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)

Hermann Senator (1834–1911)
A forgotten pioneer

Gansevoort and Ritz, Nephrol Dial Transplant 2008

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

• Ποσοτικός προσδιορισμός

» 24ωρη συλλογή ούρων

» Δείγμα ούρων: πρωτεΐνη/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.
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>Albumin (mg/l)</th>
<th>Gender</th>
<th>Albumin/Creatinine Ratio</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>M</td>
<td>1.25 to &lt;2.5</td>
<td>10 to &lt;20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30 to &lt;300</td>
<td></td>
<td></td>
<td>M</td>
<td>1.75 to &lt;2.5</td>
<td>15 to &lt;30</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;300</td>
<td></td>
<td></td>
<td>M</td>
<td>&gt;200</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Moderately increased albuminuria - Μέτρια αύξηση
Severely increased albuminuria - σημαντική αύξηση
The Spectrum of Albuminuria

- **Normal**: Microalbuminuria
- **Increased CV Risk and Presence of Vascular Dysfunction and Renal Dysfunction**: Albuminuria (Proteinuria)

The graph illustrates the spectrum of albuminuria, showing the increase in cardiovascular risk associated with higher levels of albuminuria.
Is albuminuria a myocardial infarction risk equivalent for atherothrombotic events?

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.

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).
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

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

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

Pathophysiological mechanism
Diabetic nephropathy

- Glomerular hyperfiltration
- Nephrin expression
- Impaired podocyte-specific insulin signaling
- Hyperglycemia and AGEs
- Cytokines
Μηχανισμοί Νεφρικής βλάβης στην ΥΠ

Μηχανισμοί

- 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

↓ GFR

Renal scarring

Renal growth factor & cytokine activation

Fibrogenesis

Transdifferentiation of renal cells to fibroblast phenotype

Influx of monocytes and macrophages

Filtration of plasma proteins (Proteinuria)

Proximal tubule protein uptake

Hyperlipidemia

Renal microvascular injury

Systemic hypertension

↓ Filtration of plasma proteins (Proteinuria)

↑ Filtration of plasma proteins (Proteinuria)

Renal injury

↓ Nephron mass

Glomerular hypertension

Progressive Loss of Filtration Surface Area

↓ GFR

Renal scarring

Transdifferentiation of renal cells to fibroblast phenotype

Influx of monocytes and macrophages

Filtration of plasma proteins (Proteinuria)

Proximal tubule protein uptake

Hyperlipidemia

Renal microvascular injury

Fibrogenesis

Renal injury

↓ Nephron mass

Glomerular hypertension

Progressive Loss of Filtration Surface Area

↓ GFR

Renal scarring

Transdifferentiation of renal cells to fibroblast phenotype

Influx of monocytes and macrophages

Filtration of plasma proteins (Proteinuria)

Proximal tubule protein uptake

Hyperlipidemia

Renal microvascular injury

Fibrogenesis

**Equivalent renal risk in type 1 & 2 diabetes**

**TYPE 1:** The incidence of overt nephropathy was 25 to 45 percent. 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
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
Tight glucose control (Goal <6.0 mmol/l or 108 mg/dL)

Tight BP control (Average 144/82 mmHg)

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% Reduction in Relative Risk

-50 -40 -30 -20 -10 0

Stroke

Any Diabetic Endpoint

DM Deaths

Microvascular Complications

-50 -40 -30 -20 -10 0

*P <0.05 compared to tight glucose control

Pıyrimisi sakkhárou énanthi pıyımisi AΠ sthn ékvasi karðiaγγeiaikwn eπiπlokon se aσtheβeiíc me ΣΔ túpou 2
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

Cascade of intratubular RAS in Ang II–dependent hypertension. In Ang II–dependent hypertension, the kidney maintains intrarenal Ang II formation, enhanced proximal tubule AGT formation and spillover into distal nephron segments coupled with enhancement of CD renin and stimulation of tubular ACE.

PT indicates proximal tubule; IC, intercalated cell; PC, principal cell; AA, afferent arteriole; EA, efferent arteriole.
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.
MICRO-HOPE Events Per Patient Group for Secondary Endpoints

**Events per patient group (%)**

- **Total mortality**: RR=24%, P=0.03
- **Revascularization**: RR=17%, P=0.004
- **Overt nephropathy**: RR=24%, P=0.03
- **Heart failure**: NS
- **Unstable angina**: NS

**Legend**
- **Placebo**
- **Ramipril**

- Based on positive 24h urine collection or albumin/creatinine ratio ≥36 mg/mmol
- *Requiring hospital admission* NS ≥0.05
- RR=Relative risk reduction

**3557 ασθενείς**

↓ 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

*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.

In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent.

* Doubling of serum creatinine, end stage renal disease, death

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RENAL; Albuminuria at Baseline Predicts ESRD in Type 2 Diabetics With Nephropathy (N=1513)

Baseline Albuminuria

With ESRD End Point (%)

Month

≥3.0 g/g 8.10
≥1.5<3.0 g/g 3.23
<1.5 g/g 1.0

HR

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.

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

The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m² if the initial estimated GFR was ≥60 ml per minute per 1.73 m² or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m²), end-stage renal disease (ESRD), or death.
Other antihypertensive drugs and combinations
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

Reprinted by permission, Blackwell Science, Inc.
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.

Among patients with diabetic nephropathy, most receiving an ACE inhibitor or an angiotensin receptor blocker, the addition of finerenone compared with placebo resulted in improvement in the UACR.

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 ≥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>497/2102 (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 (2.9)</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 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.
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.

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).

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.

*Diabetes Obes Metab 2017; 19(2):239–247*
GLP-1RAs 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.

*Nature Reviews Nephrology volume 13, pages 605–628 (2017)*
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

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].
Salt restriction and/or diuretics enhance the effect of renin-angiotensin blockade on proteinuria in these patients.

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.

Hyperlipidemia

Lipid lowering (at least with statins) may slow the rate of progression of chronic kidney disease, including diabetic nephropathy

Kidney Int. 2006;70(1):177
### The Role of Statins in Chronic Kidney Disease

#### Table 1. Statins and CKD progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects in the study, n</th>
<th>Follow-up</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS [36]</td>
<td>retrospective analysis</td>
<td>5,963</td>
<td>4–6 years</td>
<td>simvastatin 40 mg/day of placebo</td>
<td>GFR decline (5.9 vs. 6.9 ml/min; p = 0.003) in the simvastatin group vs. placebo</td>
</tr>
<tr>
<td>GREACE [32]</td>
<td>post-hoc subgroup analysis</td>
<td>1,600</td>
<td>3 years</td>
<td>atorvastatin 10–80 mg/day or usual medical care</td>
<td>CrCl had a 12% increase in atorvastatin group (p &lt; 0.0001); CrCl had a 5.2% decrease in patients not treated with statins (p &lt; 0.0001); CrCl had a 4.9% increase in the usual care group on various statins; HR 0.84 (CI: 0.73–0.95; p = 0.003) with every 5% increase in CrCl</td>
</tr>
<tr>
<td>ALLIANCE [54]</td>
<td>post-hoc subgroup analysis</td>
<td>2,442</td>
<td>4 years</td>
<td>atorvastatin 10–80 mg/day or usual medical care</td>
<td>CrCl did not change in the atorvastatin group (p &lt; 0.0001 vs. baseline); CrCl declined by 4.4% in the usual care group (p = 0.0001 vs. baseline)</td>
</tr>
<tr>
<td>CARE [33]</td>
<td>post-hoc subgroup analysis</td>
<td>3,402</td>
<td>5 years</td>
<td>pravastatin 40 mg/day vs. placebo</td>
<td>in patients with GFR of 30–59.9 ml/min per 1.73 m², pravastatin reduced the adjusted rate of kidney function loss by approximately 34%; the absolute reduction in the rate of loss was small (0.22 ml/min per 1.73 m²/year; 95% CI: 0.07–0.37)</td>
</tr>
<tr>
<td>CARE [35]</td>
<td>post-hoc subgroup analysis</td>
<td>3,384</td>
<td>4 years</td>
<td>pravastatin 40 mg/day vs. placebo</td>
<td>in patients with eGFR &lt; 60 ml/min per 1.73 m², the rate of change in the pravastatin group vs. placebo group was 2.5 ml/min per 1.73 m²/year slower (95% CI: 1.4–3.6; p = 0.0001)</td>
</tr>
<tr>
<td>TNT [55]</td>
<td>post-hoc subgroup analysis</td>
<td>9,656</td>
<td>59.5 months</td>
<td>atorvastatin 10 vs. 80 mg</td>
<td>mean change in eGFR showed an increase of 3.5 ± 0.14 ml/min per 1.73 m² with atorvastatin 10 mg and 5.2 ± 0.14 ml/min per 1.73 m² with atorvastatin 80 mg, respectively (p &lt; 0.0001)</td>
</tr>
<tr>
<td>PREVEND-IT [26]</td>
<td>randomized controlled trial</td>
<td>3,440</td>
<td>4 years</td>
<td>pravastatin 40 mg/day or placebo for 2 × 2 factorial</td>
<td>GFR fell in both statin users and nonusers (4.6 ± 13.5 and 2.4 ± 11.2, respectively); statin treatment was not associated with a significant change in GFR with only modestly impaired GFR (p = 0.11)</td>
</tr>
</tbody>
</table>
(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.
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.
Multiple Risk Factors Intervention In diabetic nephropathy
Steno-2: Multiple Risk Factor Intervention Improves Outcomes in Type 2 Diabetics With Microalbuminuria

- 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%

COMBINED THERAPY - the Steno trial

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

$P = .007$

Conventional therapy

Intensive therapy

The Kidney, Hypertension and remaining challenges

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

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

<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 at 5 months</td>
<td>−14% for metoprolol−20% for ramipril+58% for amlodipine</td>
<td>Ramipril slowed the progression of renal disease when compared with the other groups</td>
</tr>
<tr>
<td>RENAAAL*</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.
Untreated HTN

Δ = 10 mmHg

r = 0.43; P < 0.05

130 134 138 142 146 150 154 158 170 180

SBP (mm Hg)

GFR (mL/min/year)

-14 -12 -10 -8 -6 -4 -2 0

-4 -6 -8 -10 -12 -14

Kalaitzidis R, Bakris G, 2011 by Lippincott Williams & Walking
### 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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</tr>
</thead>
<tbody>
<tr>
<td><strong>Albuminuria</strong></td>
<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>
</tr>
<tr>
<td><strong>Overt proteinuria</strong></td>
<td>Lowering &lt;130/80 mmHg in individuals with overt proteinuria</td>
<td>Lowering SBP to &lt;140 mmHg</td>
<td>Lowering &lt;140/90 mmHg for individuals at high risk of cardiovascular disease</td>
<td>Lowering ≤130/80 mmHg</td>
</tr>
<tr>
<td><strong>Recommended initial antihypertensive treatment</strong></td>
<td>ACE inhibitor or ARB if ACE inhibitor is not tolerated</td>
<td>ACE inhibitor or ARB</td>
<td>ACE inhibitor or ARB</td>
<td>ACE inhibitor or ARB</td>
</tr>
<tr>
<td><strong>Other comments</strong></td>
<td>A 10% to 25% increase in serum creatinine may occur in some patients with CKD as a result of RAAS therapy</td>
<td>RAS blockade is more effective in reducing albuminuria than other antihypertensive agents and is also effective in preventing incident microalbuminuria</td>
<td>Patients and clinicians should engage in a shared decision-making process to determine individual BP targets.</td>
<td>The antihypertensive and antialbuminuric effects ACE inhibitor or ARB are complemented by dietary sodium restriction or administration of diuretics.</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>
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<tr>
<td>CONVINCE</td>
<td>137</td>
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<tr>
<td>ALLHAT</td>
<td>138</td>
</tr>
<tr>
<td>UKPDS</td>
<td>144</td>
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<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