



Weill Cornell Medicine-Qatar
Continuing Professional Development

Advances in the Diagnosis and Management of the Diabetic Triopathy

R A Malik

Professor of Medicine

Weill Cornell Medicine-Qatar
& Weill Cornell Medicine in NY



DISCLOSURE STATEMENT

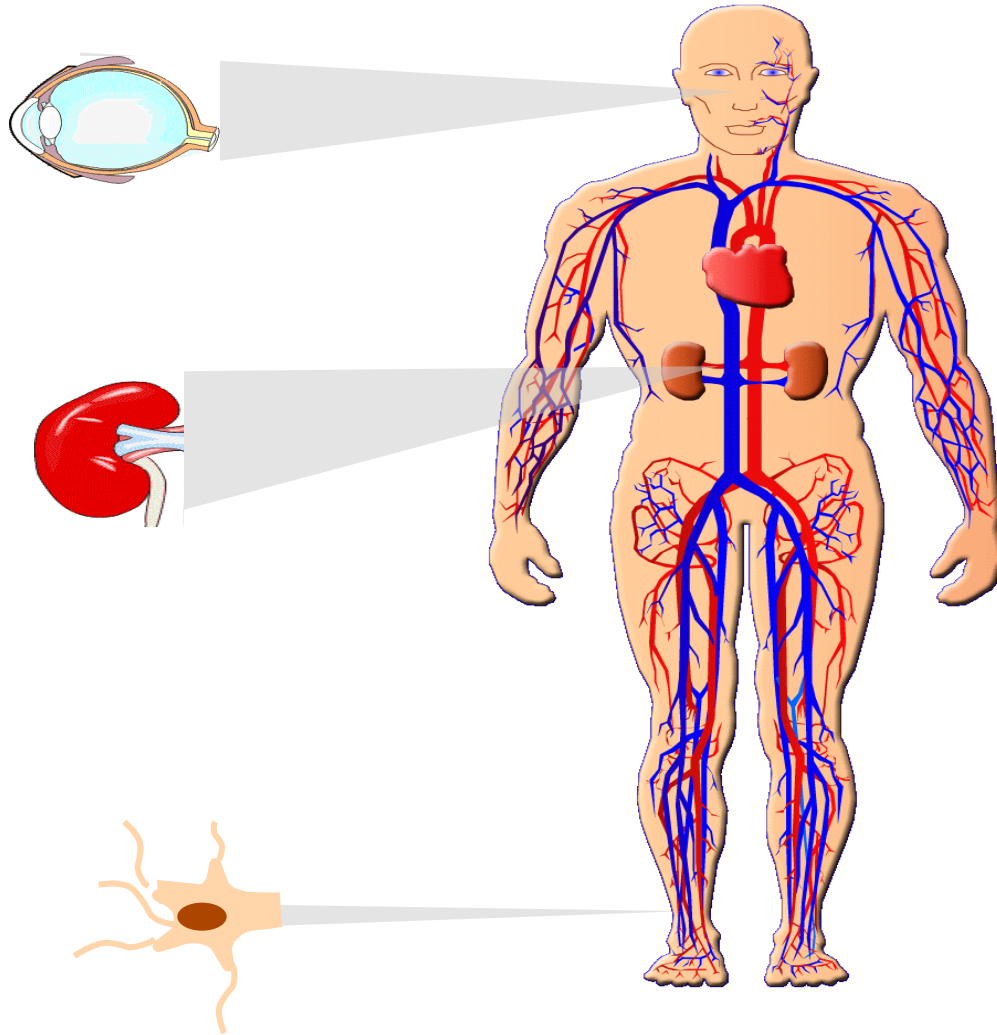
Speaker:

Rayaz A. Malik, MD

- Has disclosed that he serves on the Speaker's Bureau for Pfizer and Lilly
- Will not be discussing the off-label or investigational use of products

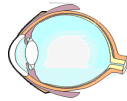


Diabetic Triopathy: Unholy Trinity



Diagnosis

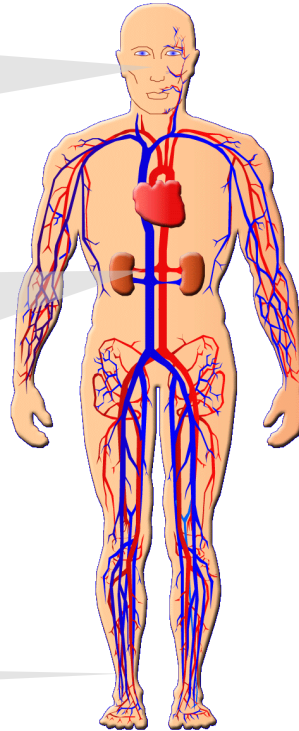
Diabetic Retinopathy
Blindness
25 patients/week.



Diabetic Nephropathy
Leading cause of
end-stage renal disease



Diabetic Neuropathy
107 amputations/week



Lucentis
Ozudrex



ACEi
ARB's



?????

Conversation in 2001 With Prof Nathan Efron about a Corneal confocal microscope!

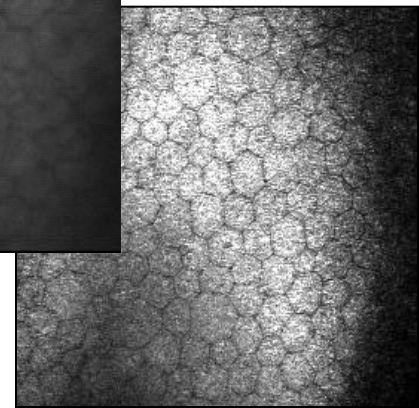
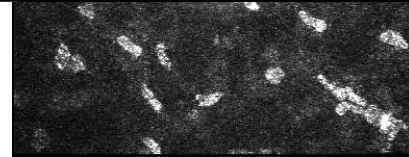
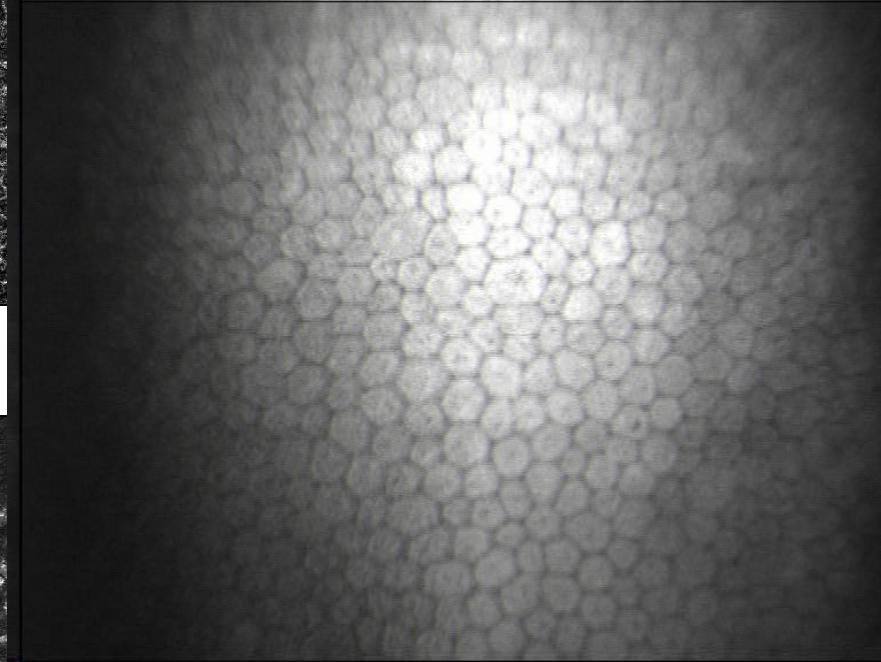
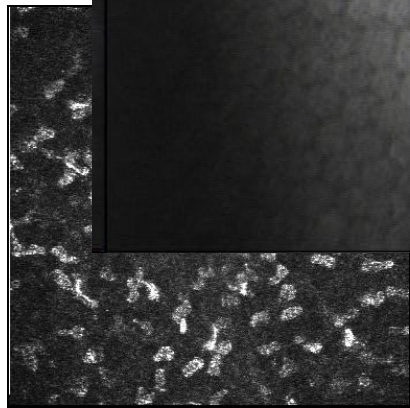
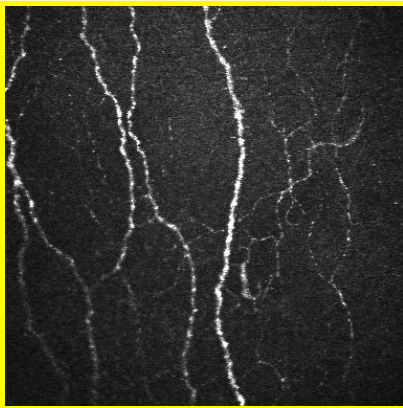
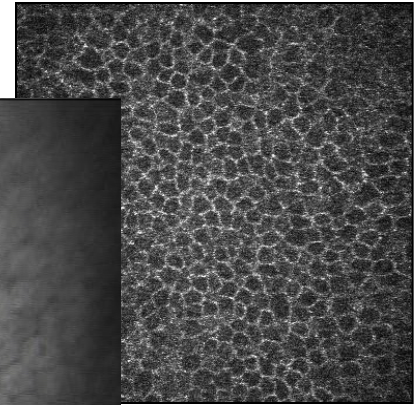
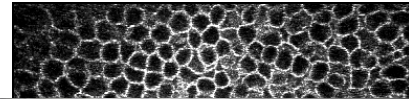
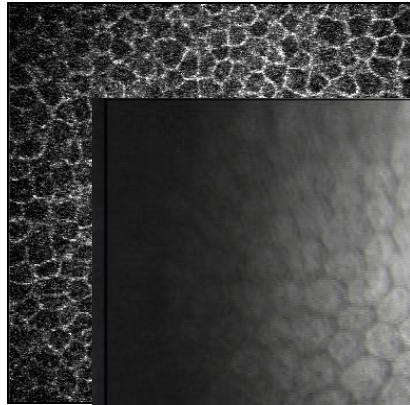
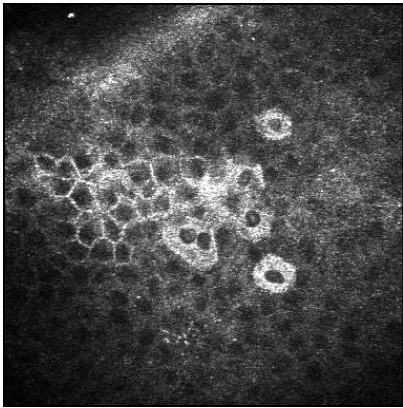


Corneal Confocal Microscopy

- Rapid (2 min)
- Non-invasive (in vivo)
- Reiterative
- Images Corneal Structure.

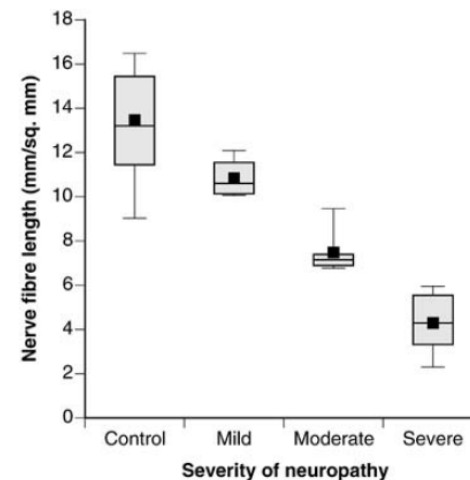
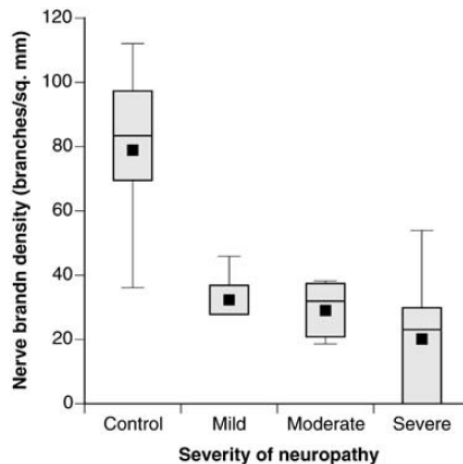
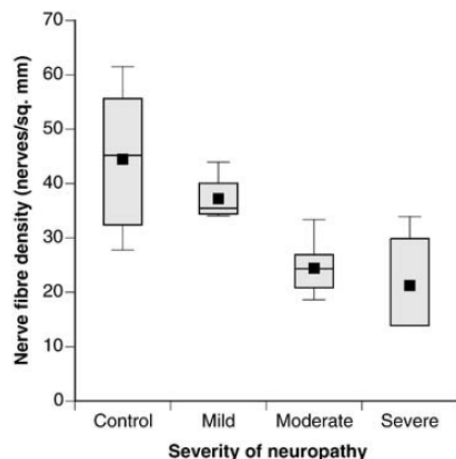


Corneal tomography



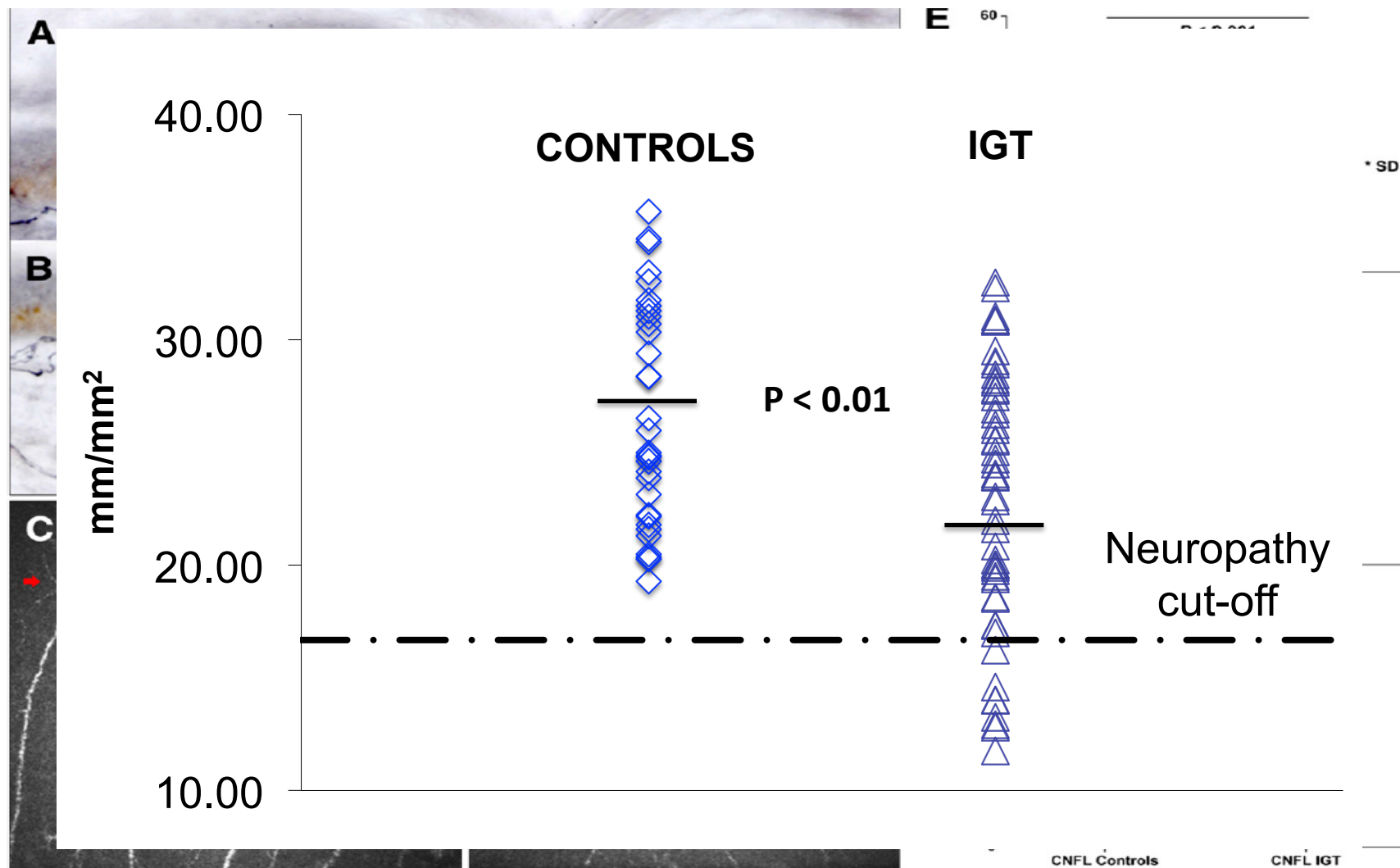
Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients

R. A. Malik¹, P. Kallinikos², C.A. Abbott¹, C.H.M. van Schie¹, P. Morgan², N. Efron², A. J. M. Boulton¹



Diabetologia (2003) 46:683–688

Corneal Confocal Microscopy Detects Neuropathy in Subjects With Impaired Glucose Tolerance

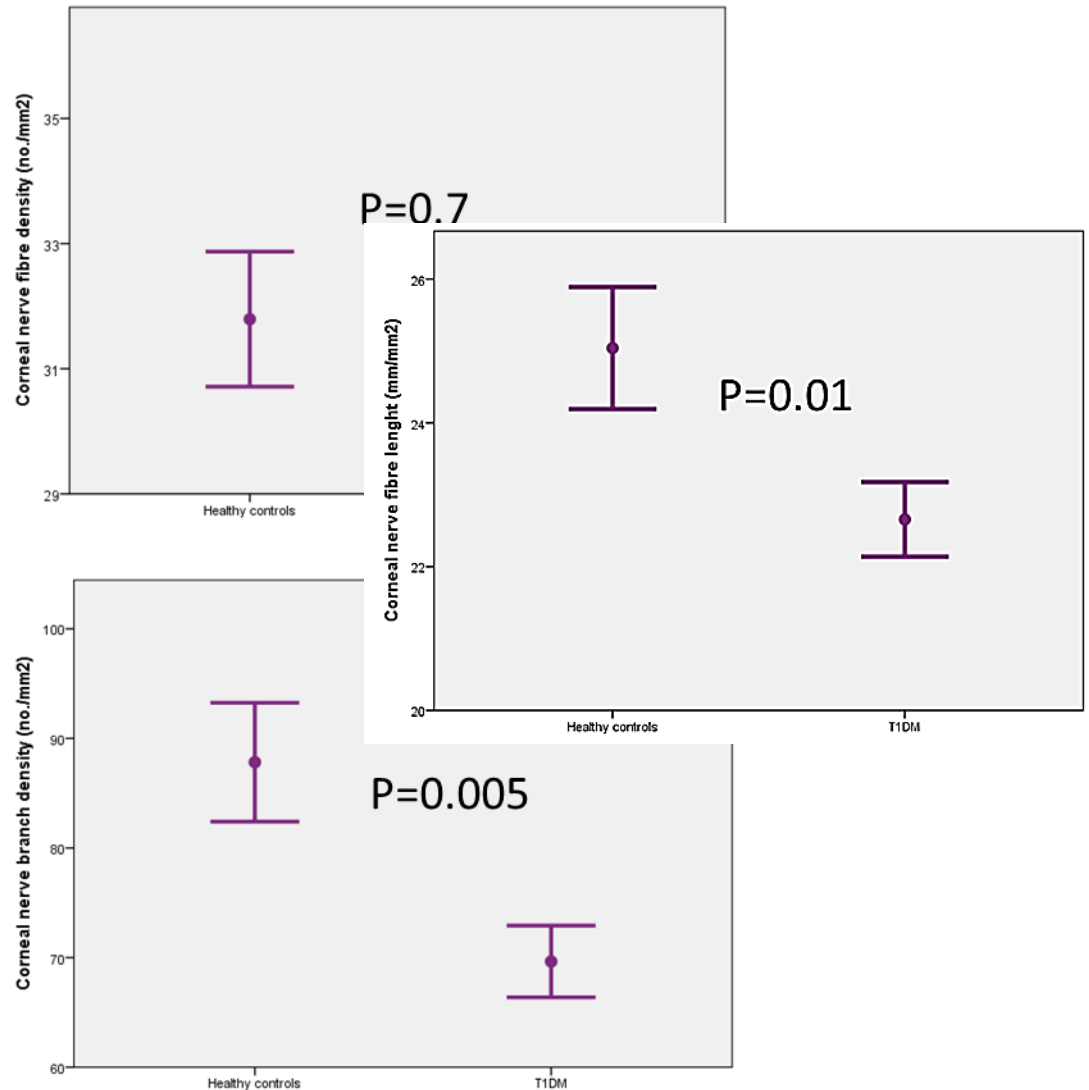
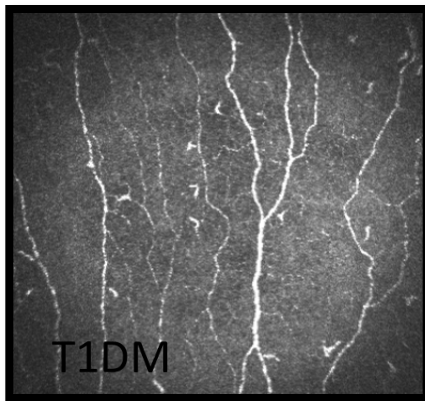
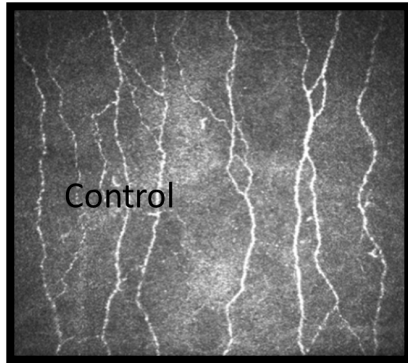


T1DM- Children

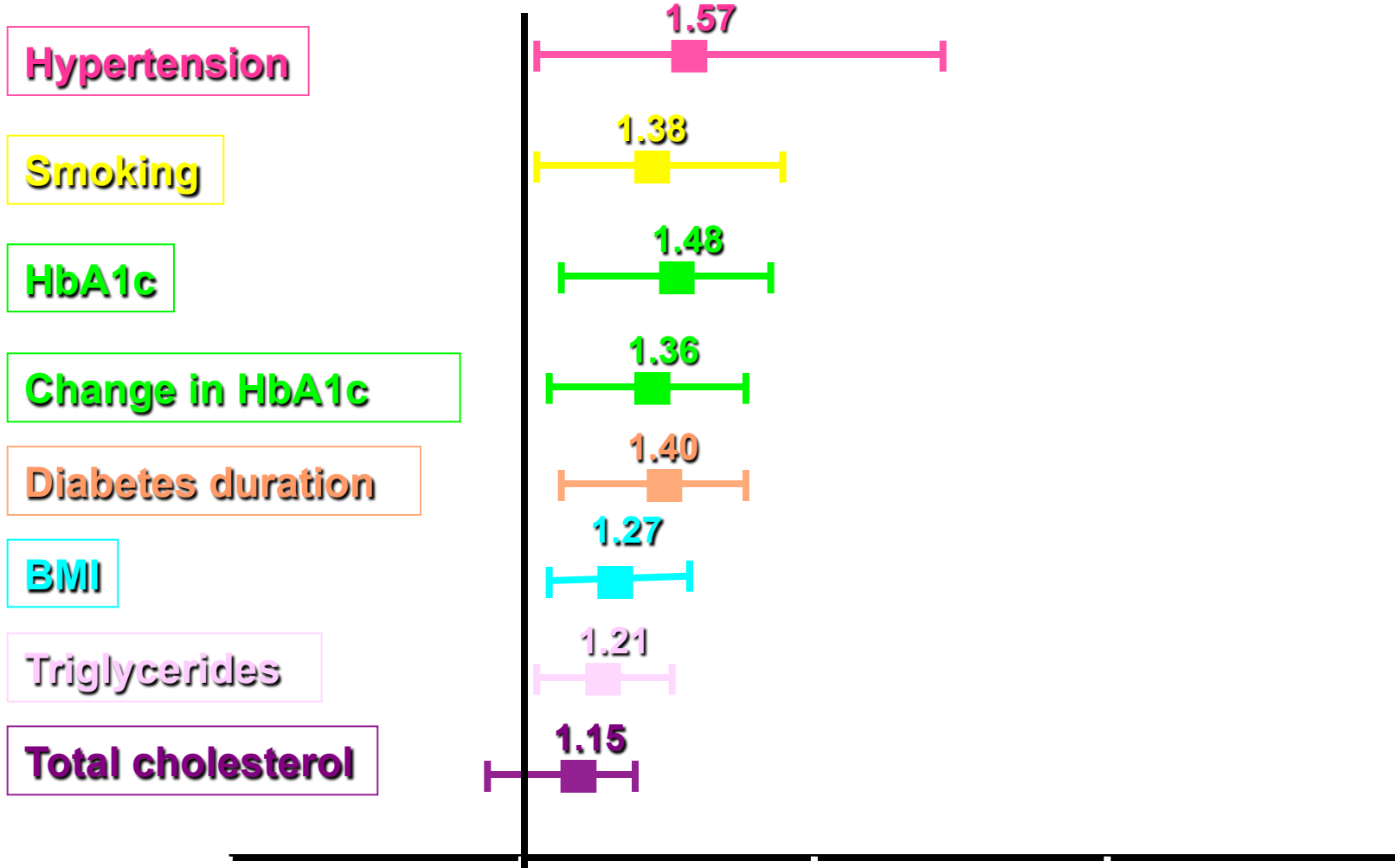
	Controls (mean± SD)	T1DM (mean± SD)	P value
Number	52	84	-
Age (years)	13.3±2.99	14.64±2.39	NS
Duration of Diabetes (years)	NA	8.74±2.62	-
HbA1C (%)	NA	8.92±1.75	-
Corneal nerve fibre Density (no./mm ²)	31.79±7.79	31.07±7.51	0.7
Corneal nerve branch Density (no./mm ²)	87.83±39.09	69.65±30	0.005
Corneal nerve fibre length (mm/mm ²)	25.04±6.12	22.66±4.75	0.01

Ferdousi et al. 2015

T1DM- Children

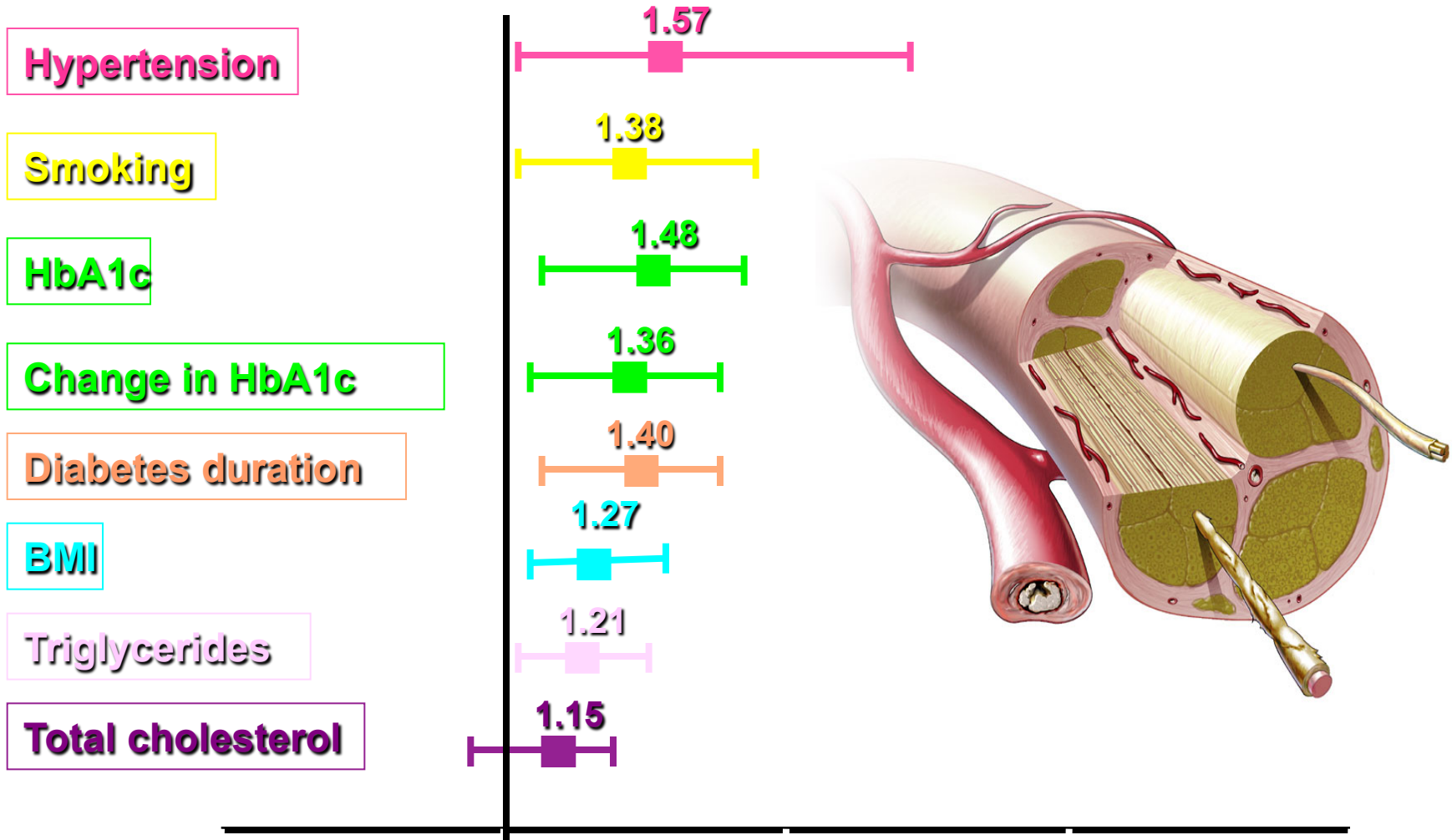


Diabetic Neuropathy: Risk Factors

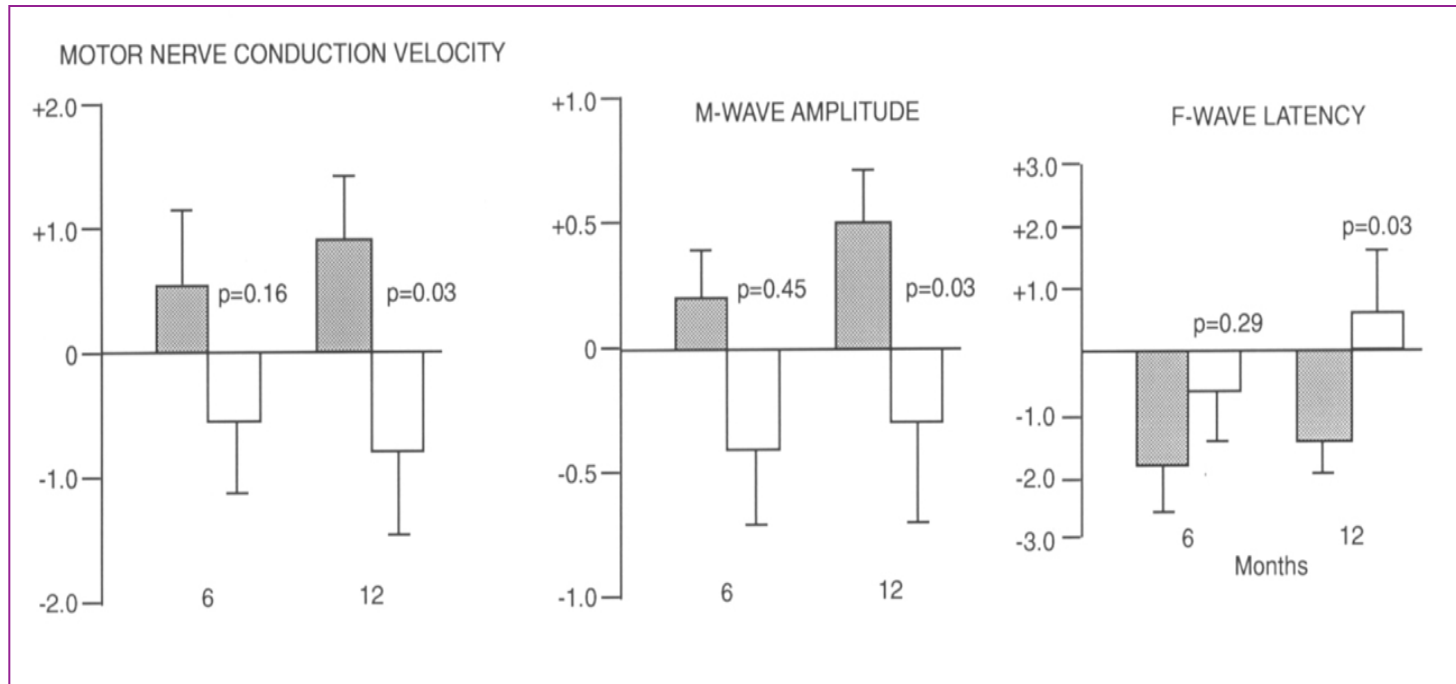


Tesfaye et al., N Engl J Med 2005; 352: 341-50

Hypertension



ACEi Neuropathy



Malik RA et al. Lancet 1998; 352: 1978-81.

DEMAND study

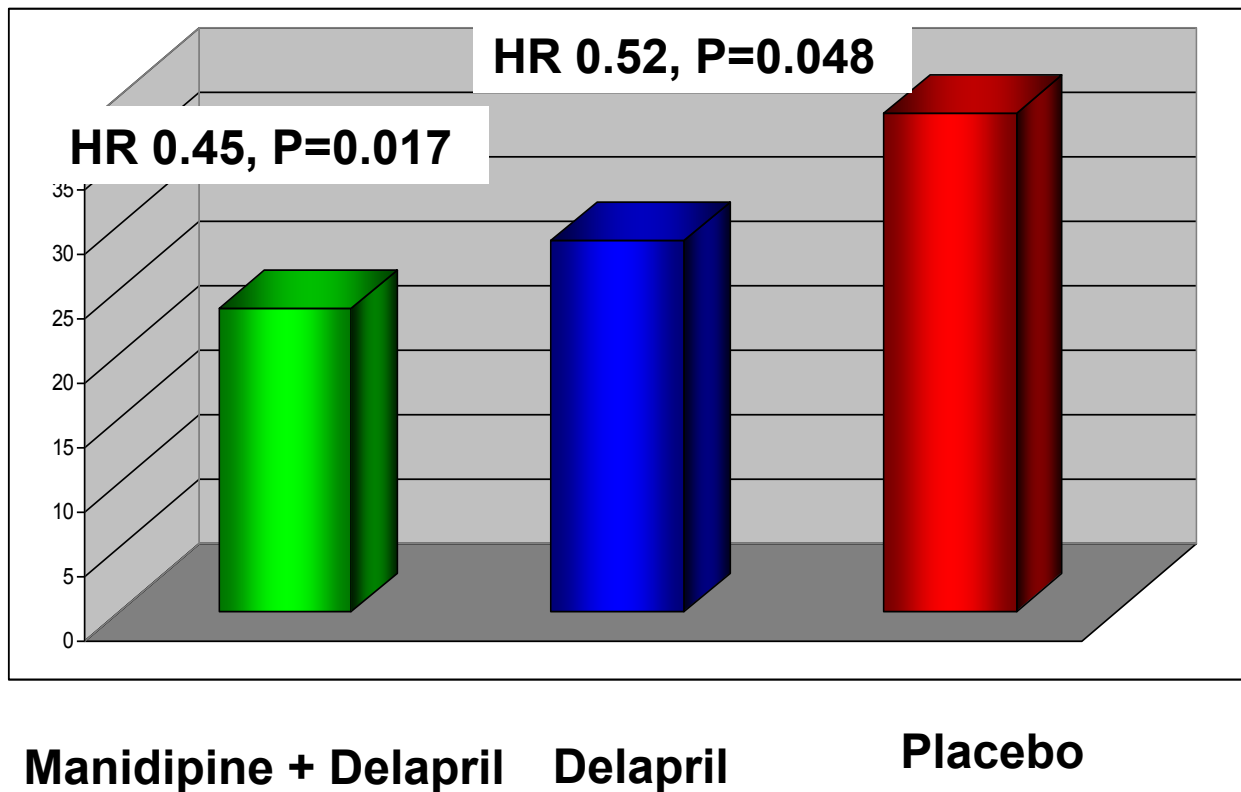
- 380 hypertensive type 2 diabetic patients without nephropathy over ~4 yrs.

Manidipine (10 mg/day) plus Delapril (30 mg/day)

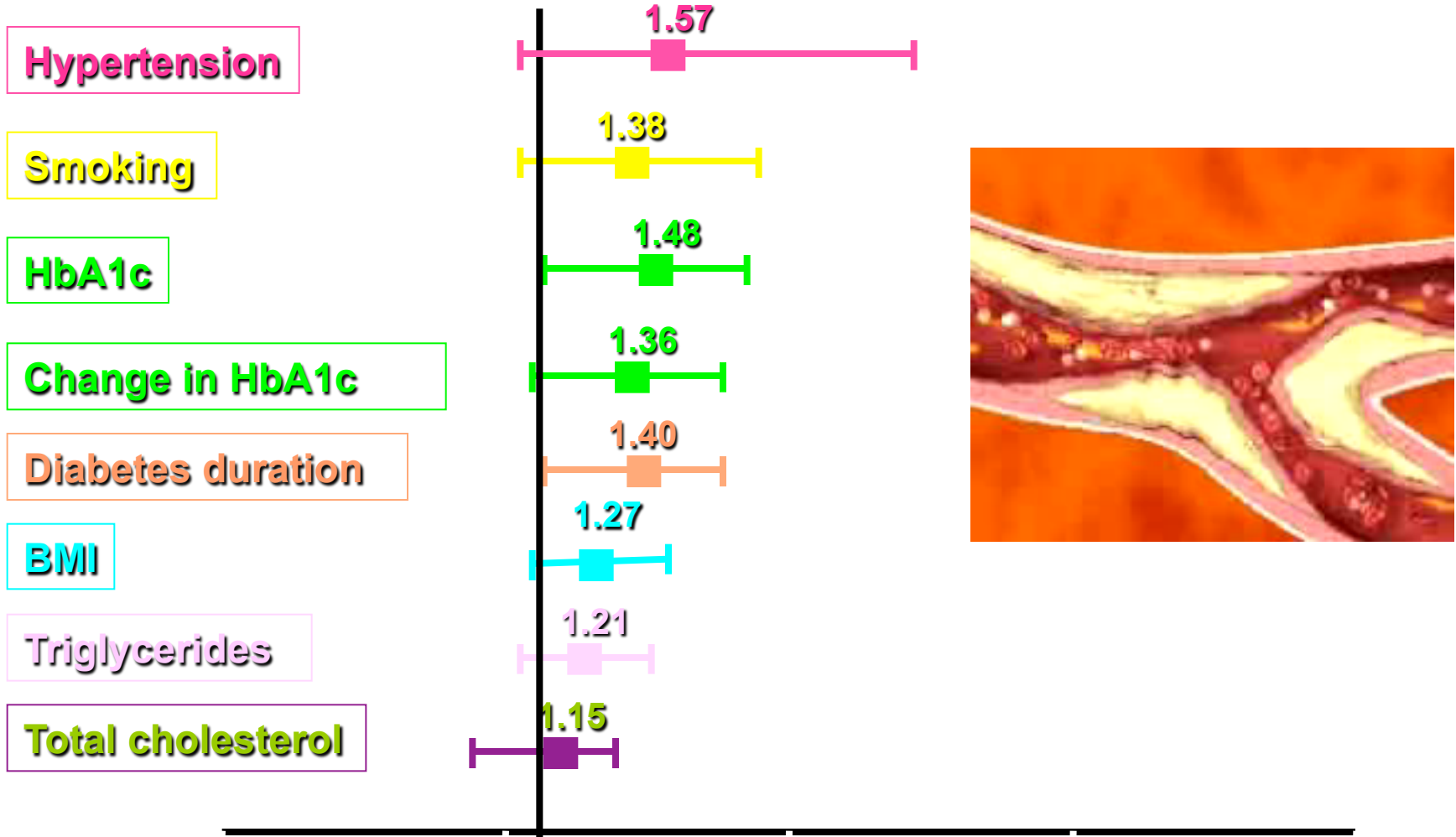
Delapril (30 mg/day)

Placebo

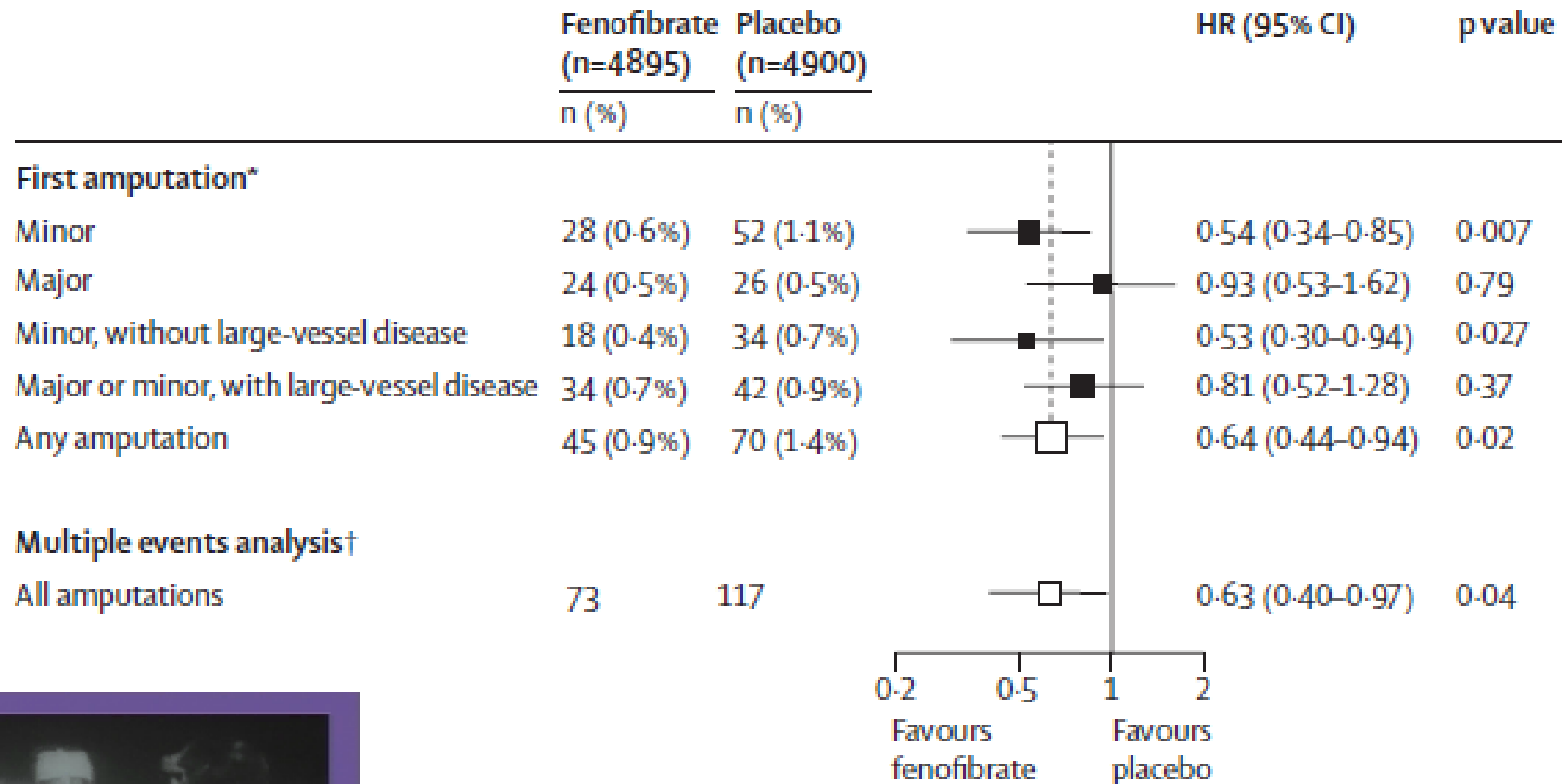
Neuropathy ↓ 40%



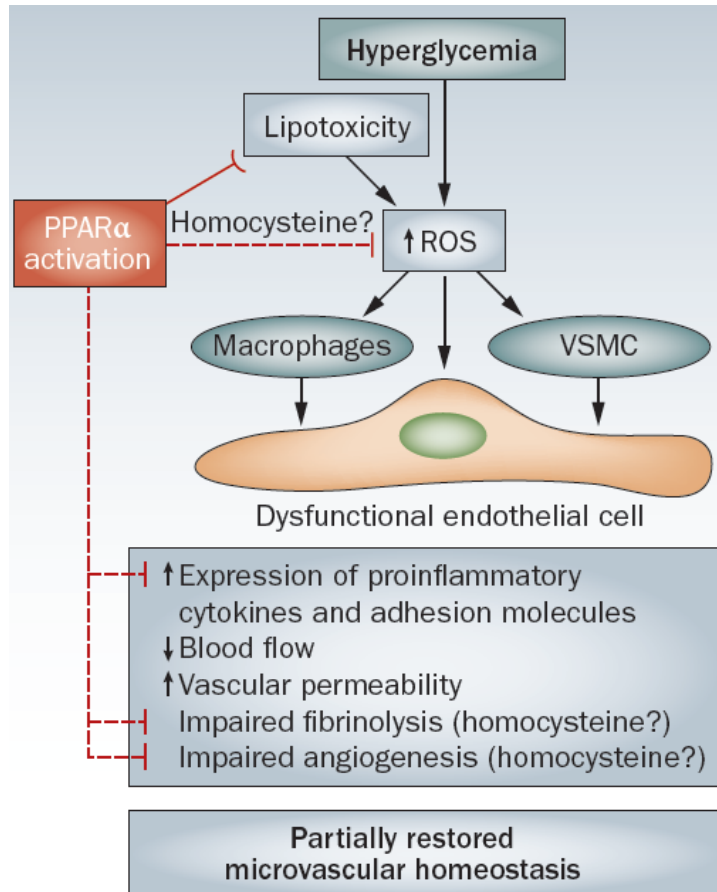
Triglycerides



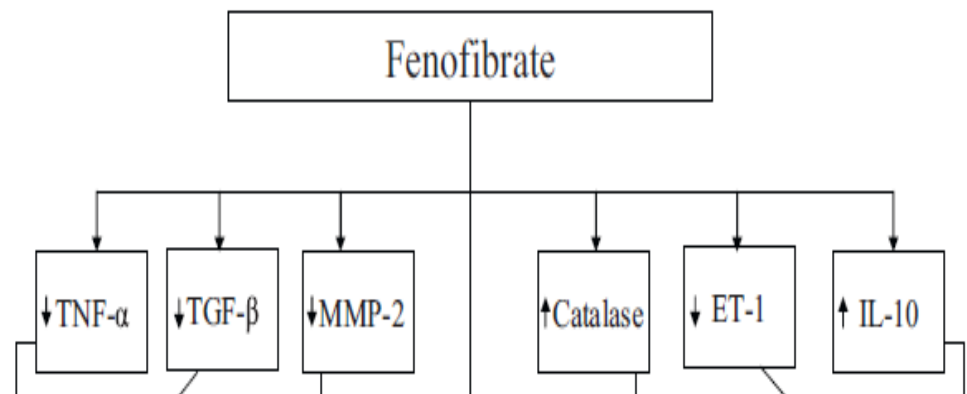
FIELD study



PPAR α : an emerging therapeutic target in diabetic microvascular damage



LIPID independent
Anti- inflammatory,
Anti-fibrotic
Anti-oxidant
ARI' s



Painful Neuropathy



2016 ADA DPN consensus

Is pain due to DSPN confirmed?

No/Not sure

Yes

Assess comorbidities, potential for AEs,
drug interactions, costs to select initial
therapy from the 3 choices below

Refer to Neurology/
Pain Clinic

Voltage gated $\alpha 2$ - δ ligand
(pregabalin, gabapentin)

Serotonin-norepinephrine
reuptake inhibitor
(duloxetine, venlafaxine)

Tricyclic Antidepressant
(Nortriptyline/Desipramine)

No clinically meaningful effect

a. Switch to another agent
from above

b. Try combining agents
from above

c. May add Tapentadol or
Tramadol if a and b fail

**No clinically meaningful effect/
Not tolerated**

Refer to Pain Clinic



“Sometimes obvious conditions and treatments are the most difficult to grasp”

Vit D and DPN

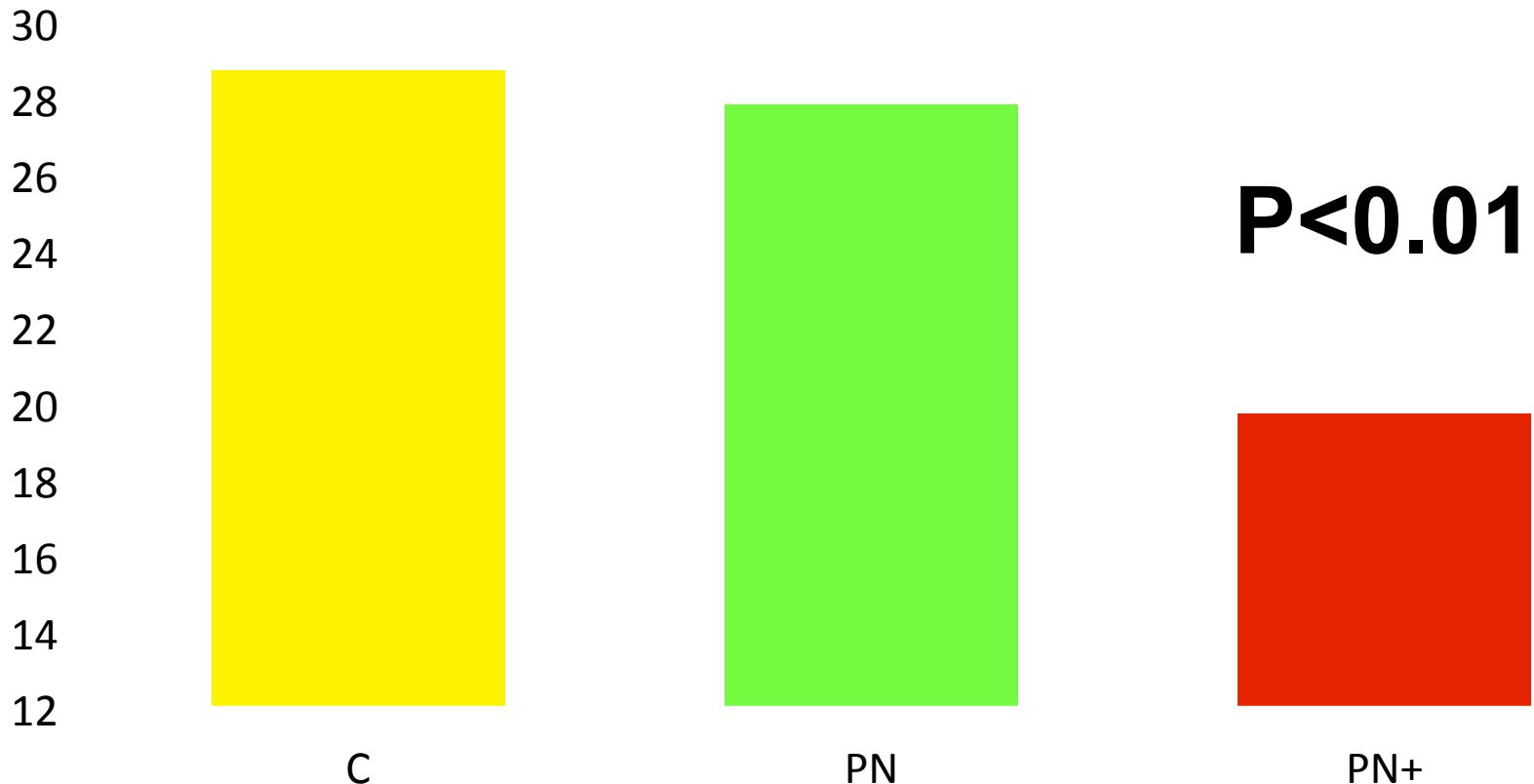


OR for Painful Diabetic Neuropathy:

Vit D deficiency (<20ng/ml): 9.8 (95% CI 2.2-76.4), P<0.003

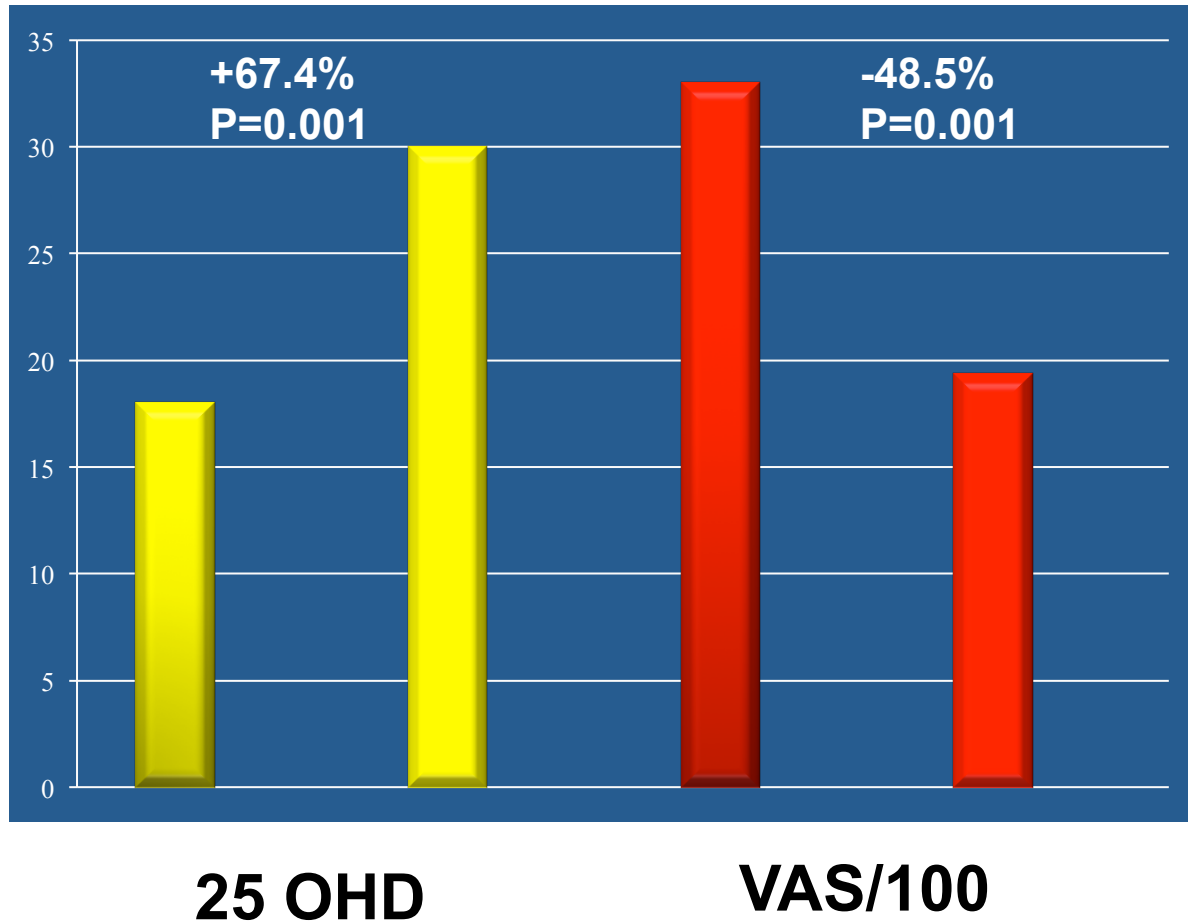
Vitamin D insufficiency (<30ng/ml): 4.4 (95% CI 1.1-19.8), P=0.03

25(OH)D



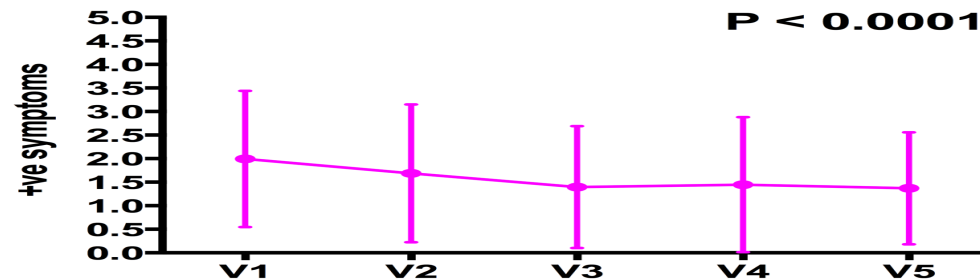
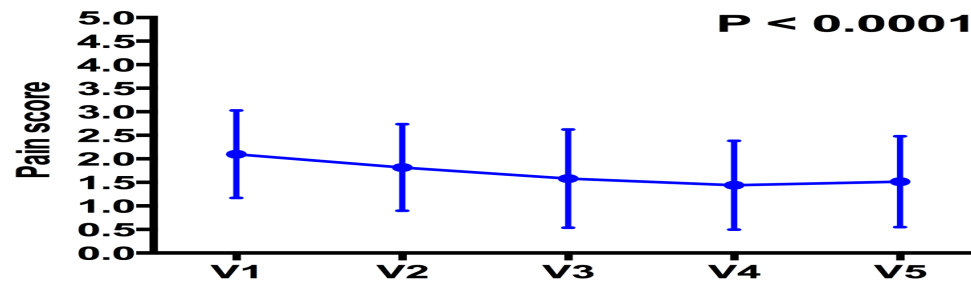
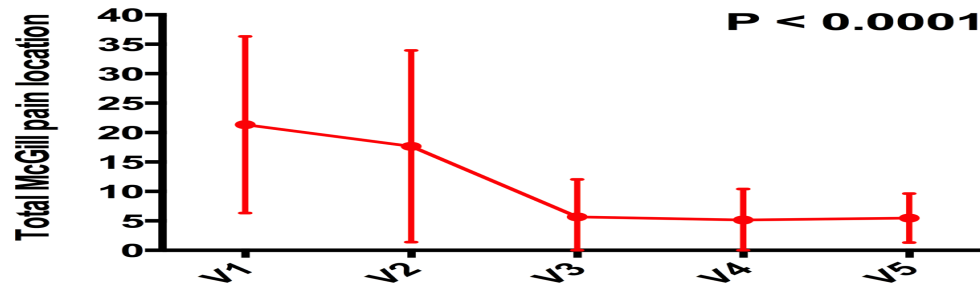
Oral Vit D

D3 2000U daily for 3 months



IM Vitamin D

D3 600,000 IU IM: FU 20 weeks



Vitamin D protocol

Target to minimize symptoms, metabolic, cardiovascular and cancer risk: 60-100ng/ml.

25 OHD

<20ng/ml: Severely Vit D deficient
20-40 ng/ml: Moderately Vit D deficient
40-60 ng/ml: Vit D deficient

Loading dose

Colecalciferol (vitamin D₃): 40,000 IU daily for 14 days (560,000 IU).

Maintenance

Colecalciferol (vitamin D₃): 20-40,000 IU once weekly.

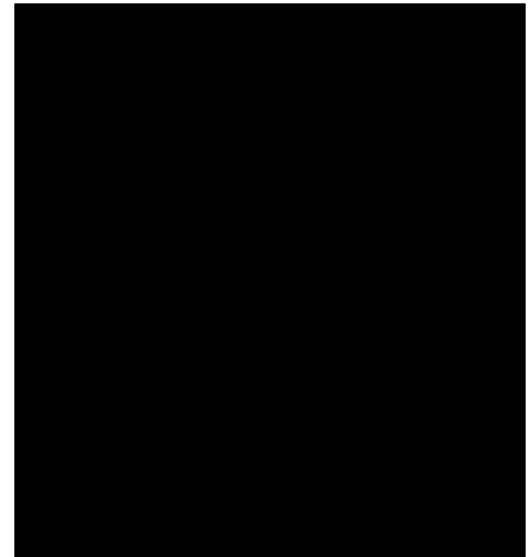
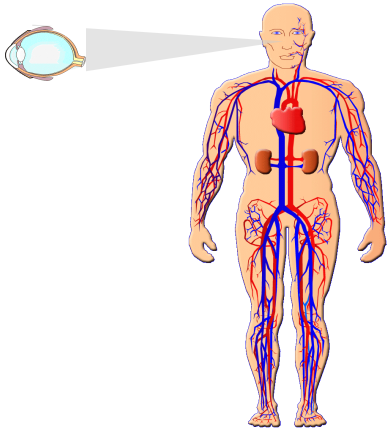
Repeat vitamin D & calcium after 3 months

If <50ng/ml

If 60-100 ng/ml

Note: Threshold for Vit D toxicity 40000-100000U daily for ~8 weeks (2.5-4 M IU)

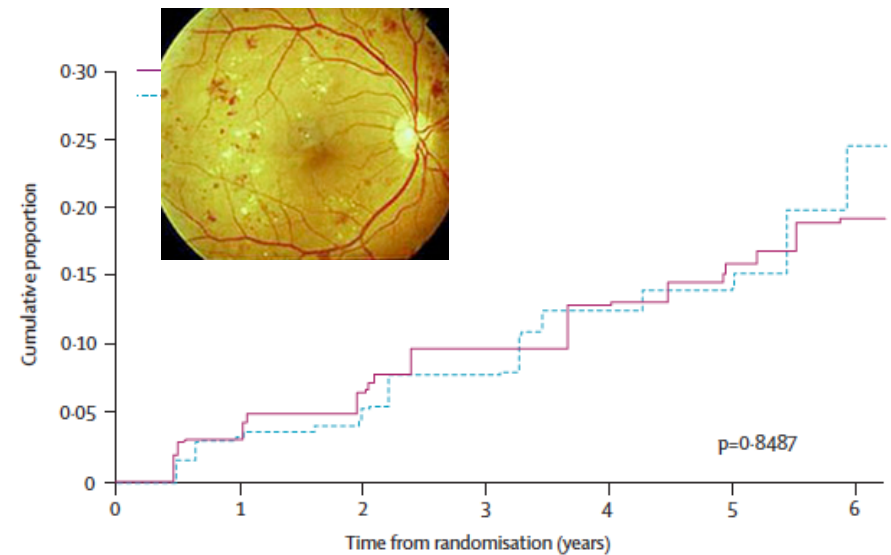
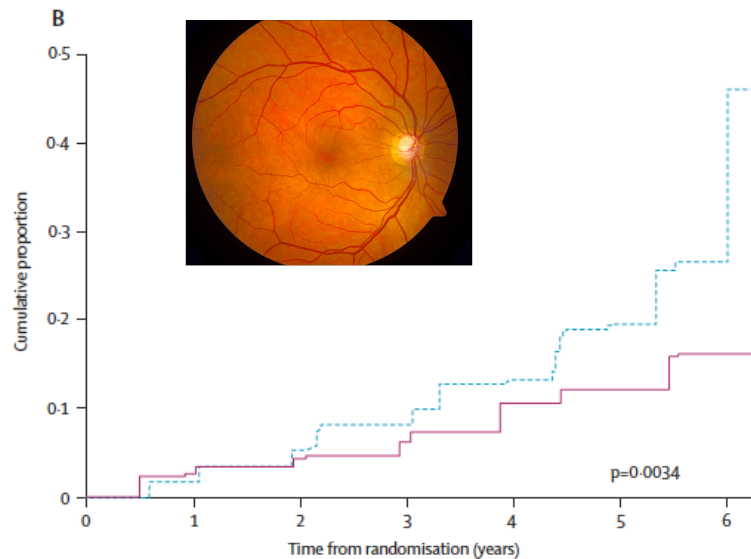
Diabetic Retinopathy



Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

1421 T1DM Candesartan 16mg v placebo over 5 years

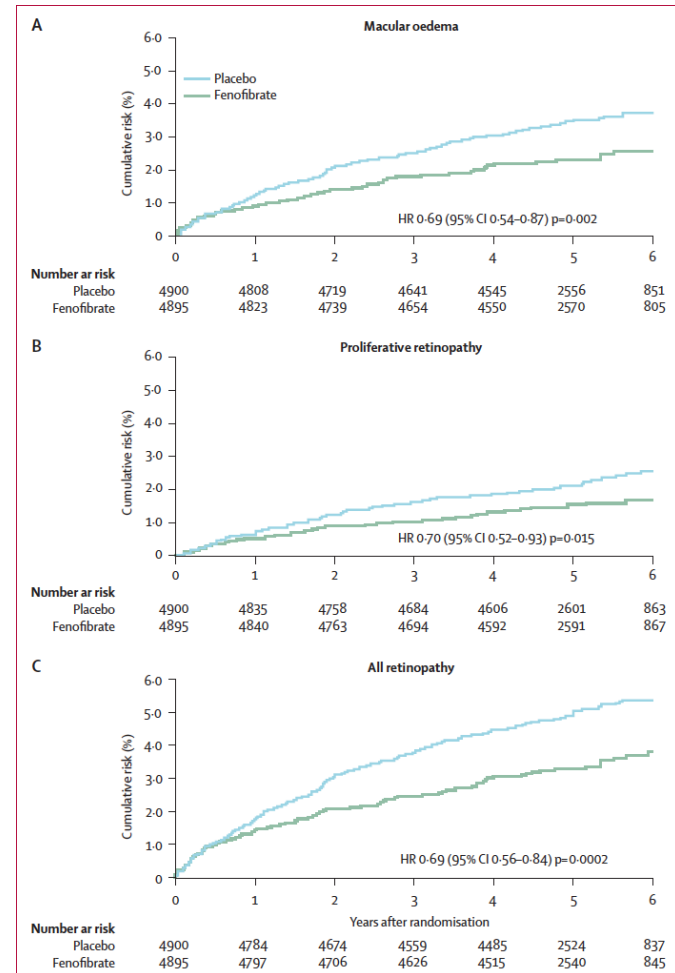
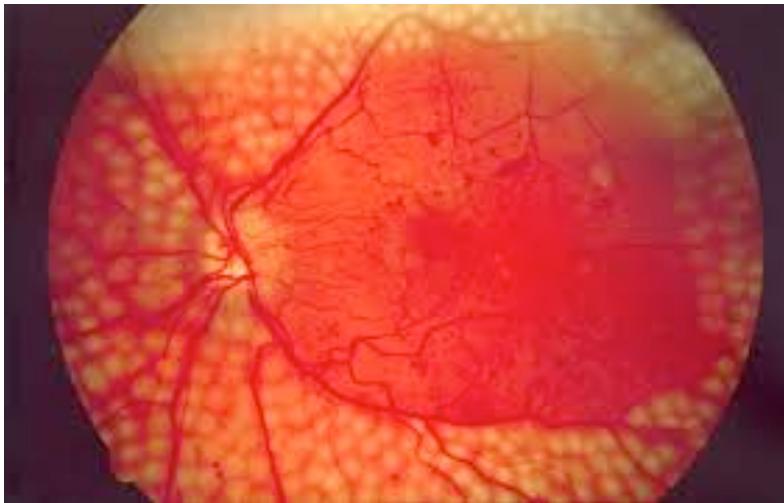
	DIRECT-Prevent 1		DIRECT-Protect 1	
	Candesartan (N=711)	Placebo (N=710)	Candesartan (N=951)	Placebo (N=954)
Men	413 (58%)	392 (55%)	538 (57%)	553 (58%)
Age (years)	29.6 (8.0)	29.9 (8.1)	31.5 (8.5)	31.9 (8.5)
Diabetes duration (years)	6.6 (3.9)	6.8 (3.9)	10.9 (4.3)	11.0 (4.3)
Caucasian	690 (97%)	685 (97%)	928 (98%)	943 (99%)
HbA _{1c} (%)	8.0 (1.7)	8.2 (1.7)	8.5 (1.6)	8.5 (1.6)
Systolic blood pressure (mm Hg)	116 (9.5)	116 (9.6)	117 (9.6)	117 (9.8)
Diastolic blood pressure (mm Hg)	72 (6.9)	72 (7.3)	74 (6.5)	73 (6.9)



Chaturvedi et al Lancet 2008; 372: 1394-402

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

9795 T2DM Fenofibrate 200mg v placebo over 5 years

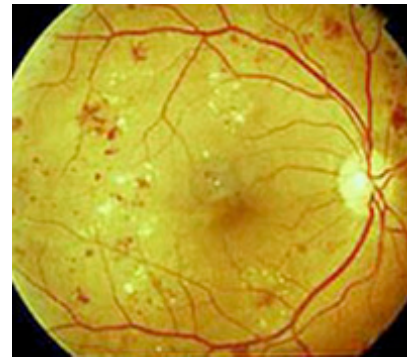


Keech et al Lancet 2007; 370: 1687-97

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group* N=2856, 4 years

3-step progression on ETDRS or Laser photocoagulation or Vitrectomy



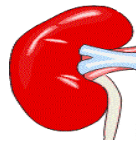
Treatment			Progression of Diabetic Retinopathy <i>no./total no. (%)</i>	Adjusted Odds Ratio (95% CI)	P Value
Glycemia therapy				0.67 (0.51–0.87)	0.003
Intensive	<6%		104/1429 (7.3)		
Standard	7-7.9%		149/1427 (10.4)		
Dyslipidemia therapy†				0.60 (0.42–0.87)	0.006
With fenofibrate			52/806 (6.5)		
With placebo			80/787 (10.2)		
Antihypertensive therapy				1.23 (0.84–1.79)	0.29
Intensive	<120		67/647 (10.4)		
Standard	<140		54/616 (8.8)		

Diabetic Nephropathy

α -blocker

B-blockers

Central



Thiazide-D

Spironolactone

ACEi

Loop-D

CCB

ARB

Super doses-SMART trial

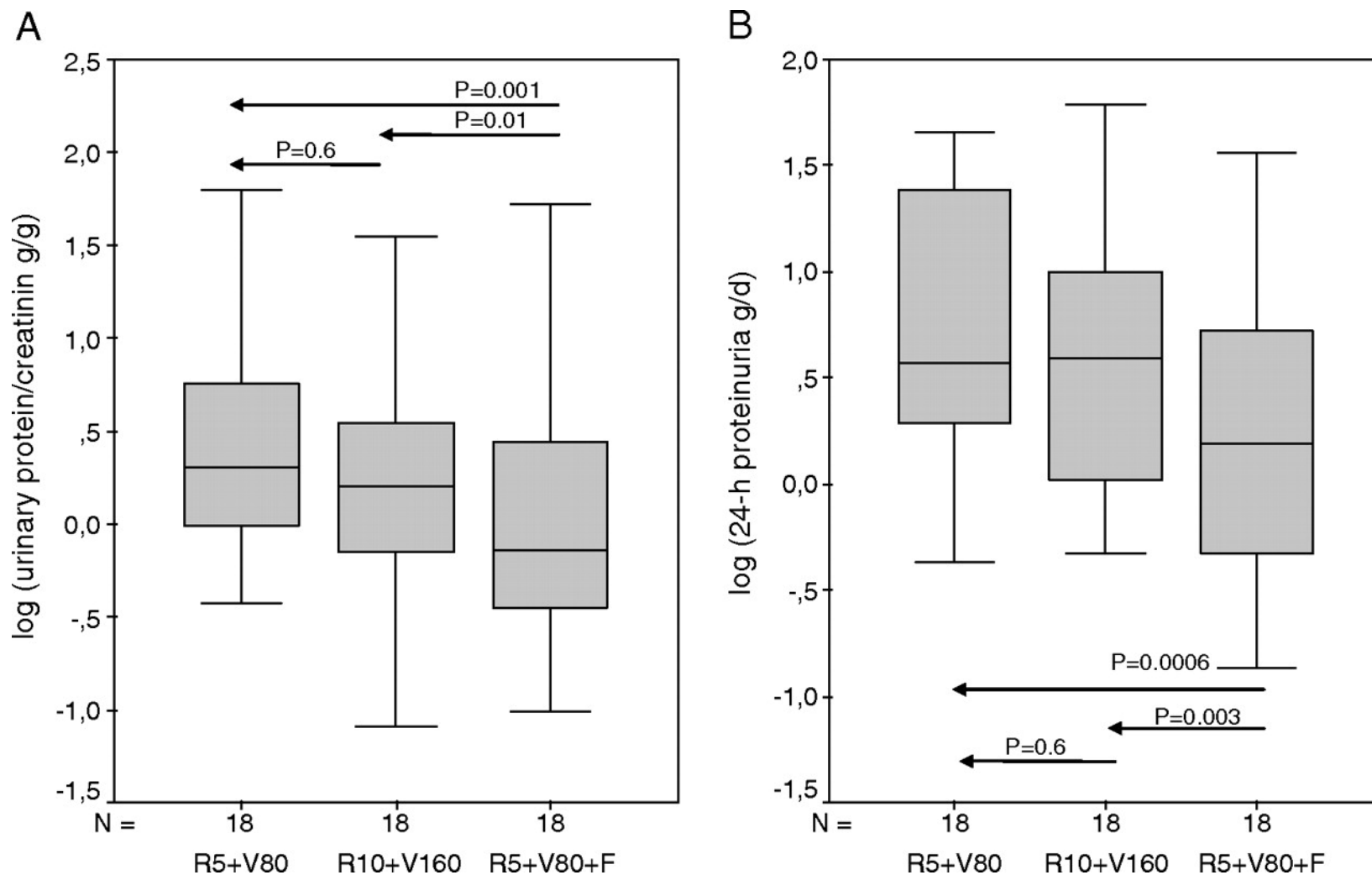
- 269 patients (53.9% diabetic nephropathy) with persistent proteinuria (1 g/d) despite 7 wk of treatment with Candesartan (16 mg/d).
- Randomized to: 16, 64, or 128 mg/d Candesartan for 30 wk.
- Median urinary protein excretion 2.66 g/d.
- Proteinuria: 16 mg/d (-17.1%), 64mg (-33.1%) $P < 0.0001$.
- 128 mg (-45.7%).
- BP no different across 3 treatment groups.
- Elevated serum potassium levels ($K^+ > 5.5$ mEq/L) led to withdrawal of 11 patients.

Burgess E et al. J Am Soc Nephrol. 2009; 20: 893–900.

What Next

- Despite adequate BP control.
- Proteinuria continues

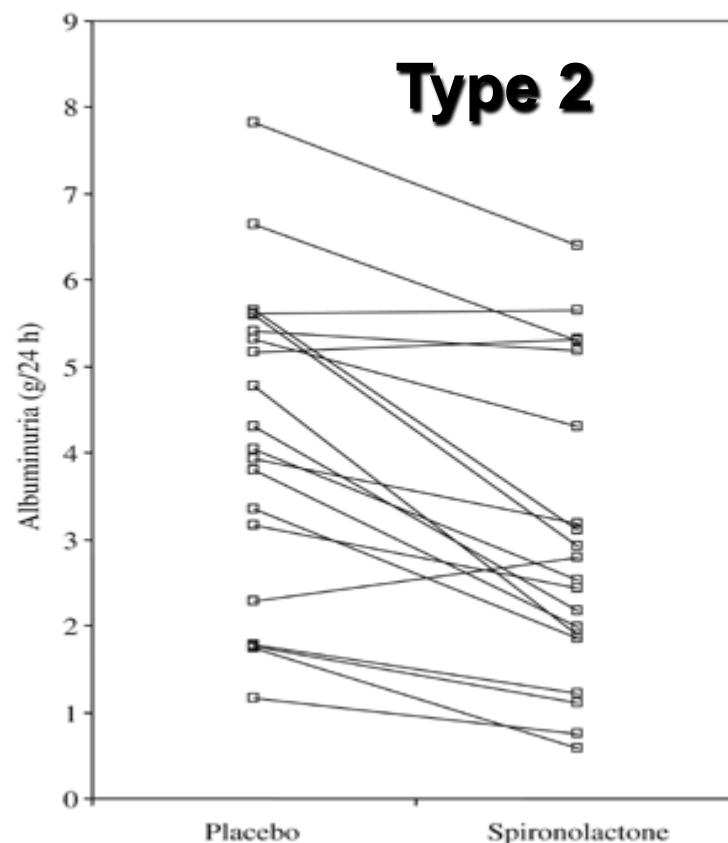
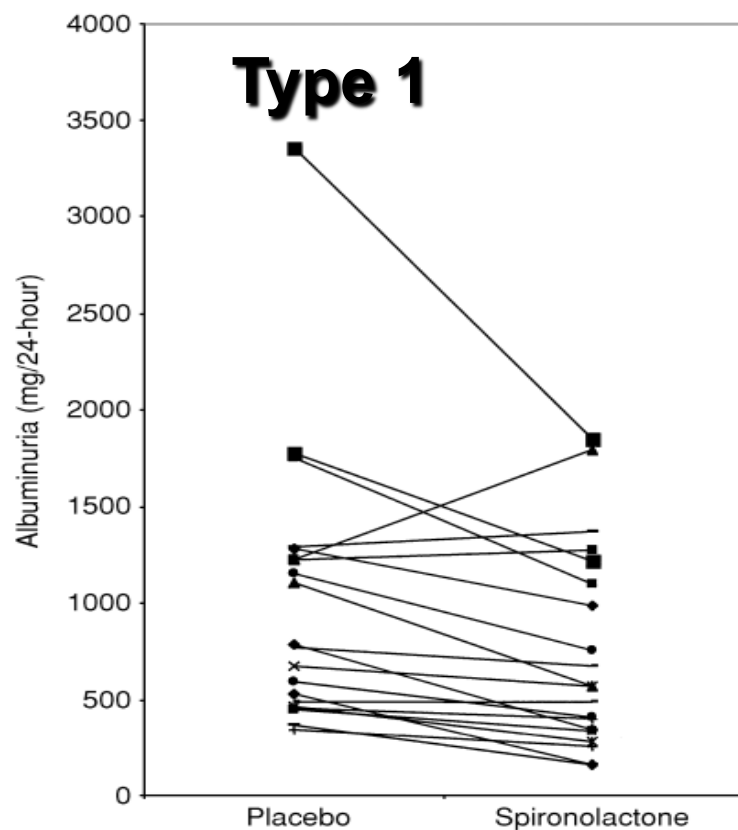
Frusemide 80mg



What Next

- Despite adequate BP control.
- Proteinuria continues

Spironolactone



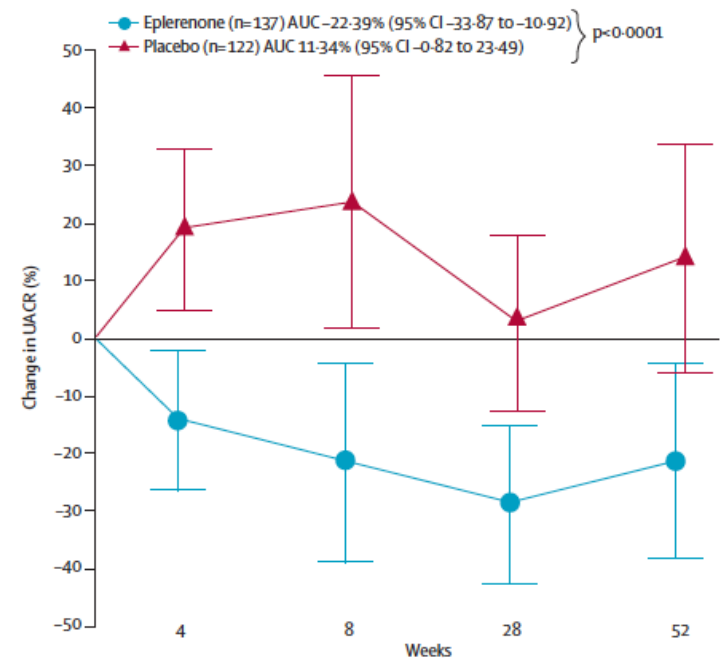
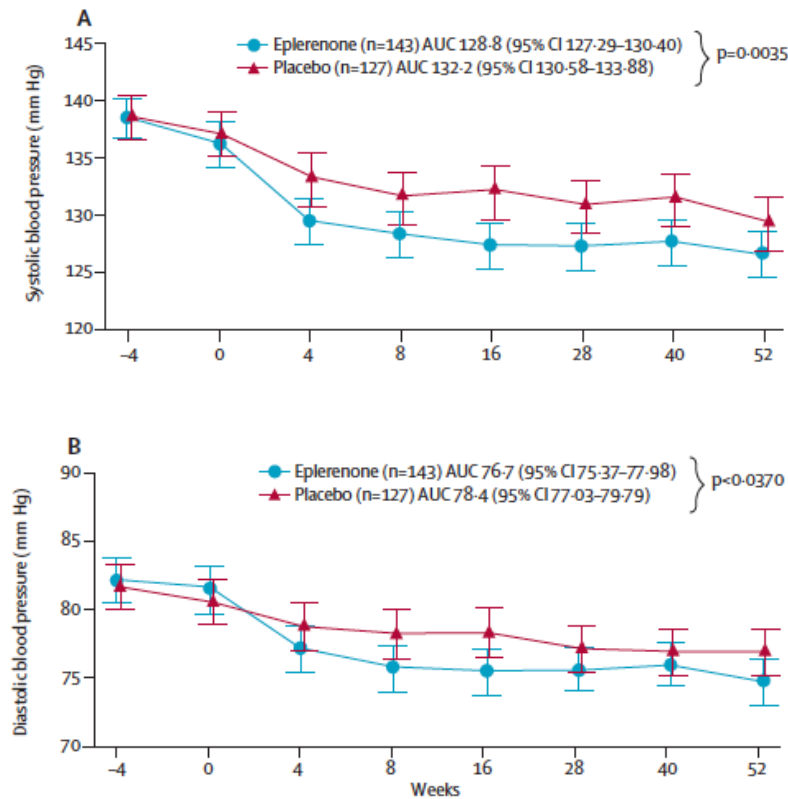
Overall further reduction UAER 30%.

Schjoedt et al. Kidney Int 2005; 68: 2829-2836

Type 2-Rossing et al. Diabetes Care. 2005;28:2106-12

Type 1 + Type 2 Schjoedt et al. Kidney Int June 2006; 1-7

Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial

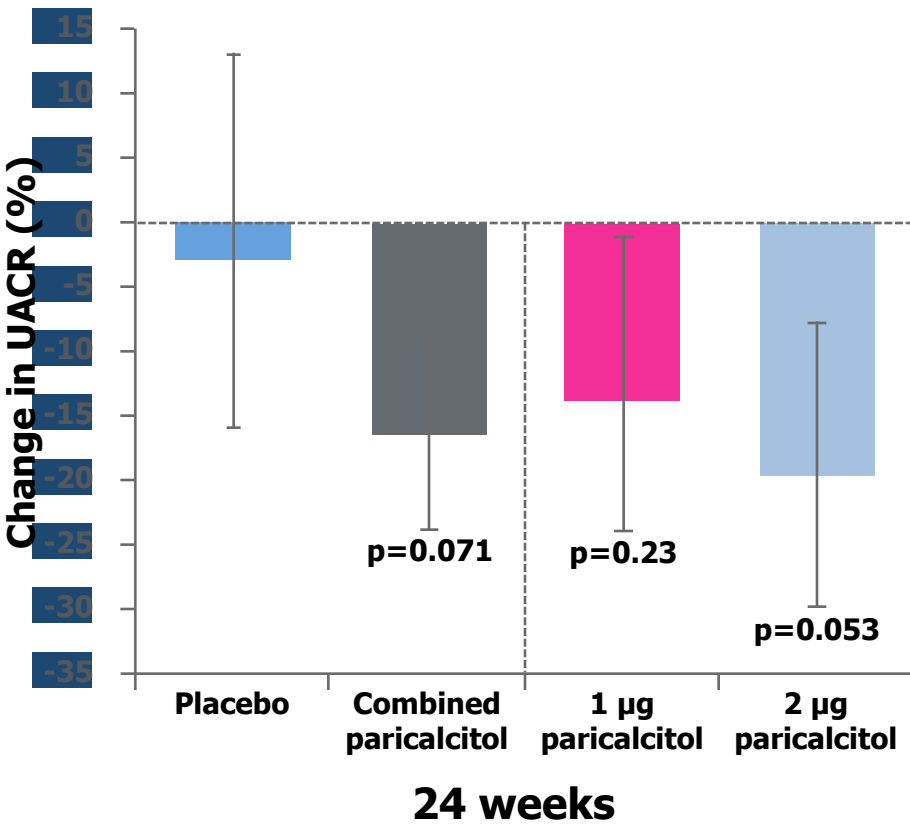


What Next

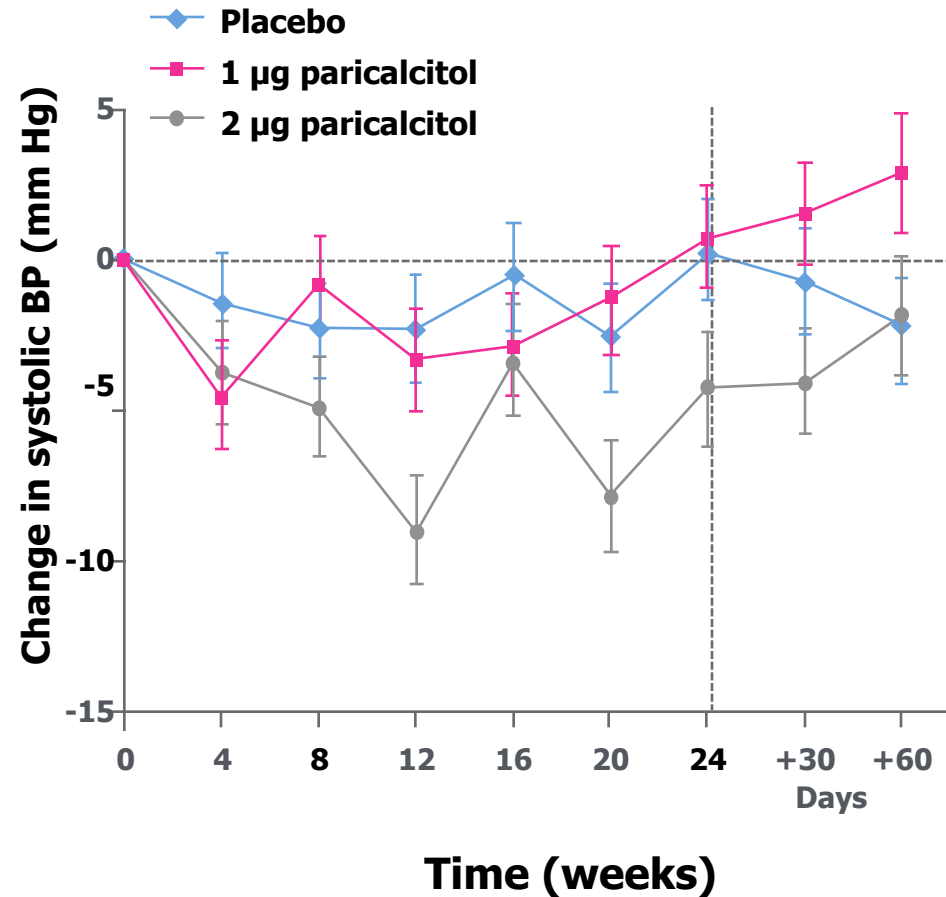
- Despite adequate BP control.
- Proteinuria continues

VITAL study

Change in UACR* from baseline to the last measurement during treatment



Change in systolic blood pressure during treatment and withdrawal



Novel Therapies

Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

**Endogenous Nrf2 activator which upregulates multiple
Antioxidant/Antiinflammtory genes**

Variable	Placebo (N= 57)	Bardoxolone Methyl		
		25 mg (N= 57)	75 mg (N= 57)	150 mg (N= 56)
Blood pressure — mm Hg				
Systolic	130.5±13.5	129.5±12.6	130.2±13.2	130.5±11.8
Diastolic	67.3±9.0	68.7±8.3	69.7±8.1	68.6±8.7
Glycated hemoglobin — %	7.2±1.2	7.2±0.9	7.3±1.0	7.1±1.1
Medications — no. (%)				
ACE inhibitor, ARB, or both	57 (100)	55 (96)	57 (100)	54 (96)
Statin	45 (79)	46 (81)	49 (86)	49 (88)
Calcium-channel blocker	35 (61)	31 (54)	34 (60)	31 (55)
Diuretic agent	51 (89)	48 (84)	47 (82)	51 (91)
Antidiabetic drug	54 (95)	56 (98)	56 (98)	54 (96)
Laboratory results				
Estimated GFR — ml/min/1.73 m ²	31.2±6.3	32.9±7.0	33.0±6.6	32.3±7.6

Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes



in the placebo group. muscle spasms, which were

Thank you



P Kallinikos
C Quattrini
M Tavakoli
H Fadavi
M Dabbah
M Mojaddidi
A Al-Sunni
U Alam
I Petropoulos
O Asghar
G Ponirakis
S Ahmed
X Chen
M Ferdousi
S Azmi

JD Ward
AJM Boulton
PK Thomas
AK Sharma
S Tesfaye
A Veves
G Rayman
G Sundkvist
N Efron
M Jeziorska
J Graham

<http://qatar-weill.cornell.edu>

<http://www.medicine.manchester.ac.uk/ena/>