>
<tr>
<th>ACE inhibitor or ARB if ACE inhibitor is not tolerated</th>
<th>ACE inhibitor or ARB</th>
<th>ACE inhibitor or ARB</th>
</tr>
</thead>
</table>

### Other comments

<p>| A 10% to 25% increase in serum creatinine may occur in some patients with CKD as a result of RAAS therapy | RAS blockade is more effective in reducing albuminuria than other antihypertensive agents and is also effective in preventing incident microalbuminuria | Patients and clinicians should engage in a shared decision-making process to determine individual BP targets Bedtime dosing: moving at least one antihypertensive medication to bedtime | The antihypertensive and antialbuminuric effects ACE inhibitor or ARB are complemented by dietary sodium restriction or administration of diuretics. |</p>
<table>
<thead>
<tr>
<th>Type of Kidney Disease</th>
<th>Blood pressure target (mm Hg)</th>
<th>Albuminuria (≥300 mg/d or ≥300 mg/g creatinine)</th>
<th>Preferred agents</th>
<th>Other agents to reach blood pressure Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic kidney disease</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>ACE inhibitor or ARB if ACE inhibitor is not tolerated</td>
<td>CCB preferred, then diuretic or BB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>All first-line agents</td>
<td>ACE inhibitor or ARB, CCB , Diuretic</td>
</tr>
<tr>
<td>Non diabetic kidney disease</td>
<td></td>
<td>Yes</td>
<td>ACE inhibitor or ARB if ACE inhibitor is not tolerated</td>
<td>CCB preferred, then diuretic or BB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>All first-line agents</td>
<td>ACE inhibitor or ARB, CCB , Diuretic</td>
</tr>
</tbody>
</table>

BP, blood pressure; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta-blocker

Kalaitzidis et al 2018
Number of antihypertensive medications required to achieve BP goals in major clinical trials over the past decade

<table>
<thead>
<tr>
<th>Trial</th>
<th>SBP (mmHg) achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>INVEST</td>
<td>136</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>137</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>138</td>
</tr>
<tr>
<td>UKPDS</td>
<td>144</td>
</tr>
<tr>
<td>HOT</td>
<td>138</td>
</tr>
<tr>
<td><strong>CKD Progression</strong></td>
<td></td>
</tr>
<tr>
<td>RENAAL</td>
<td>141</td>
</tr>
<tr>
<td>IDNT</td>
<td>138</td>
</tr>
<tr>
<td>MDRD</td>
<td>132</td>
</tr>
<tr>
<td>AASK</td>
<td>128</td>
</tr>
<tr>
<td>ABCD</td>
<td>132</td>
</tr>
</tbody>
</table>
Influence of albuminuria on blood pressure response to antihypertensive therapy

Flack, Vasc Risk Manag 2007
Conclusions

The optimal therapy of diabetic nephropathy continues to evolve.

Albuminuria can be considered a modifiable risk factor for renoprotection in diabetic nephropathy.

The larger the initial reduction in albuminuria renoprotection in diabetic nephropathy, the lower the risk of ESRD during treatment.
Conclusions

Most important is maintenance of strict blood pressure and glycemic control early in the course of the disease with agents that reduce intraglomerular pressure.

The agents slow the rate of progression, but do not stop progression.

Combined intensive therapy for multiple risk factor intervention improves outcomes.
Thank you