Duality of Interest Declaration

- **Speaker: Peter Rossing**
- I report the following potential duality/dualities of interest in the field covered by my lecture:
- Consultancy agreement Bayer AG
- Other consultancy and/or speaking fees to his institution from:Astra Zeneca, BMS, Boehringer Ingellheim, Eli Lilly, Novo Nordisk, Sanofi Aventis, Astellas, Abbvie
- Research grants from:Abbvie, Novo Nordisk, Novartis
- Personal shares in Novo Nordisk A/S
- All honorary payed to Steno Diabetes Center

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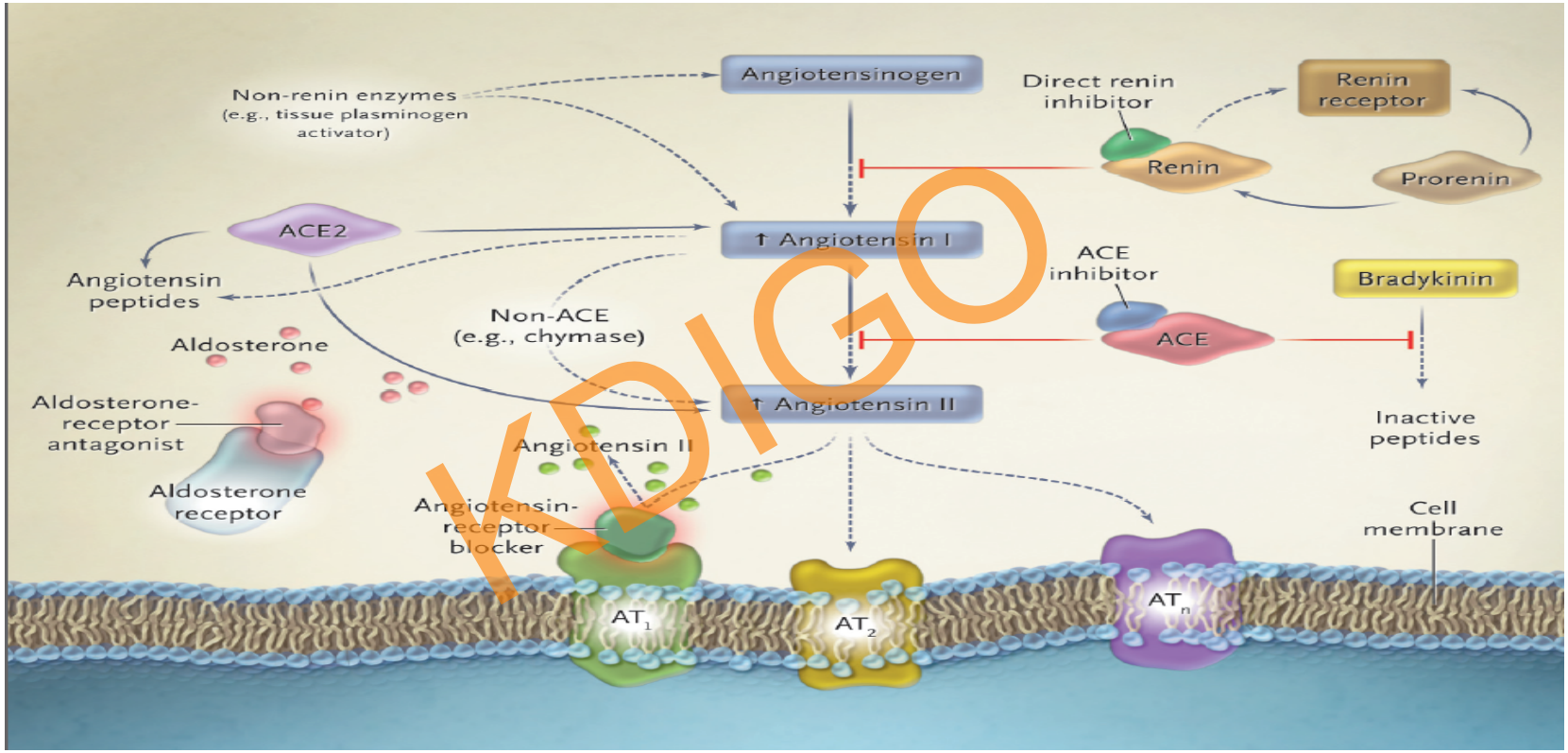


J Ingelfinger NEJM 2008

The Renin-Angiotensin-Aldosterone System (RAAS)

Angiotensinogen

↓

Angiotensin I

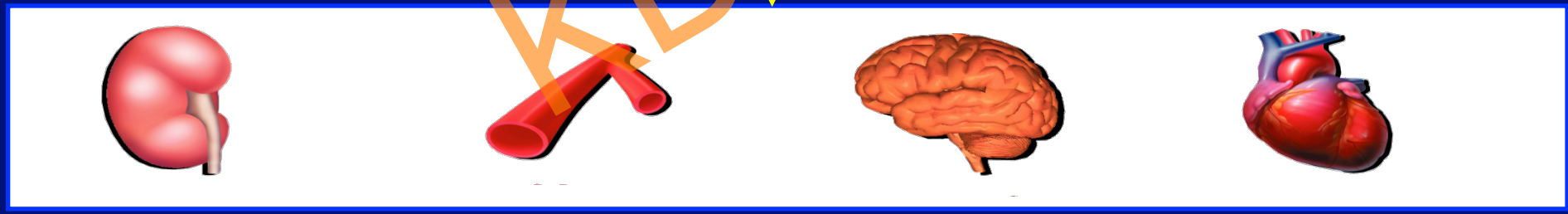
↓

Angiotensin II

↓

Aldosterone

↓



K^+-↓ Na^+ ↑ Glomerular sclerosis tubular damage

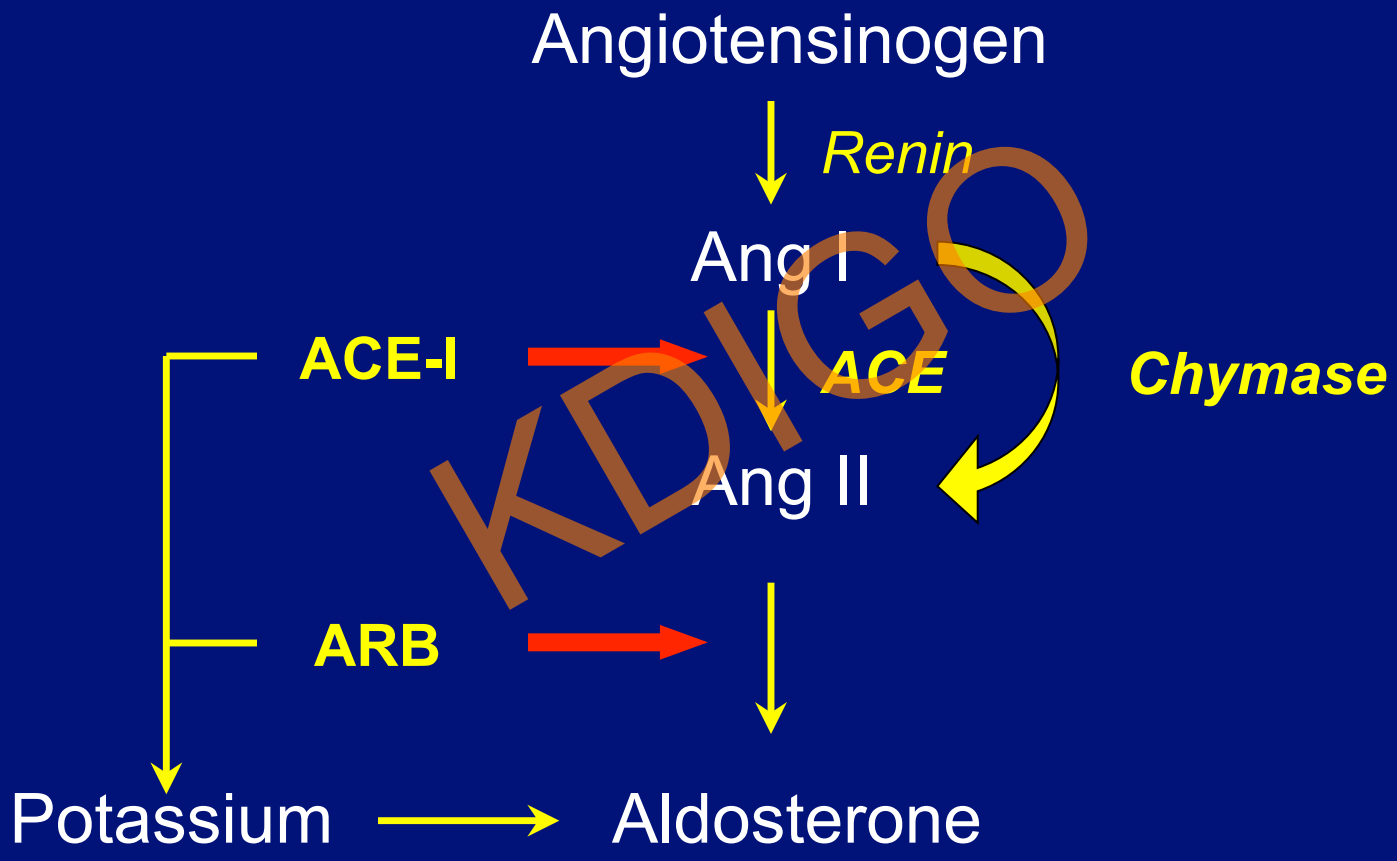
Endothelial dysfunction Inflammation

HR variability ↓ Baroreceptor sensitivity ↓

Cardiac Hypertrophy

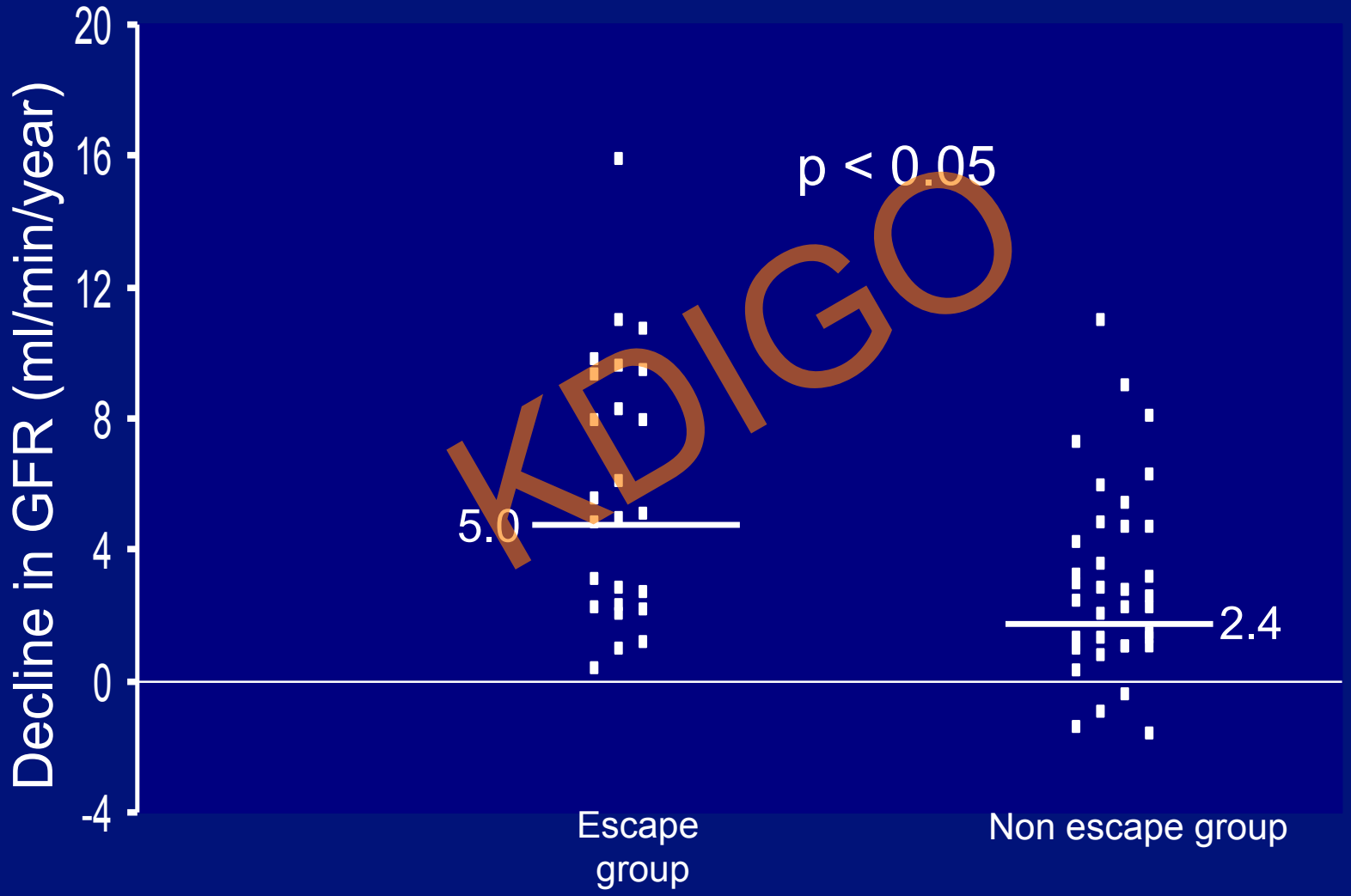
Progression of renal- and cardiovascular disease

Incomplete Blockade of Aldosterone by ACE-I & ARB



ΔGFR in 63 type 1 diabetic patients with DN

Aldosterone escape vs. non escape group
(breakthrough vs non-breakthrough)



Schjoedt et al, Diabetologia 2004

Spironolactone in Chronic Renal Disease - Uncontrolled Studies

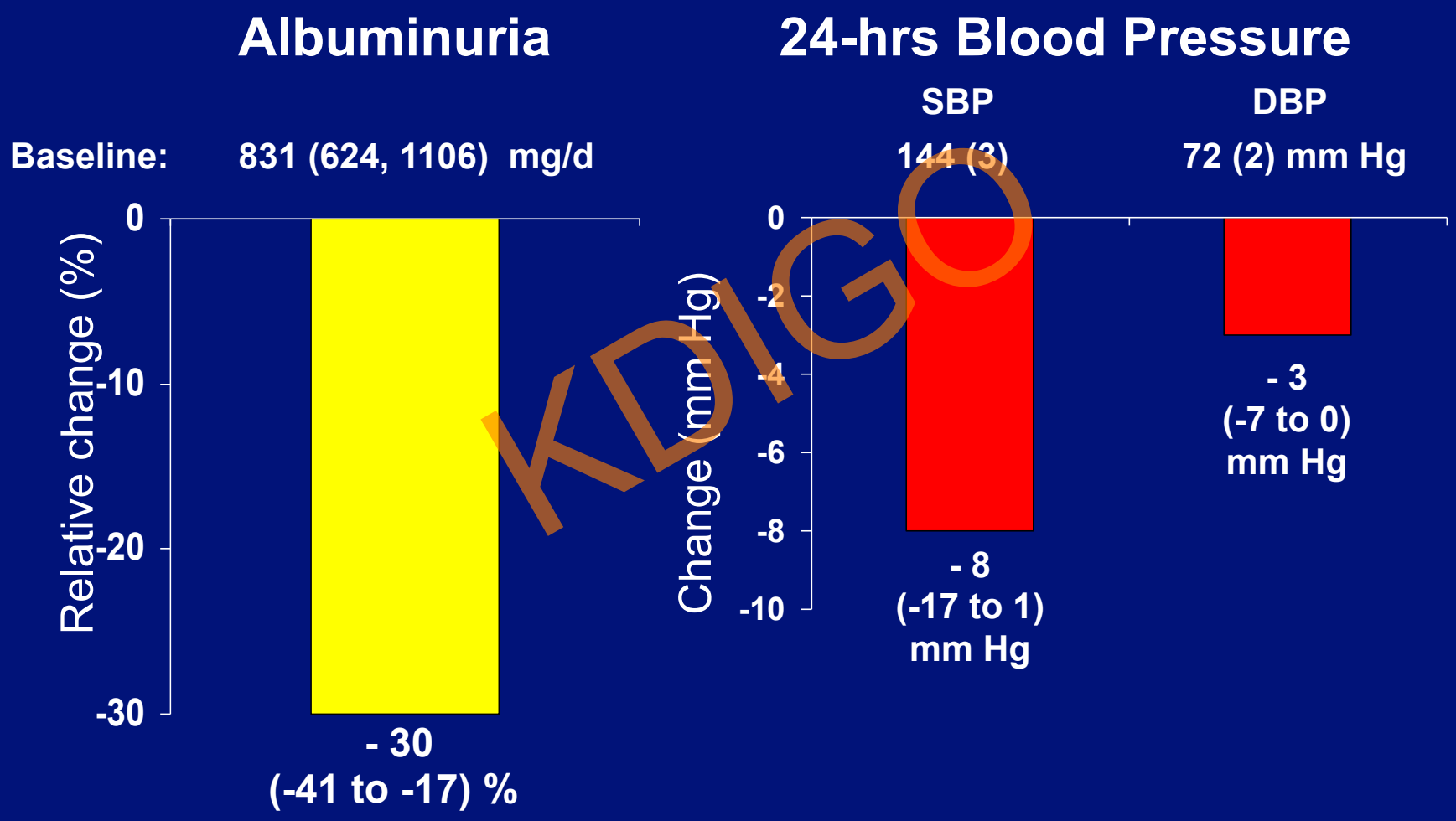
Spironolactone 25 mg added on top of previous antihypertensive treatment

Author (year)	Study Population	Duration (weeks)	Background therapy	Reduction of Proteinuria	Reduction of BP (mm Hg)
Chrysostomou (2001)	DN and non-DN (n=8)	4	ACE	54%	-
Sato A. et al (2003)	T2 DM with micro- or macro-albuminuria (n=15)	24	ACE	25%	-
Nitta K. et al (2004)	Non-DN (n=22)	26	ARB	15%	9/7
Sato A. et al (2005)	DN and non-DN (n=32)	12	ACE	38%	-
Bianci S. et al (2005)	DN and non-DN (n=42)	8	ACE-I or ARB	50%	-

DN=Diabetic Nephropathy, Non-DN=Non Diabetic Nephropathy

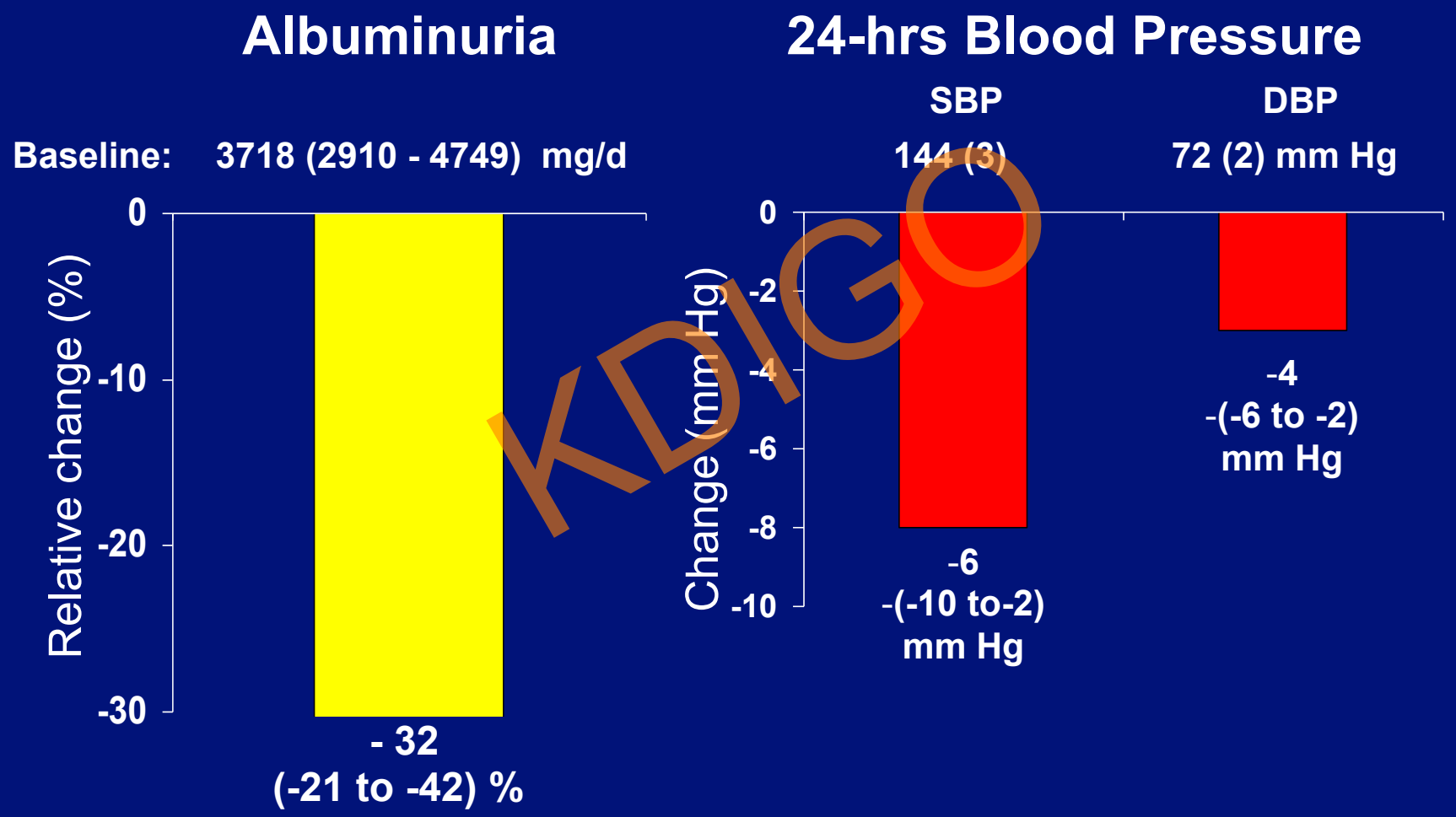
Response to spironolactone 25 mg

20 Type 1 Diabetic Patients with Diabetic Nephropathy



Schjoedt et al., Kid. Int. 2005

Response to spironolactone 25 mg
in 20 diabetic patients with nephrotic range albuminuria



nephrotic range albuminuria:
albuminuria>2500mg/d = total proteinuria>3500 mg/d

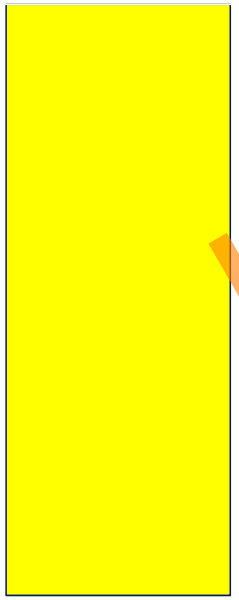
Schjoedt et al., Kid. Int. 2006

EARLY INTERVENTION

Response to spironolactone 25 mg
21 type 1 diabetic patients with microalbuminuria

Albuminuria

Baseline: **90 (61-121)mg/d**



-60%
(-21 to -80) %

24hour Blood Pressure

	SBP	DBP
Baseline:	**135 (3)**	**65 (2) mm Hg**

0
(-3 to 3)
mm Hg

-3
(-8 to 3)
mm Hg

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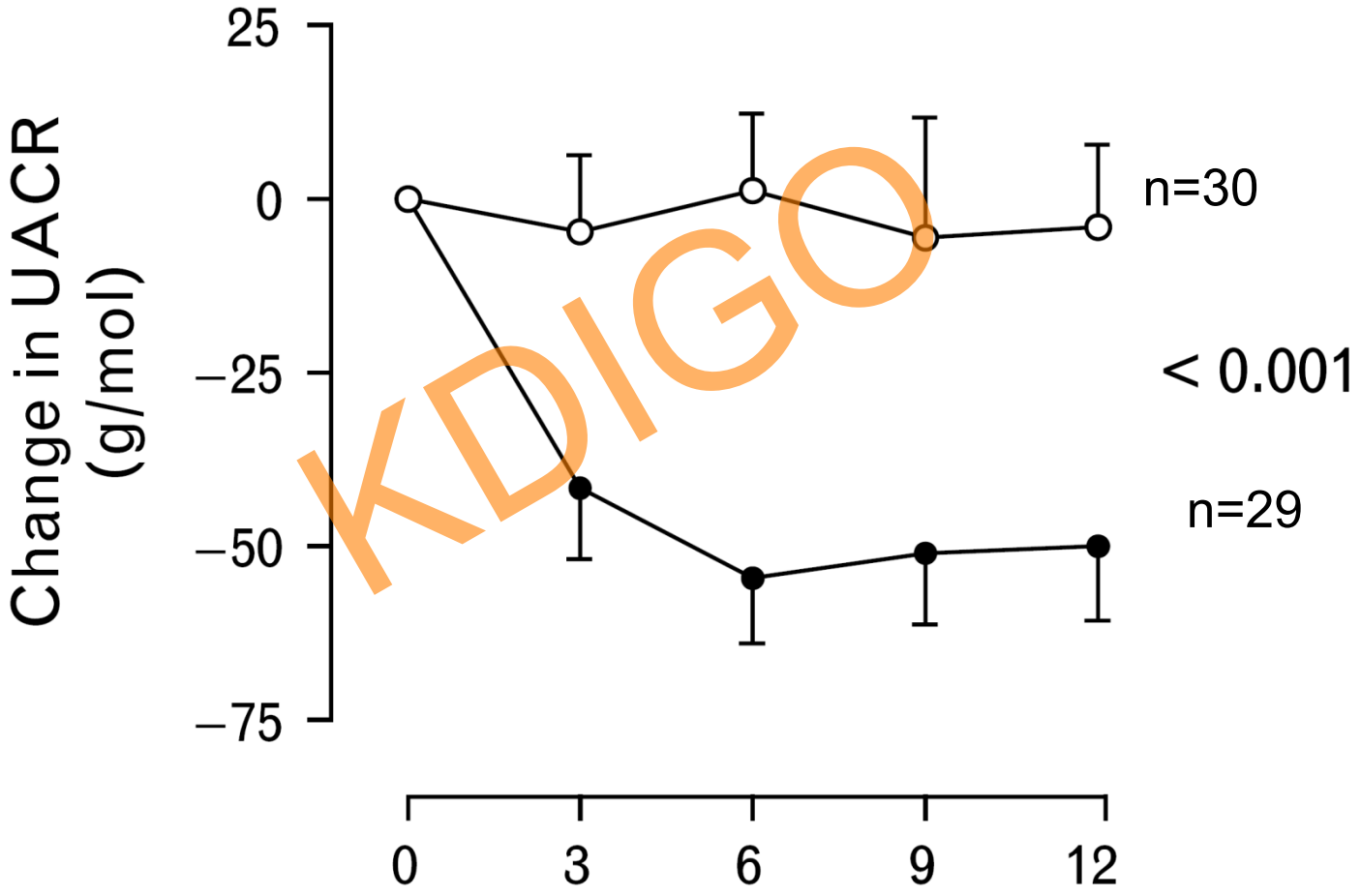
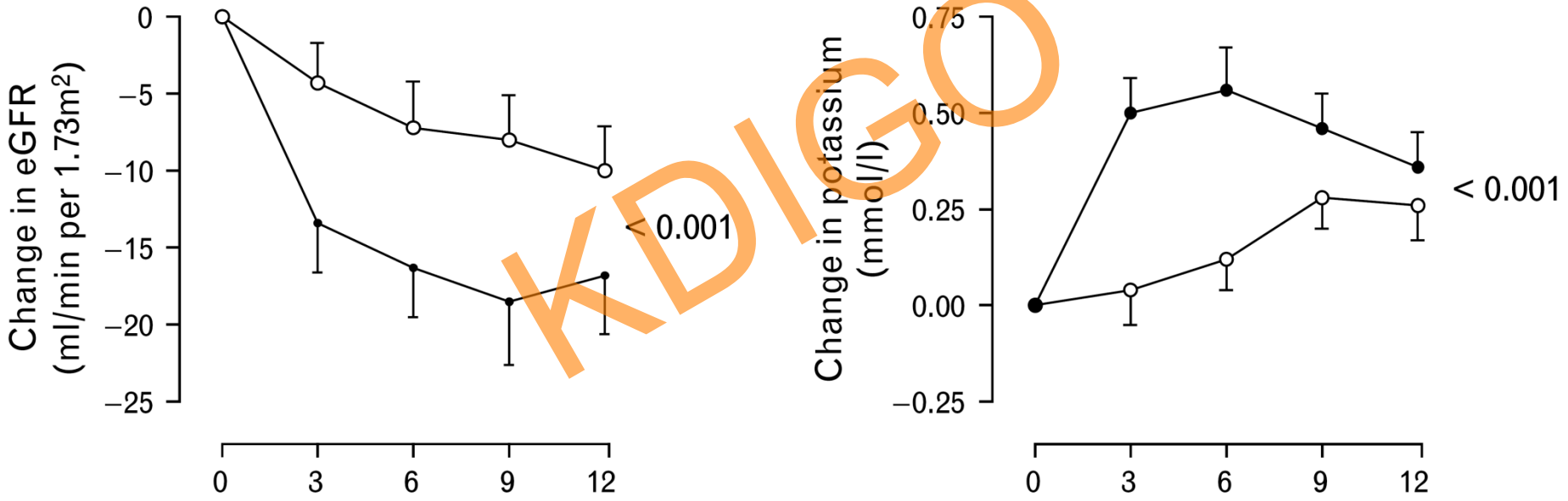
S Nielsen Diabetic Medicine 2011

Spironolactone in diabetic nephropathy



van den Meiracker et al. Journal of Hypertension 2006;24:2285-2292

Spironolactone in diabetic nephropathy



van den Meiracker et al. Journal of Hypertension 2006;24:2285-2292

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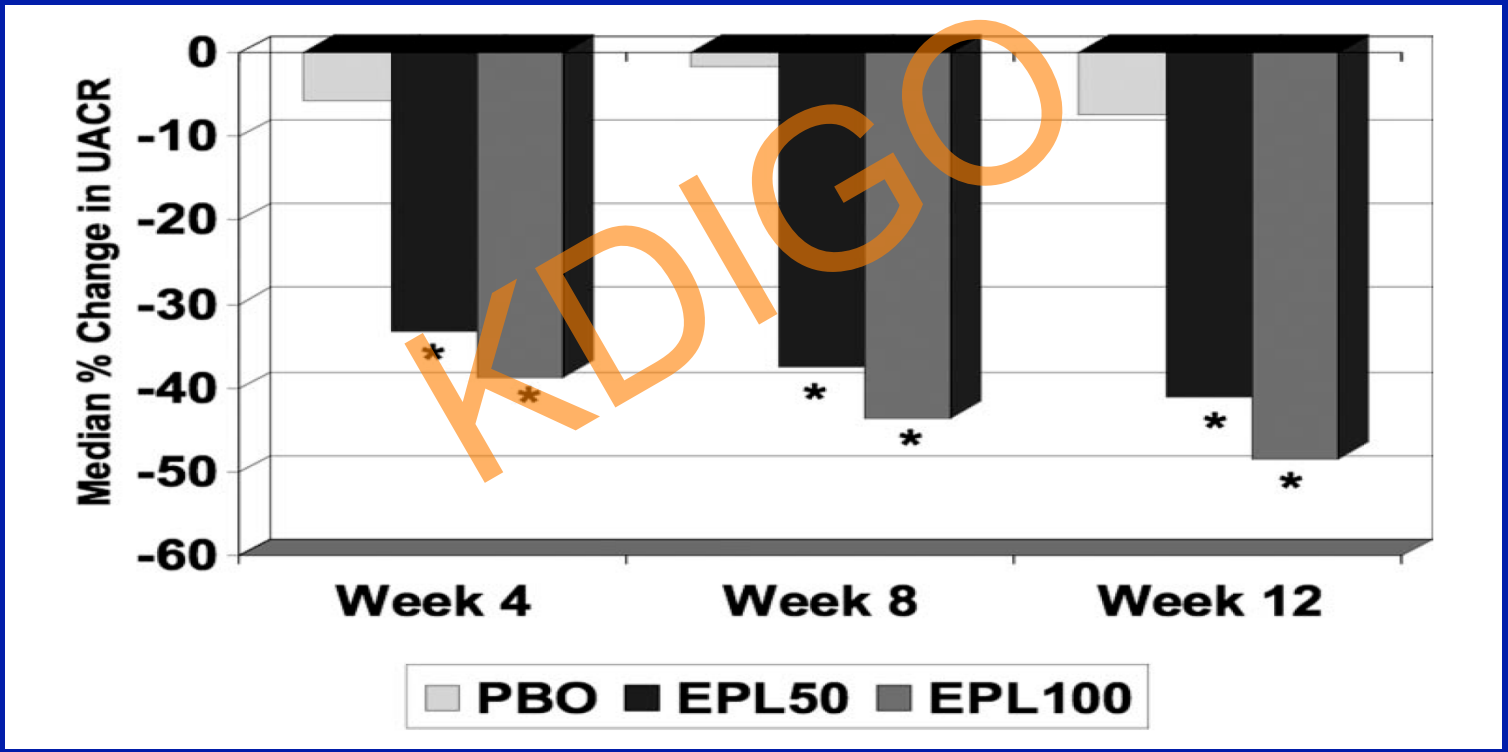
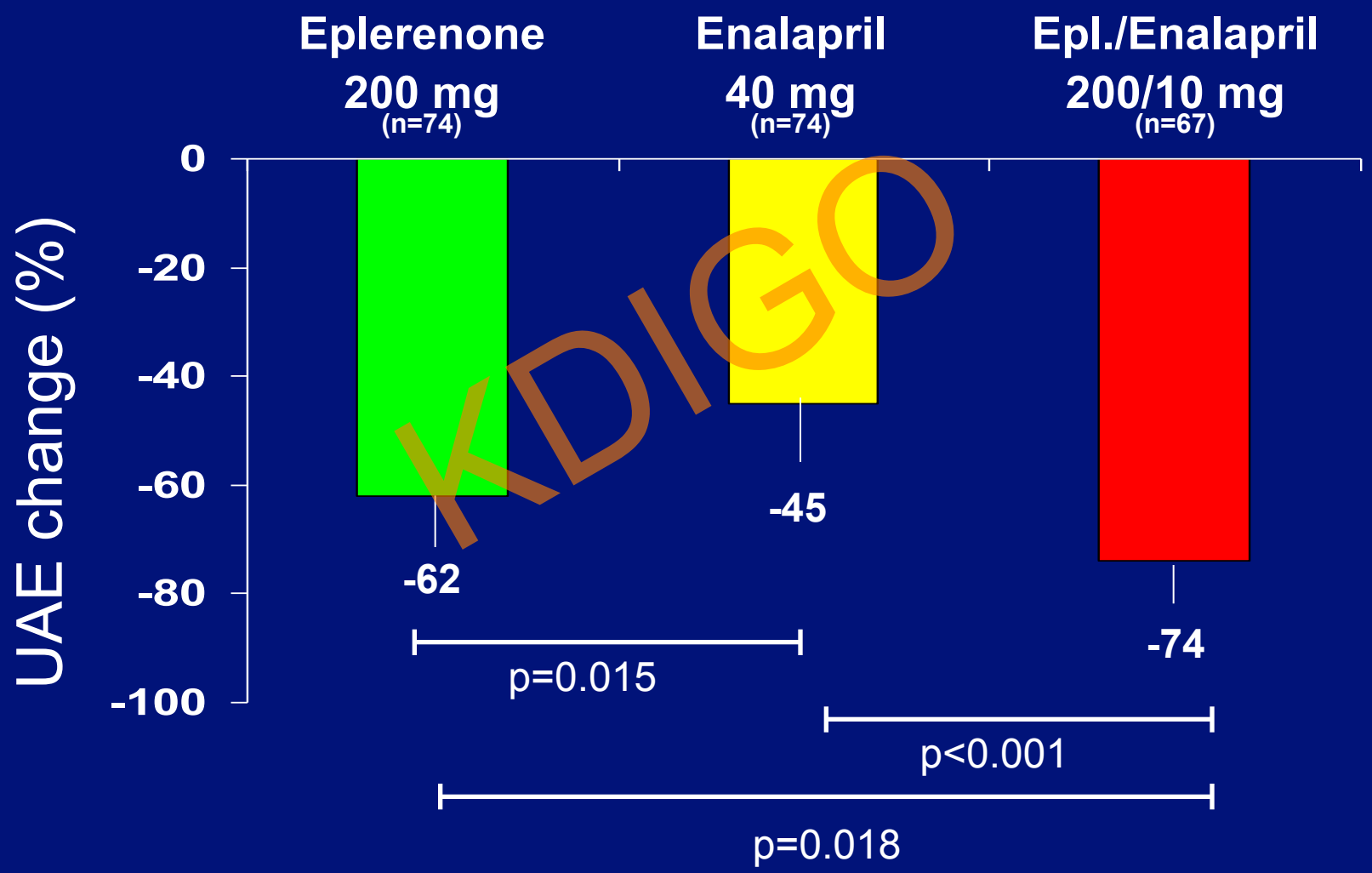
Aldosterone Blockade with Eplerenone in pts with Type 2 DM and albuminuria



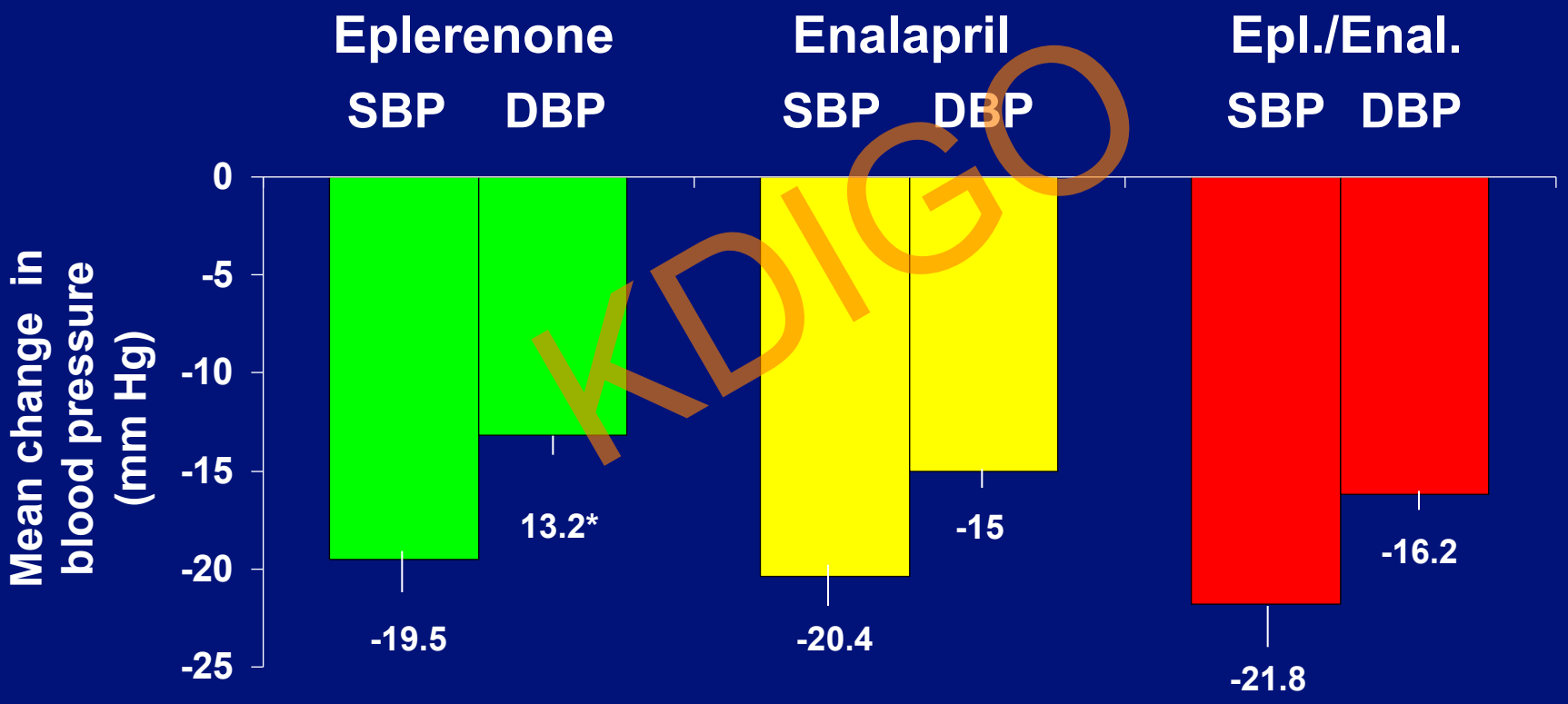
Epstein et al. Clin J Am Soc Nephrol 2006;1:940-951

Eplerenone Efficacy in Diabetic Hypertensive Patients with Proteinuria



Epstein M et al. Am J Hypertens. 2002; 15(4) part 2:24A

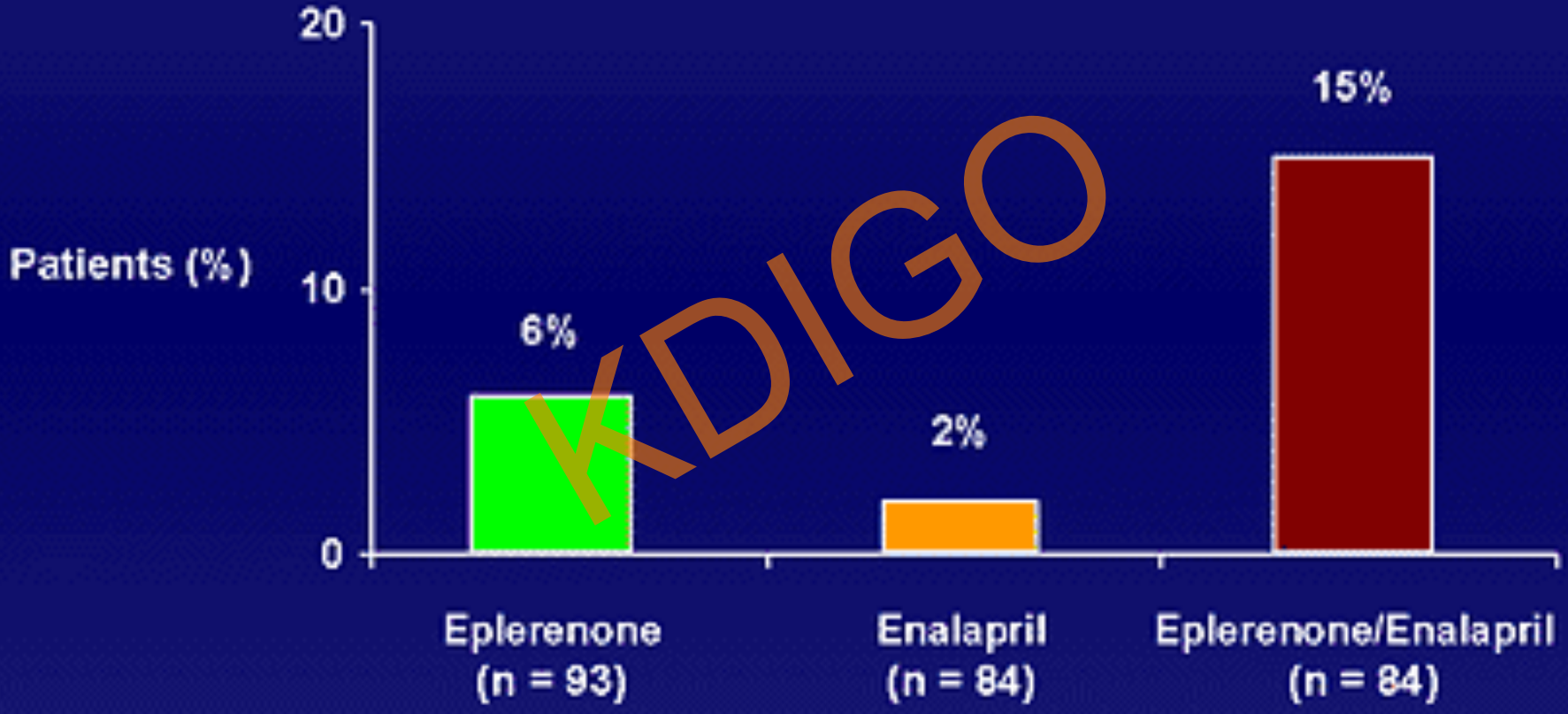
Eplerenone Efficacy in Diabetic Hypertensive Patients with Proteinuria



*p=0.015 vs Epl/Enal

Epstein M et al. Am J Hypertens. 2002; 15(4) part 2:24A

Percent of Patients Withdrawn Due to Potassium Elevations*



*>5.5 mmol/L on 2 consecutive occasions

Epstein M et al. *Am J Hypertens.* 2002;15(4) part 2:24A.

Reducing the Risk of Hyperkalemia During Aldosterone Blockade

- Withdraw potassium supplements
- Use low doses – spironolactone 25 mg /eplerenone 50 mg
- Monitor potassium regularly
- Pause RAAS blocking agents during dehydration
- Particular caution when GFR is severely reduced

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Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment: An emerging paradigm in diabetic nephropathy A systematic review

Thomas A. Mavrakanas [a,*], Karim Gariani [a], Pierre-Yves Martin [b]

[a] General Internal Medicine Division, Geneva University Hospitals, Geneva, Switzerland
[b] Nephrology Division, Geneva University Hospitals, Geneva, Switzerland

Original Article

Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial

Christina S. Oxlund[a], Jan E. Henriksen[a], Lise Tarnow[b], Karoline Schousboe[c], Jeppe Gram[d], and Ib A. Jacobsen[a]

Type 2 DM
resistant hypertension (3drugs BP>130/80)
placebo (n=55) or 25 mg spironolactone(n=57)

C Oxlund et al, J Hyp 2013

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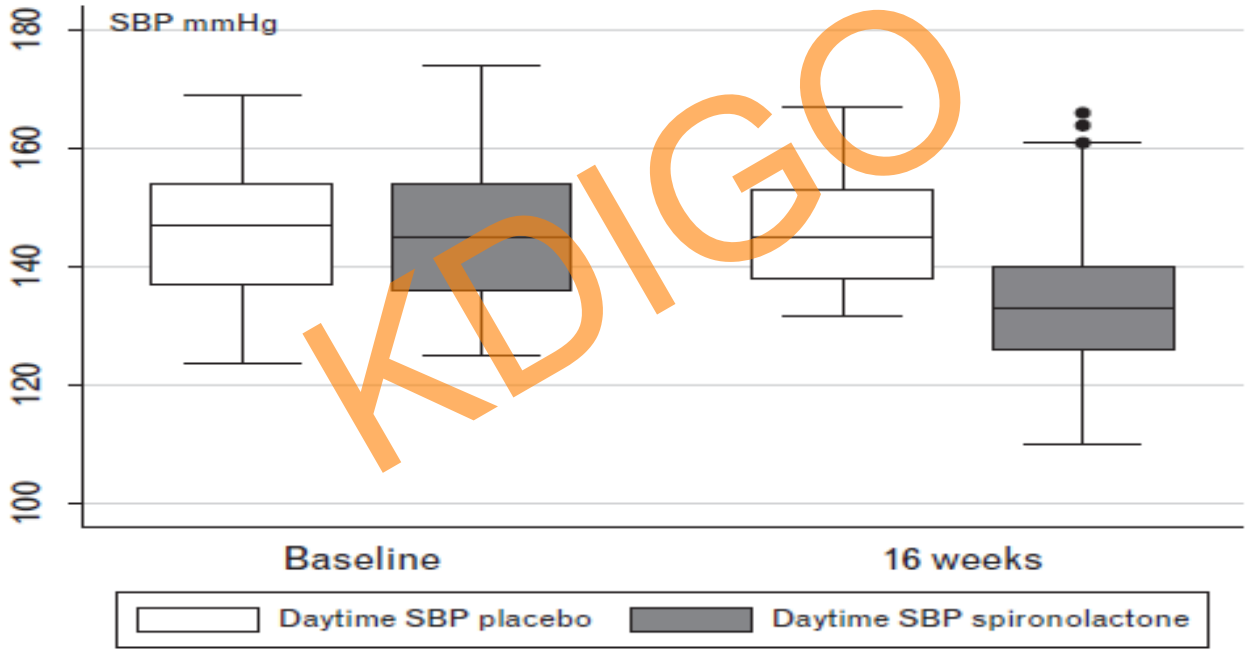
Spironolactone for resistant hypertension in type 2 DM



C Oxlund et al, J Hyp 2013

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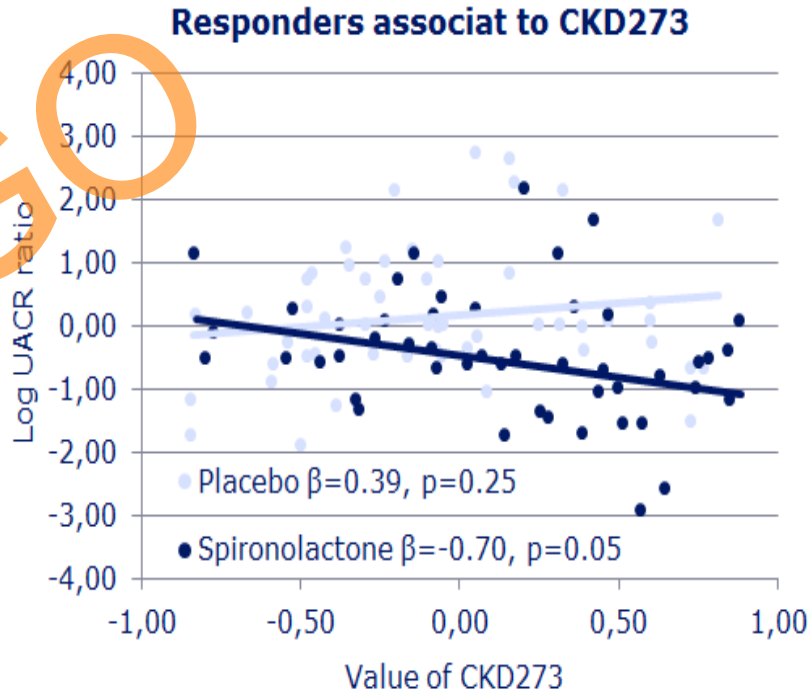
Responder Prediction

- Reduction of urine albumin/creatinine excretion on 50 mg Spironolactone by 56% (95% CI 24-88%; p= 0.002)
- Range of urine albumin response was though massive from 66 mg/g increase to 560 mg/g reduction.
- Urinary peptide pattern (CKD273) at Baseline predict responders



Oxlund, J Hypertension 2013,
Lindhardt, ASN 2014

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Early prevention of DN in T2DM

n ~ 3280

Proteomic test

High-risk n ~ 656

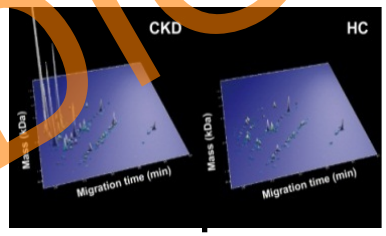
Randomised
Double-blinded
Placebo controlled

Placebo

Spironolactone

Low-risk n ~ 2624

Observational

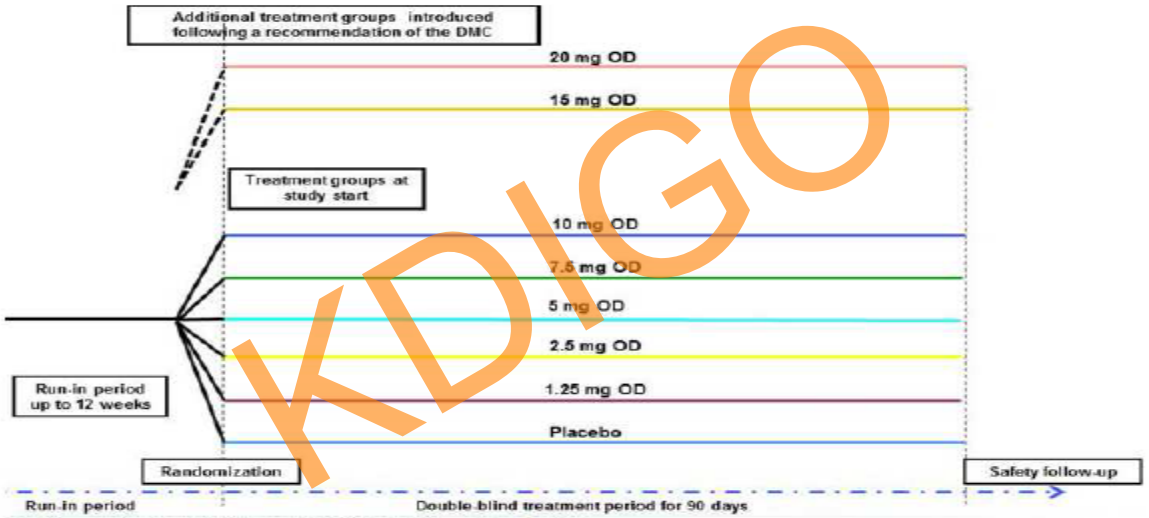


Three years follow-up

Finerenone: Why a new Aldo blocker?

- Based on preliminary experimental and clinicalearly studies, it is assumed that finerenone protects the heart, and perhaps the kidney, with less adverse effects
- In particular it is hoped that potassium problems are smaller compared to spironolactone/eplerenone

Study Design



DMC = data monitoring committee; OD = once daily

Figure 4-1: Study design

Baseline Data

Finerenone

Characteristic	Total (n = 821)
Men, n	639 (77.8)
Age, years	64.2±9.2
Ethnicity, n	
Not hispanic/latino	797 (97.1)
Hispanic/latino	18 (2.2)
Not reported	6 (0.7)
Race, n	
White	691 (84.2)
Black	28 (3.4)
Asian	84 (10.2)
Mixed	16 (1.9)
Not reported	2 (0.2)
BMI, kg/m^2	31.8±5.5
Blood pressure, mm Hg	
Systolic	138.1±14.4
Diastolic	77.1±9.7
Baseline laboratory variables	
UACR, mg/g	192.8 [6.3–4,948.0]
>300 mg/g, n	301 (36.7)
≥30 to <300 mg/g, n	498 (60.7)
<30 mg/g, n	22 (2.7)
Serum potassium, mmol/l	4.29±0.42
eGFR (CKD-EPI), ml/min/1.73 m^2	66.3 [24.5–130.7]
<30 ml/min/1.73 m^2, n	16 (1.9)
30–45 ml/min/1.73 m^2, n	138 (16.8)
>45–60 ml/min/1.73 m^2, n	175 (21.3)
>60 ml/min/1.73 m^2, n	492 (59.9)

Results

Finerenone

?

To be presented at WCN in March 2015

Phase 3 study in planning phase

Conclusions

- Short-term clinical studies have shown renoprotective effects of aldosterone blockade in patients with chronic renal diseases
- Aldosterone blockade is generally well tolerated but potassium should be monitored regularly
- Long-term clinical studies are needed to confirm the beneficial effects on principal renal end-points

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Thank you for listening !