

49 Year Old Female with Type 2 Diabetes presented with Worsening Nephropathy

Endorama 10/10/2013

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HPI

- 49 year old F with PMH of DM II, HTN and HLD
- DM diagnosed 9 years ago
- Treated with Glipizide and Metformin
- Doing well until 5 months ago
 - Developed GI upset
 - Attributed it to metformin, discontinued
 - A1c increased from 6.9 → 9.7% over last 5 months
- Initially started on Lantus 10 units and increased to 14 units about 1 month ago
- Check BG twice (average fasting 115, average bedtime 150). No hypoglycemia
- Last time she has dilated eye exam was 2 months ago.

- **PMH:**

- ✓ DM type 2
- ✓ HTN
- ✓ HLD

- **Family History:**

- ✓ Type 2 DM in mother and brother. HTN Father and mother.

Surgical history: Non

Social history

- ✓ Never smoke, drink alcohol socially, no illicit drugs.

Home medications:

- Norvasc 5 mg po daily
- ASA 81 mg po daily.
- Lipitor 20 mg po daily.
- HCTZ 25 mh po daily
- Glipizide 10 mg po daily
- Metformin 500 mg po daily (stopped 6 months)
- Losartan 100 mg po daily.

ROS

- **Constitutional:** negative
- **HENT:** No blurred vision, No sore throat
- **Neck:** No neck swelling or tenderness
- **Cardio/pulm:** No CP, no palpitation, no orthopnea or PND
- **GI:** epigastric upset worsen with Metformin, No N/V/D, no constipation, no melena or hematochezia
- **GU:** Negative
- **Skin/MSK:** negative
- **Neuro:** no numbness, no tingling

On Examination

- **Vitals:** BP 127/78 | Pulse 78, no fever, RR 14. BMI 26
- **General:** awake alert, setting comfortable on exam table
- **HEENT:** normocephalic non traumatic
- **Neck:** supple, no LN enlargement, no thyromegaly, no acanthosis nigricans
- **CVS/Pulm:** clear equal air entry no added sounds, S1 + S2, no murmur.
- **Abd:** soft lax, no organomegaly, no tenderness, audible bowel sounds.
- **Skin:** warm, no rash, no acanthosis nigricans
- **Neuro:** CN intact, sensation normal, Monofilament and vibration test intact. Small callus against the head of First metatarsal bone on the Rt side.
- **Psych:** normal mood, and affect

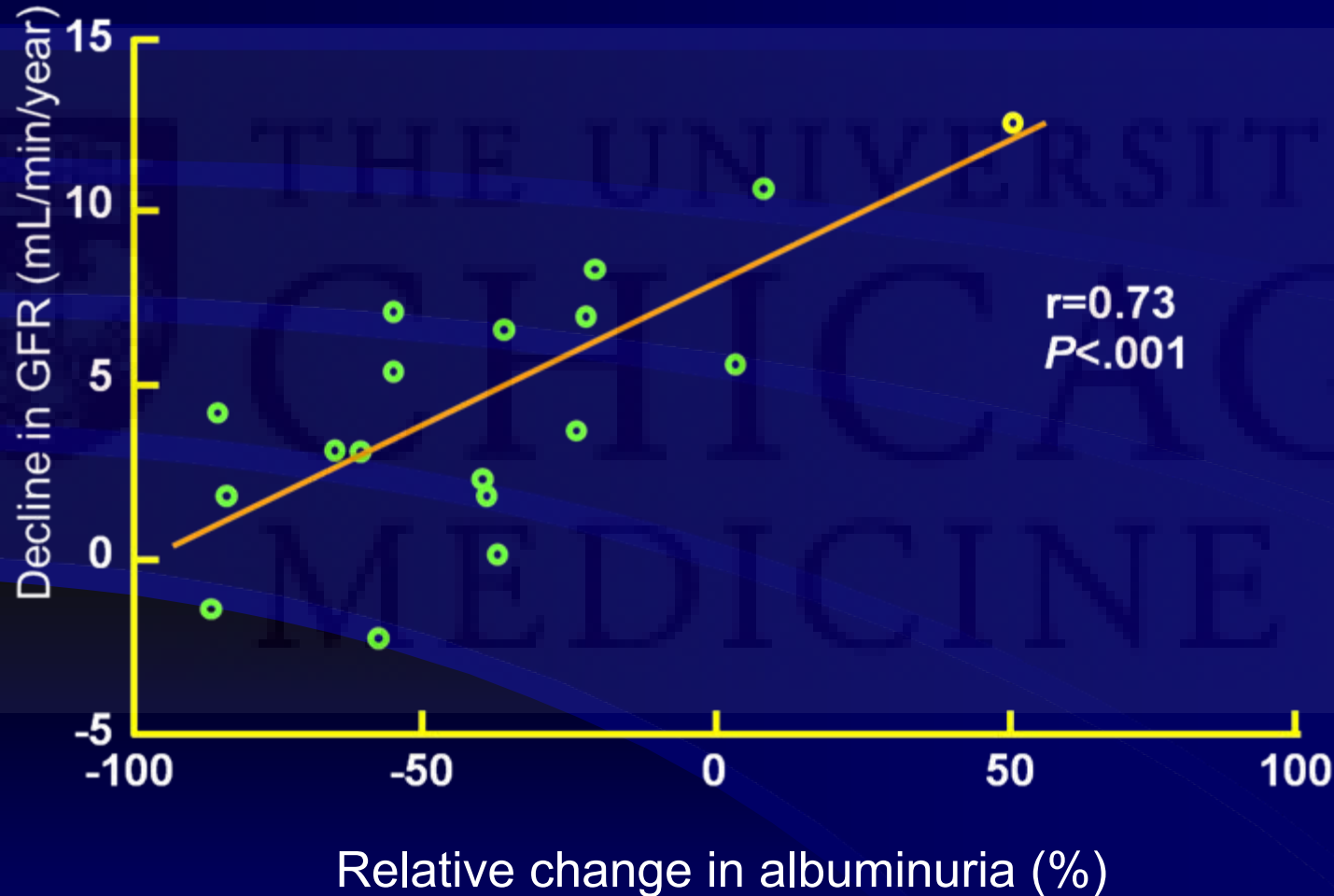
Labs over the past 3 years

Test	6/2010	3/2011	2/2013	7/2013	9/2013
Glucose	103	117	145	176	178
Na	136	137	135	138	137
K	3.5	3.5	3.7	3.4	3.5
HbA1c	6.6	7.4	6.9	8.6	9.0
Alb/Cr	/	12	10.1	/	37.5
LDL	101	/	109	/	146
BUN/Cr	12/0.9	/	14/1.0		15/1.0
eGFR	73	74	68		55

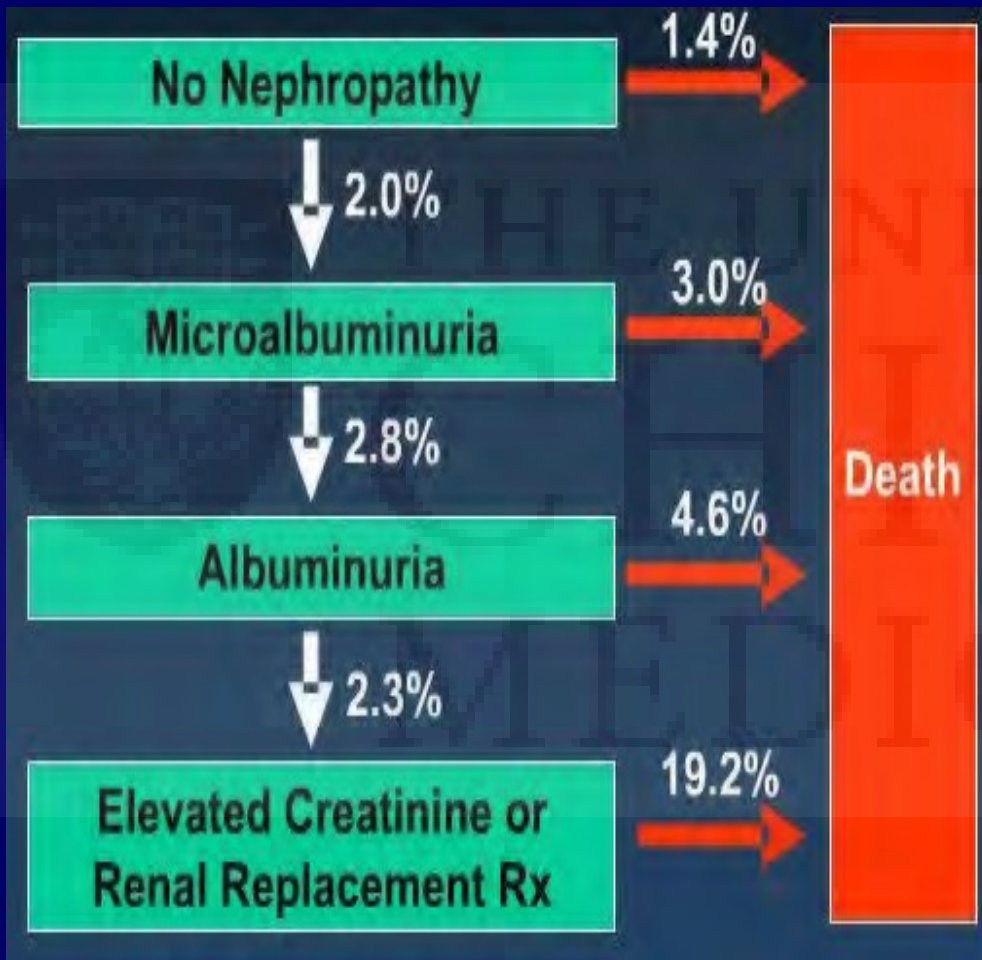
My Clinical Qs

- Which is more important glycemic control or blood pressure control?
- In pt with BP at Goal already on ARBs what medication can one add to prevent worsening her kidney failure?
 - Role of combination of ACEI and ARBs
 - Role of calcium channel blockers
 - Role of aldosterone antagonist
 - Role of Thiazolidinedione
 - Role of Statin and Fibrate
- Was metformin, independent of glycemic control, reno-protective?

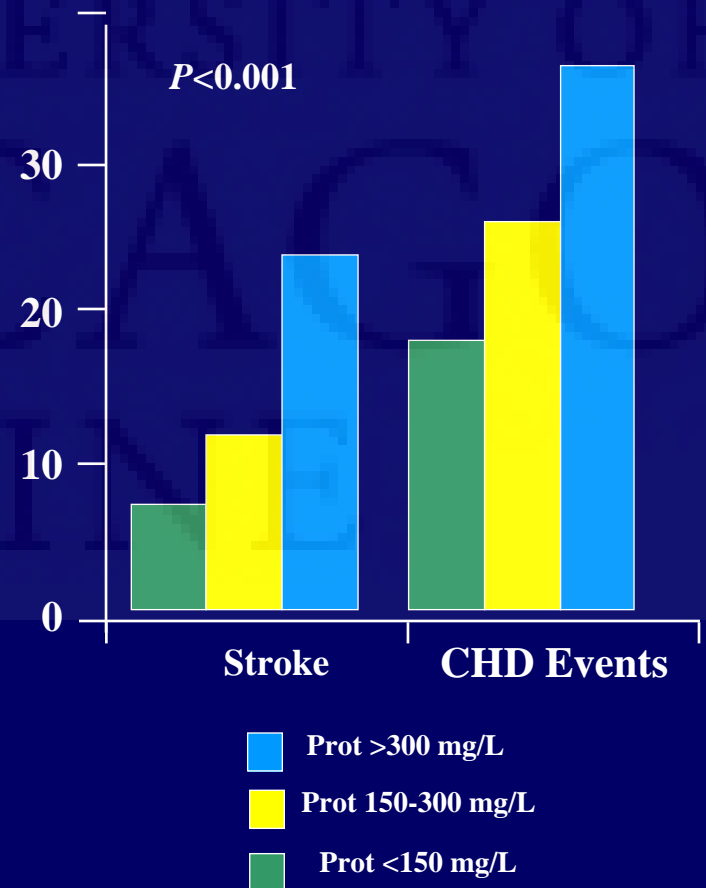
Proteinuria & Progression to ESRD



Proteinuria & mortality: yearly risk

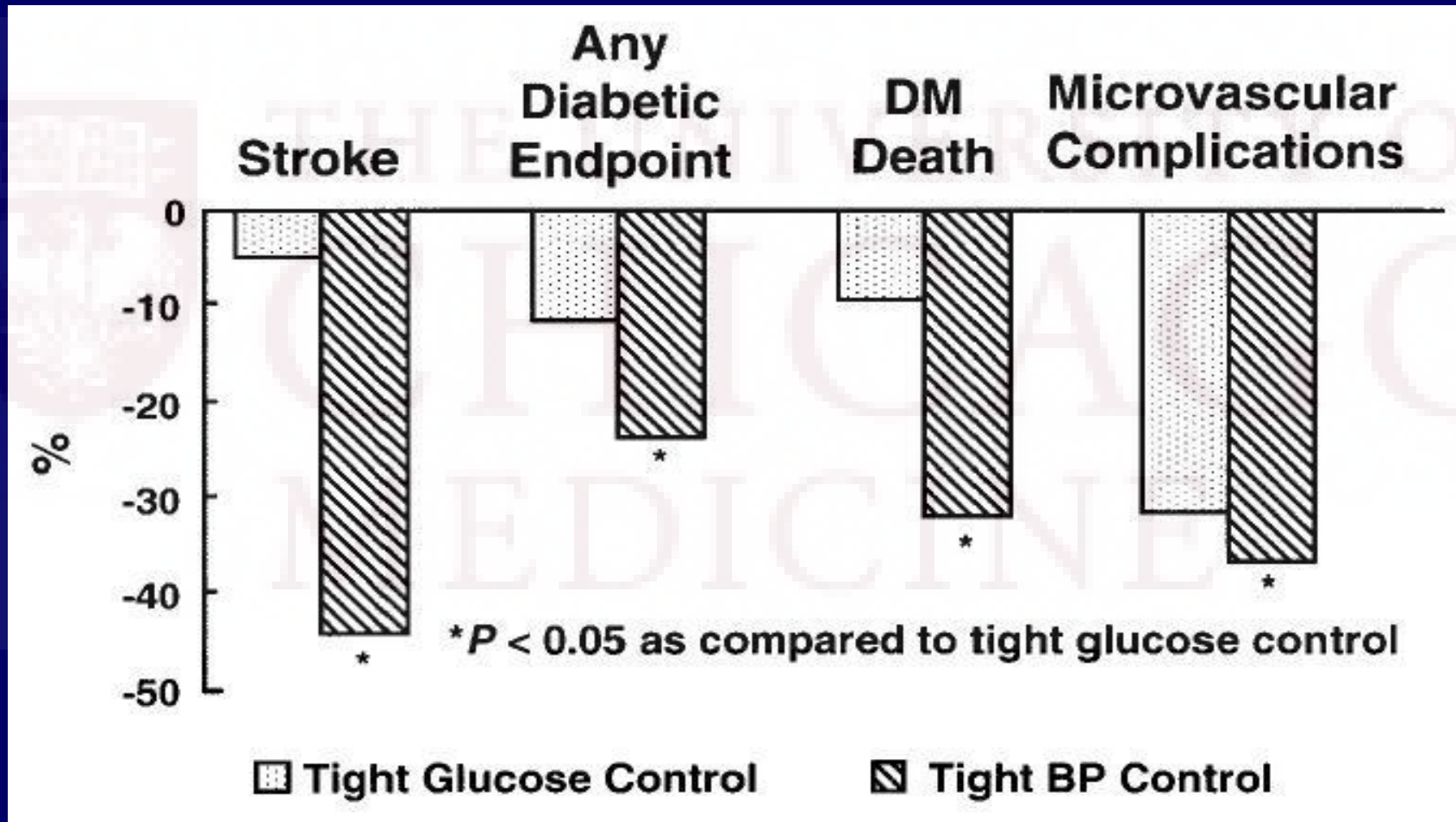


Proteinuria Predicts Stroke and CHD



Role of metabolic and hemodynamic factors in DN

Which is better Tight DM control or tight BP control?

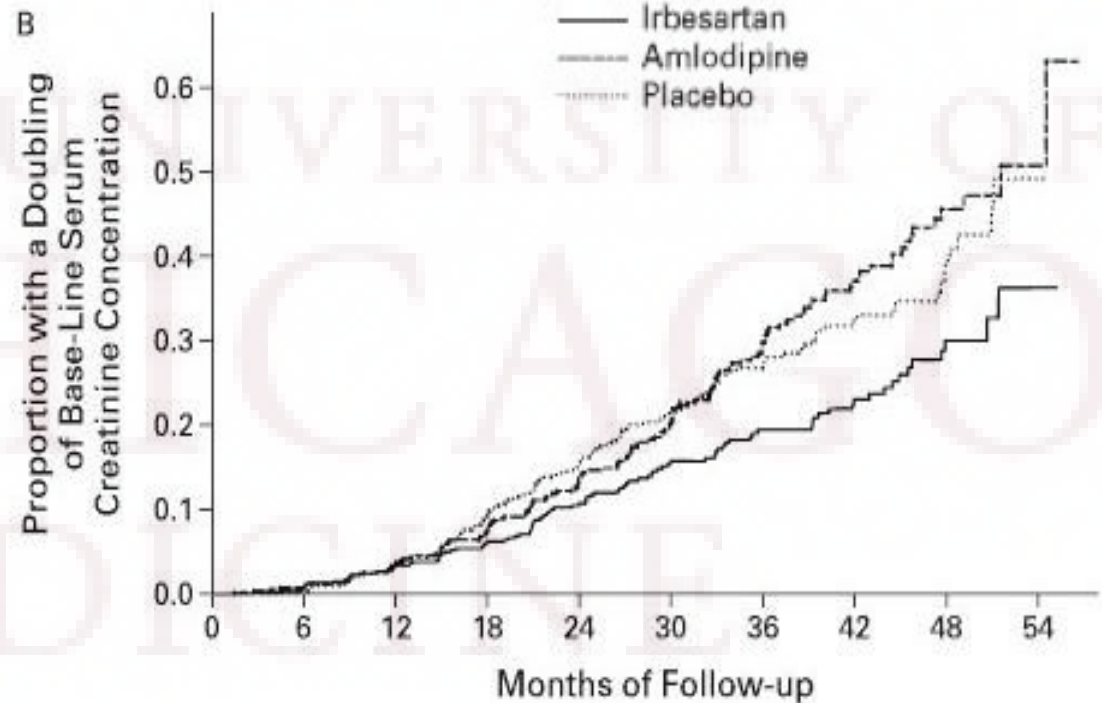


ARB vs CCB

1715 pt type 2 DM + HTN

✓ Irb 300 mg vs amlo 10 mg vs placebo, F/u 2. years

✓ **End points:** Doubling creatinine, ESRD, De



No. AT RISK

Irbesartan	579	534	495	457	363	273	191	131	57	5
Amlodipine	567	516	476	439	347	254	166	108	40	5
Placebo	569	527	482	436	360	252	173	107	47	2

ACEi or ARB?

Prospective multicenter double blind study.

- ✓ 250 pts with type 2 DM and DN
- ✓ Telmisartan 80 mg vs Enalapril 20 mg
- ✓ 5 years follow up
- ✓ **End point:** change in GFR, Cr, UAE, BP

No Difference

Table 3. Secondary Renal End Points after Five Years of Treatment, According to Analysis of the Last Observation Carried Forward.*

End Point	Change from Baseline		Difference between Groups (95% CI)
	Telmisartan Group	Enalapril Group	
Serum creatinine (mg/dl)	0.10	0.10	0 (−0.66 to 0.65)
Urinary albumin excretion (ratio) [†]	1.03	0.99	1.04 (0.71 to 1.51) [‡]

* One hundred sixteen subjects (35 with the last observation carried forward) in the telmisartan group and 128 (44 with the last observation carried forward) in the enalapril group were included in the analysis of serum creatinine, and 115 (35 with the last observation carried forward) and 125 (42 with the last observation carried forward), respectively, were included in the analysis of urinary albumin excretion.

[†] Urinary albumin excretion rates were determined as the ratio of the final value to the baseline value.

[‡] The ratio of the difference between treatment groups is shown. Because of the skewed distribution of the albumin excretion rate, the log analysis (when log values are converted back to nonlog values, or “anti-logged”) yields treatment ratios, both for treatment means (ratio of year 5 value to baseline value) and treatment differences (ratio of telmisartan to enalapril).

Is there a role from ACEI/ARB combination in type 1 DM with DN

Randomized, double-blind cross-over trial

- ✓ Enalapril 40 mg vs Enalapril 40 mg + Irbesartan 300 mg
- ✓ 24 patients with type I DM and DN
- ✓ 8 weeks treatment

Different Urine Albumin Excretion but also different BP

Table 2. Dual blockade of the renin-angiotensin system (RAS) with irbesartan 300 mg once daily in 24 type 1 patients with diabetic nephropathy (DN) treated with enalapril 40 mg once daily

	Enalapril 40 mg + placebo	Enalapril 40 mg + irbesartan 300 mg	Mean difference (95% CI)	P value
Albuminuria mg/24 hour ^a	519 (342,789)	373 (224,622)	-25% (-34, -15)	<0.001
24-hour blood pressure mm Hg	131 (3)/74 (1)	123 (3)/70 (2)	-8 (-12, -4)/-4 (-7, -2)	0.002/0.003
Day (7-23)	135 (3)/76 (1)	128 (4)/73 (2)	-7 (-12, -2)/-4 (-6, -1)	0.012/0.008
Night (23-7)	118 (3)/70 (2)	110 (3)/63 (2)	-9 (-14, -3)/-6 (-9, -3)	0.007/0.001
Glomerular filtration rate mL/min/1.73 m ²	65 (5)	63 (5)	-3 (-1, 7)	0.222
Plasma renin concentration mU/L ^b	177 (86, 364)	283 (133, 602)	64% (8, 150)	0.031
Plasma creatinine μmol/L	134 (7)	139 (7)	4 (-4, 13)	0.290
Plasma potassium mmol/L	4.2 (0.1)	4.3 (0.1)	0.1 (-0.1, 0.3)	0.178
Hemoglobin mmol/L	8.0 (0.2)	7.6 (0.2)	-0.4 (-0.6, -0.1)	0.005
Hemoglobin A _{1c} %	9.1 (0.3)	9.3 (0.2)	0.3 (0.1, 0.5)	0.019
Plasma cholesterol mmol/L	5.0 (0.2)	4.7 (0.2)	-0.3 (-0.6, 0.0)	0.109
Plasma low-density lipoprotein mmol/L	2.6 (0.2)	2.4 (0.2)	-0.3 (-0.6, 0.0)	0.052
Plasma high-density lipoprotein mmol/L	1.7 (0.1)	1.7 (0.1)	0.0 (-0.1, 0.1)	0.876

Values represented are mean (SEM).

^aMean (95% CI).

ACEI/ARB combination in type 2 DM

Randomized, double-blind cross-over trial

Enalapril 40 mg vs Enalapril 40 mg + candesartan 16 mg

20 patients with type 2 DM and DN
8 weeks treatment

No difference in blood pressure

Table 1—Effect of adding candesartan 16 mg o.d. to maximal recommended doses of ACEI (enalapril/lisinopril 40 mg daily) on kidney function and ABP in 20 patients with type 2 diabetes and diabetic nephropathy

	ACEI + placebo	ACEI + candesartan 16 mg	Mean difference (95% CI)*	P* value
Albuminuria (mg/24 h)†	706 (349–1,219)	508 (228–909)	28% (17–38)	<0.001
Blood pressure (mmHg)				
24-h	138 (3)/72 (2)	135 (3)/70 (2)	3 (–2 to 8)/2 (–2 to 5)	0.21/0.38
Day (7:00 a.m. to 11:00 p.m.)	142 (3)/74 (2)	139 (3)/72 (2)	3 (–2 to 7)/3 (–2 to 7)	0.32/0.31
Night (11:00 p.m. to 7:00 a.m.)	131 (4)/67 (2)	126 (4)/65 (3)	5 (–2 to 11)/2 (–3 to 7)	0.16/0.51
GFR (ml · min ^{–1} · 1.73 m ^{–2})	77 (6)	74 (5)	4 (–1, 9)	0.10
Plasma creatinine (μmol/l)	121 (10)	123 (10)	2 (–7 to 10)	0.66
Plasma renin (mU/l)	42 (1)	53 (1)	–24% (–60 to 12)	0.19
Plasma potassium (mmol/l)	4.0 (0.1)	4.2 (0.1)	–0.13 (–0.3 to 0.1)	0.13
HbA _{1c} (%)	7.9 (0.2)	8.1 (0.2)	–0.1 (–0.1 to 0.4)	0.31
Cholesterol (mmol/l)	4.5 (0.2)	4.6 (0.2)	–0.1 (–0.2 to 0.4)	0.60
Urinary sodium (mmol/24 h)	195 (13)	188 (12)	6 (–19 to 32)	0.63
Protein intake (g · kg ^{–1} · 24 h ^{–1})	0.92 (0.06)	0.93 (0.04)	–0.01 (–0.07 to 0.07)	0.94

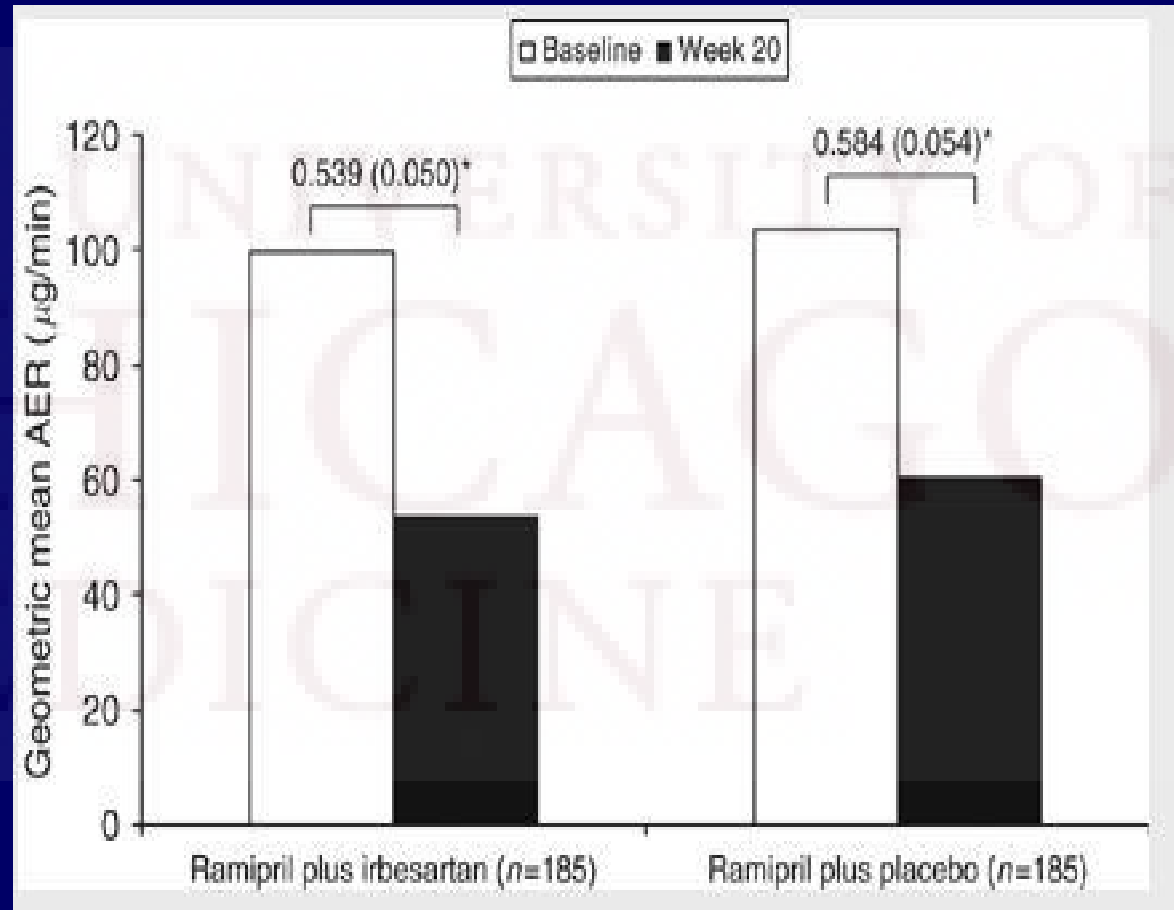
Data are means (SE). *Mean difference of (ACEI + placebo) – (ACEI + candesartan 16 mg); †geometric mean (IQR).

ACEI/ARBs in type 2 DM (continue)

838 patients with HTN, Type 2 DM and microalbuminuria

20 weeks treatment

No change in MA despite significant effect on BP



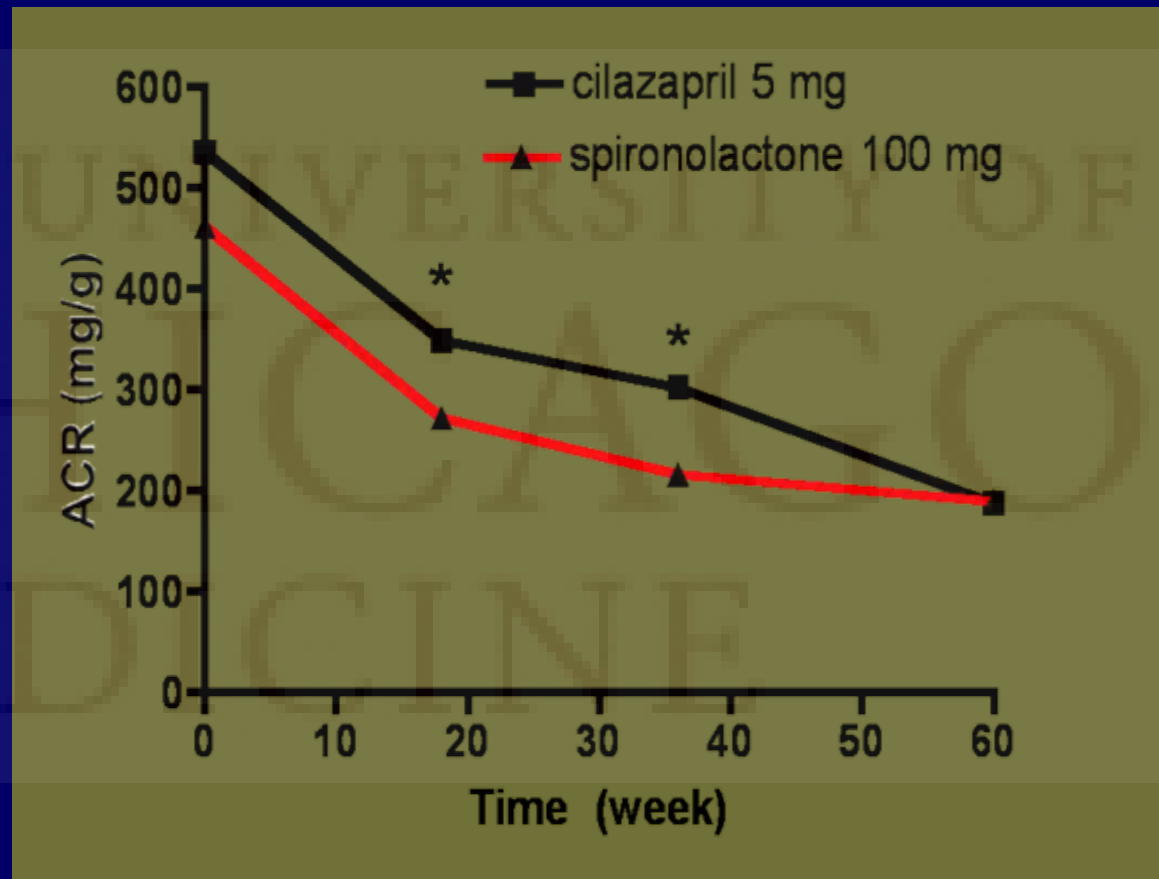
AER = Albumin Excretion Rate

Aldosterone antagonism versus ACEi in DN

Randomized trial

- ✓ 78 Females with type 2 DM + MA.
- ✓ Follow up 60 weeks
- ✓ On Atenolol and HCTZ.
- ✓ Comparing b/w adding 100 mg Spironolactone vs Cilazapril 5mg

BP equal between two groups

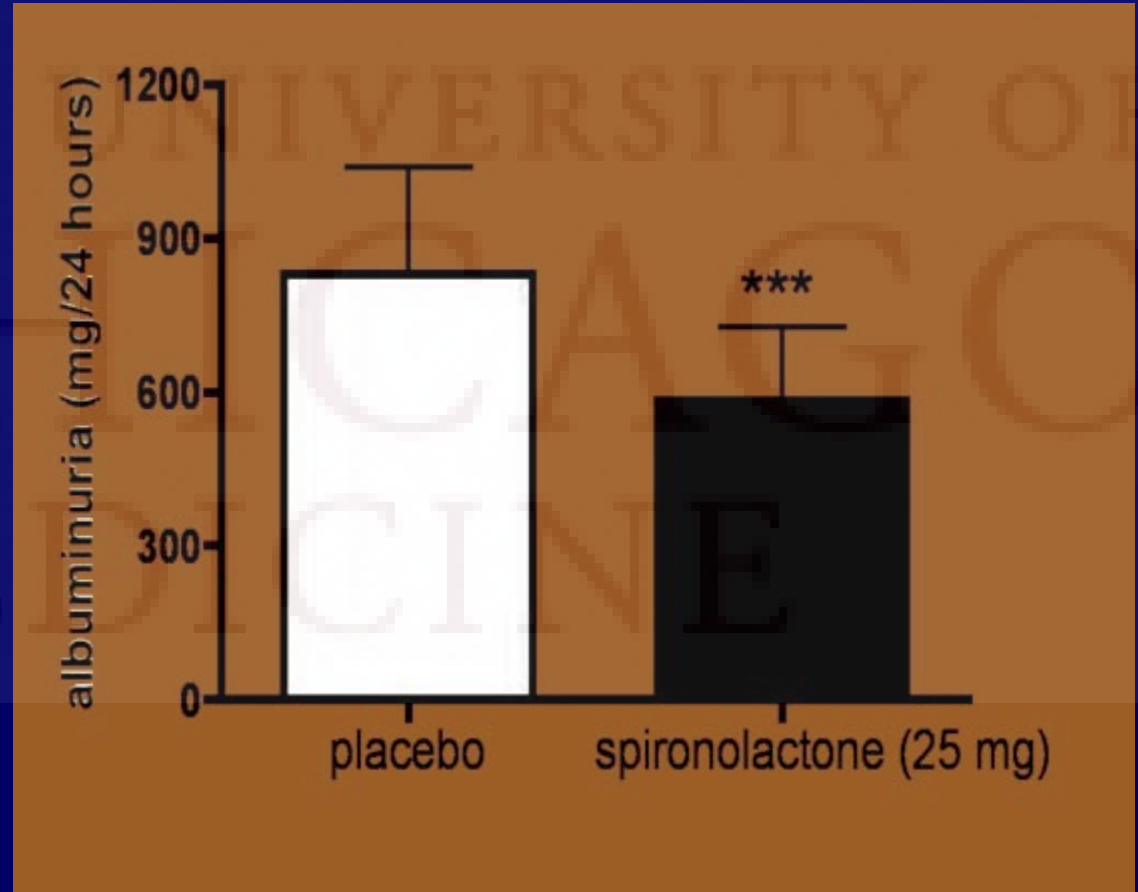


Aldosterone antagonism in DN

Randomized cross-over trial

- ✓ 20 type 1 DM
- ✓ Macroalbuminuria/GFR 85 cc/min
- ✓ 25 mg spironolactone x 2 month

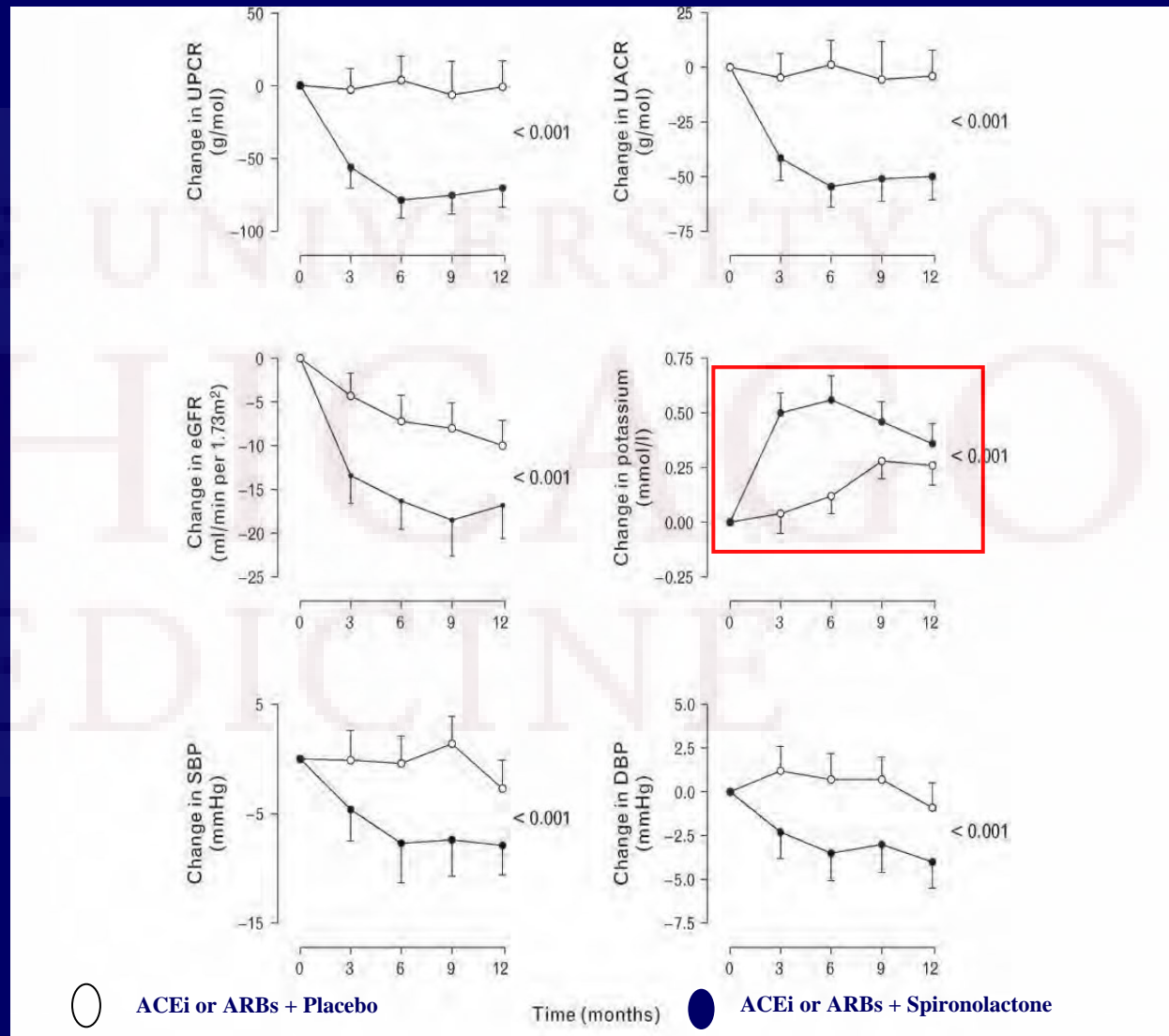
Equal BP among groups



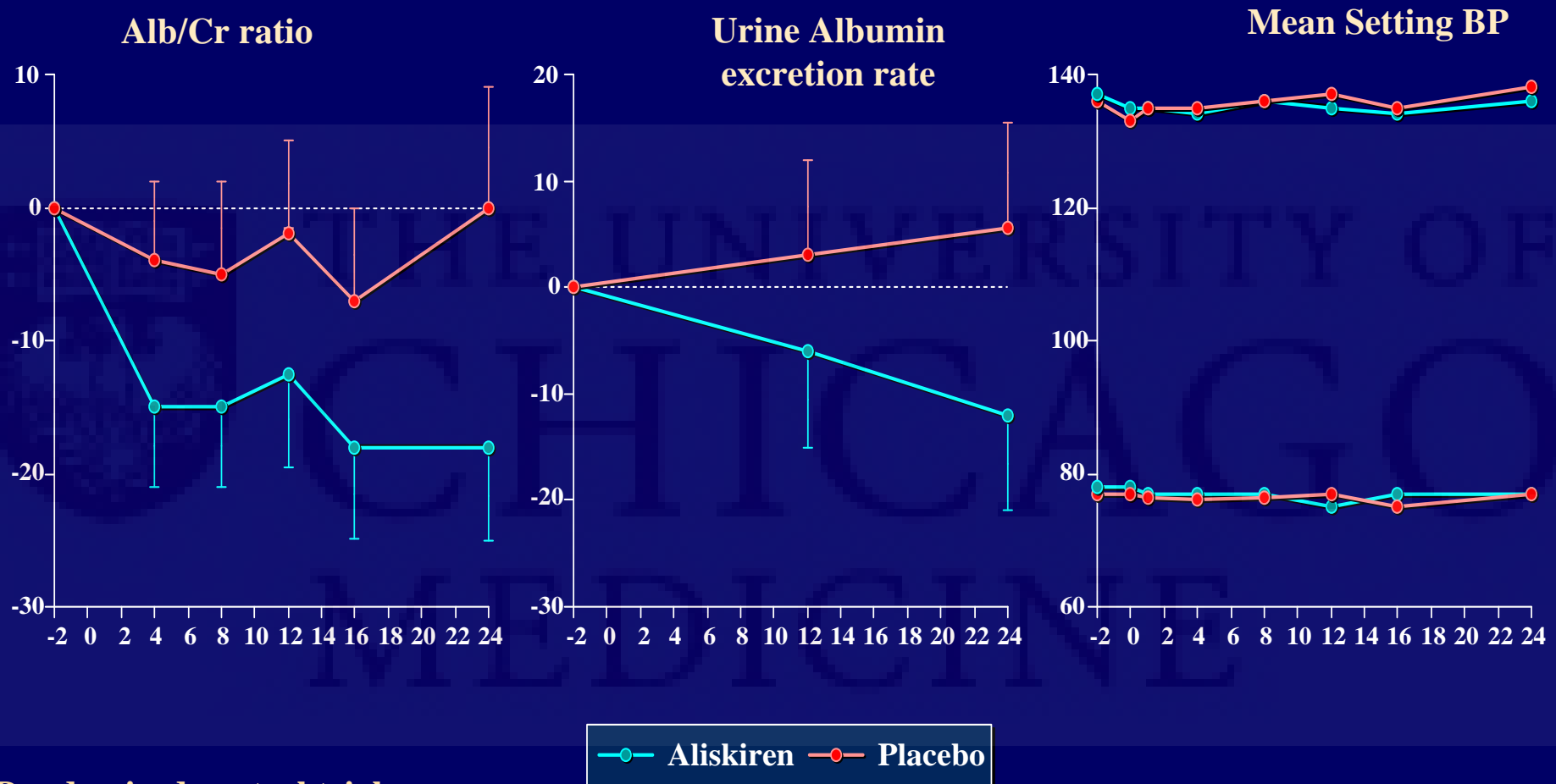
Aldosterone antagonism in DN

Randomized trial

- ✓ 95 patients with type 2 DM + MA
- ✓ On ACEI or ARBs
- ✓ Added 25-50 mg Spironolactone x 1 year
- ✓ Compare: UA/CR, UP/CR, SBP, DBP, eGFR, Potassium



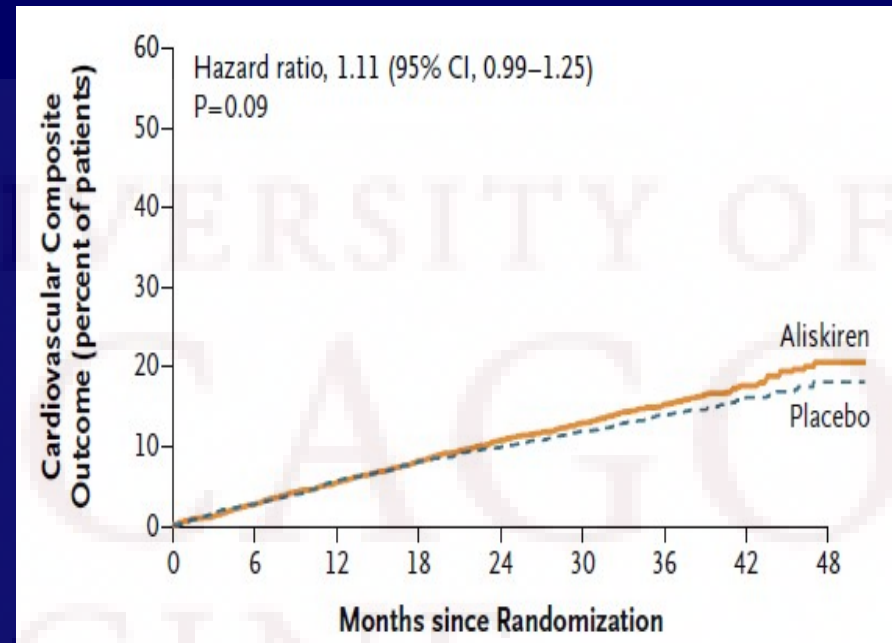
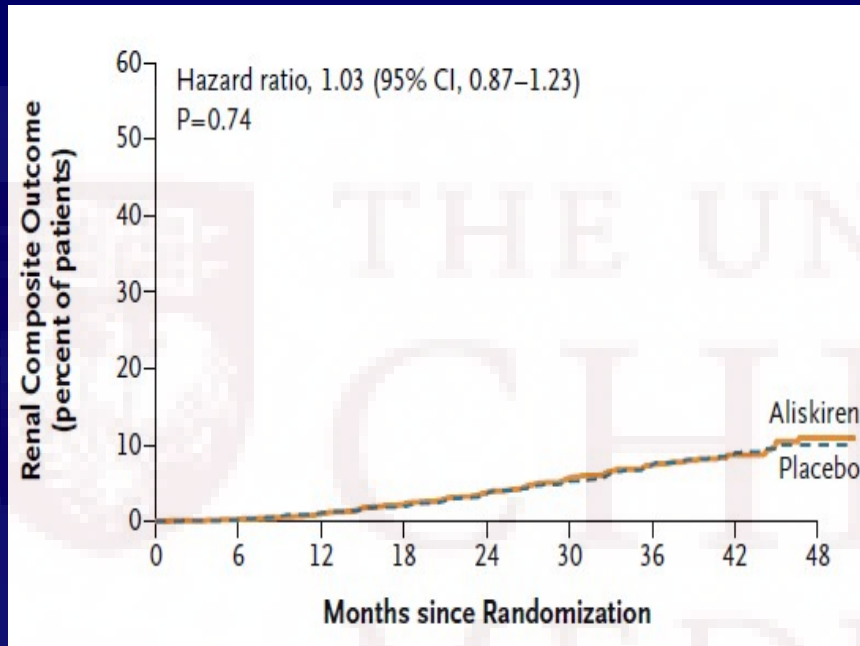
Renin inhibition in DN: AVOID Trial



Randomized control trial

- ✓ 599 patients with DM2 HTN and DN and poor glycaemic control
- ✓ Losartan + placebo **vs** Losartan + Aliskiren. No significant change in BP between two groups

ALTITUDE Trial of Aliskiren in type 2 DM



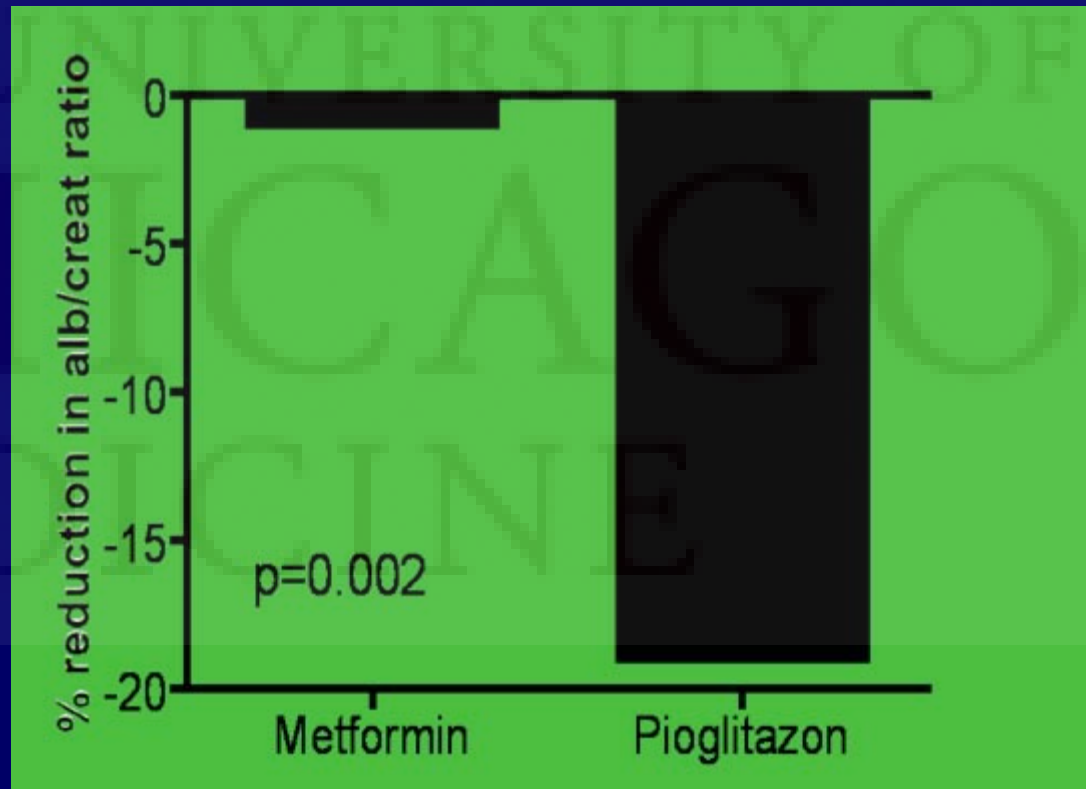
- ✓ **Double-blind, multi-centered, randomized control trial**
- ✓ Evaluate Aliskiren in combination with either ACE inhibitors or ARBs in patients with type 2 diabetes. Cardio-renal effect
- ✓ 8,561 type 2 DM
- ✓ Unfortunately, on 12/20/2011 ALTITUDE study was terminated because increase risk of stroke and no benefit from adding Tekturna.

Independent of glycemic control, was metformin reno-protective?

Multicenter Randomized Control trial

✓ 597 pts on Metformin & 597 pts on Pioglitazone.

✓ Alb/Creat at 52 wks:



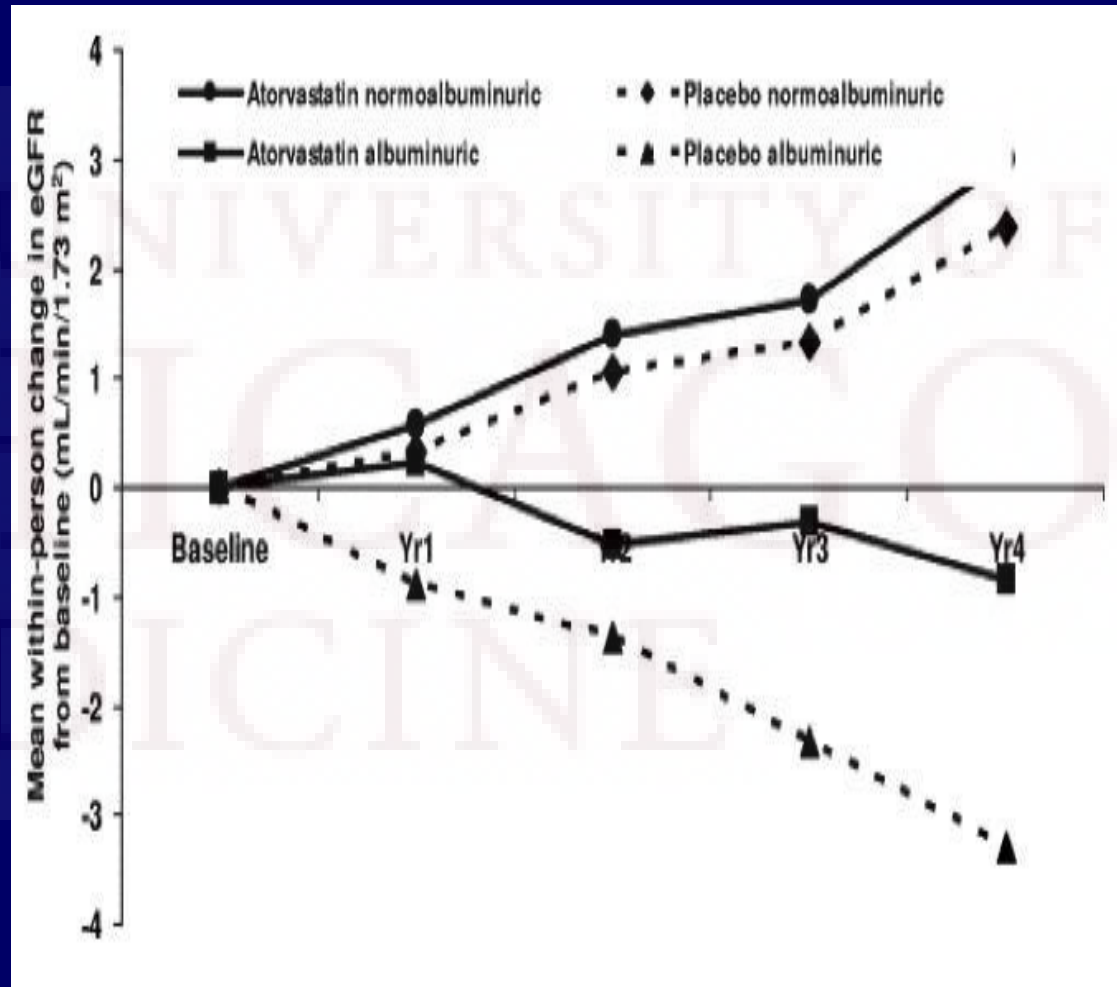
Role of statins in clinical DN

Randomized control trial

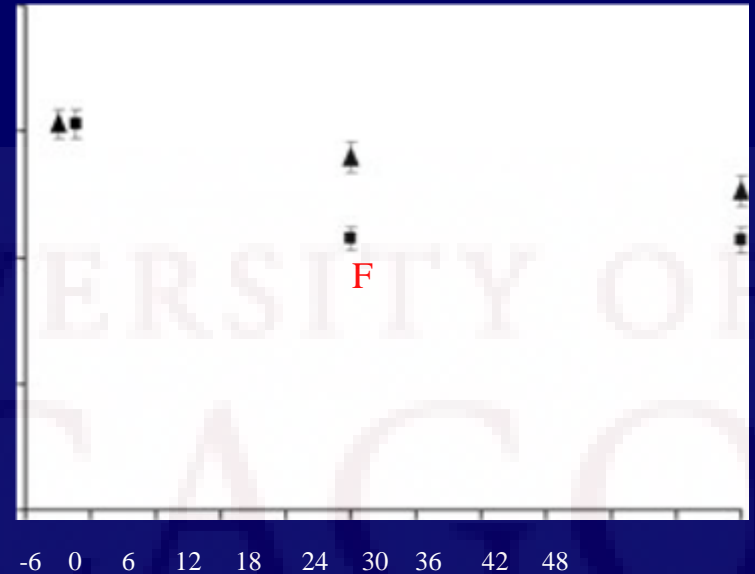
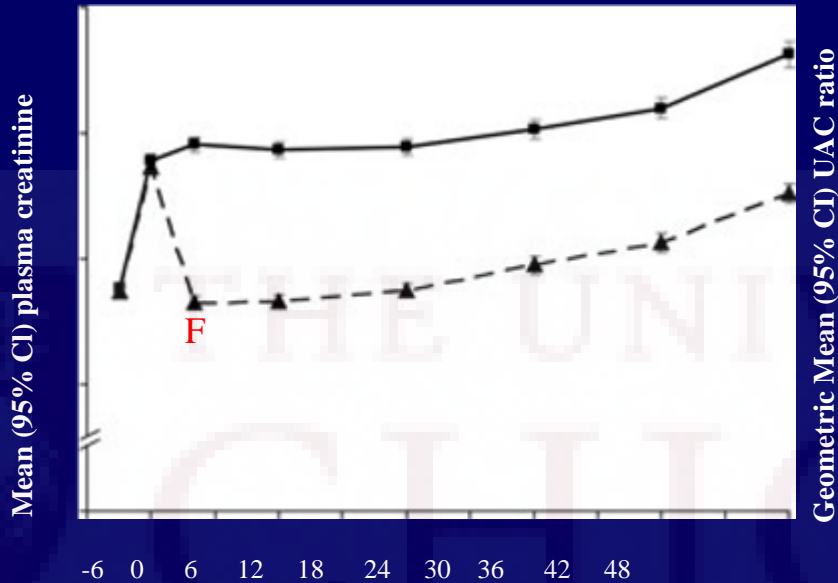
- ✓ Atorvastatin, 10 mg/d, or placebo
- ✓ Median follow-up of 3.9 years
- ✓ Out come: eGFR, albuminuria, CVD.

Result:

- Modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria.
- Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR



Role of Fenofibrate in clinical DN



Randomized control trial

- ✓ Patient number 9795, DM type 2
- ✓ Fenofibrate 200 mg vs placebo
- ✓ 5 Years follow up
- ✓ Outcome: ESRD, ACR, Cr

Result: F vs P: less albuminuria progression less ESRD

Back to my patient

- Our plan was to control DM first, Januvia 25 mg daily started (goal to wean of insulin)
- After controlling her DM, if Albuminuria continue to worse, will consider starting Spironolactone

Summary ((ADA 2012))

- Diabetes with Micro-albuminuria either **ACEI** or **ARBs**
- When not tolerated, **substitute one for the other**
- Combination treatment still need further study.

References

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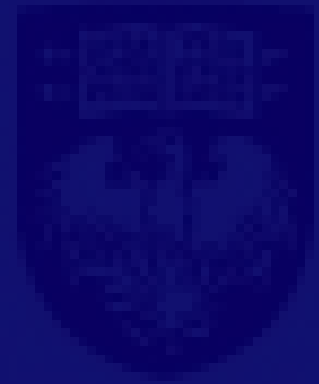
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Thank you



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