"There are, in truth, no specialties in medicine, since to know fully many of the most important diseases a man must be familiar with their manifestations in many organs."

William Osler 1894.

Diabetic Nephropathy

- **Objectives**:

- Recognise the importance of detection of Diabetic nephropathy.

- Screening for Diabetic nephropathy.

- Know how to manage patients with diabetic nephropathy as an integral part of their diabetic management.

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Mrs M

- 29 years of age
  - Abnormal vision, tired
  - Nocturia, weight loss, thrush
- Past history
  - Polycystic ovarian syndrome
- BMI 29
- Investigations
  - Random glucose 16.9 mmol/L
  - C-Peptide 1040pmol/L
  - GAD Abs negative
  - HBA1c 12%
  - Creatinine 79umol/L
  - UACR 220 mg/mmol
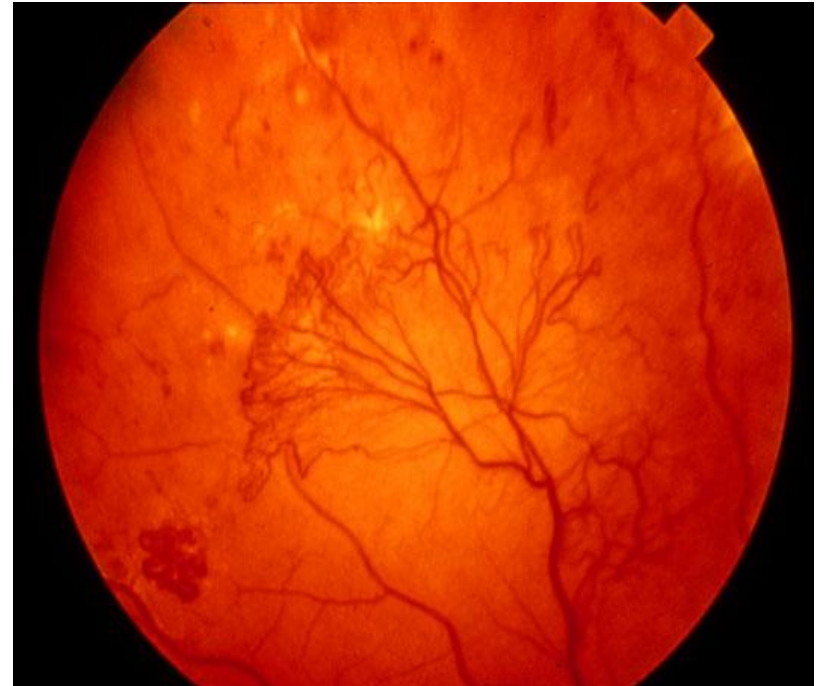
Mrs M – clinical questions

- Does she have Type 1 or Type 2 diabetes?
- What is her expected tracjectory to end stage kidney disease?
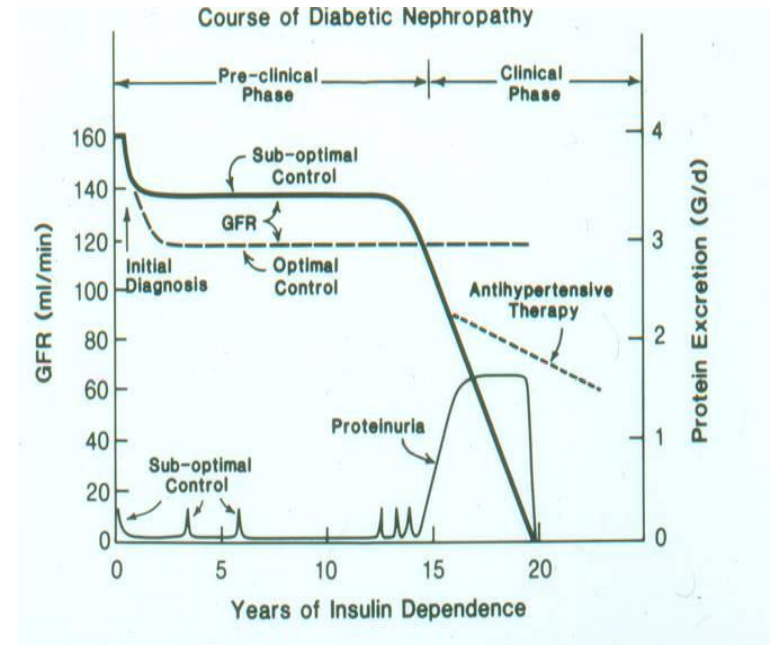- Can we modify this?

Exclude Non-Diabetic Kidney Disease

- Rapid deterioration in renal function
- Sudden develoment of nephrotic syndrome
- Persistent haematuria
- Absence of diabetic retinopathy
- Short duration of Type 1 diabetes
- Known other systemic disorder

Time-course for Diabetic Nephropathy

Progression of Renal Disease in Patients with Type I Diabetes

Stage	Characteristics	Onset	% Progressing to Next Stage
1	Early Hypertrophy and Hyperfiltration	Onset of Diabetes	100
2	Renal Lesions No Clinical Signs	2-3 Years	35-40
3	Incipient Nephropathy	7-15 Years	80-100
4	Overt Nephropathy	10-30 Years	75-100
5	End-Stage Renal Disease	20-40 Years	–

Adapted from Mogensen CE et al., Diabetes 1983;32(suppl 2):64-78.
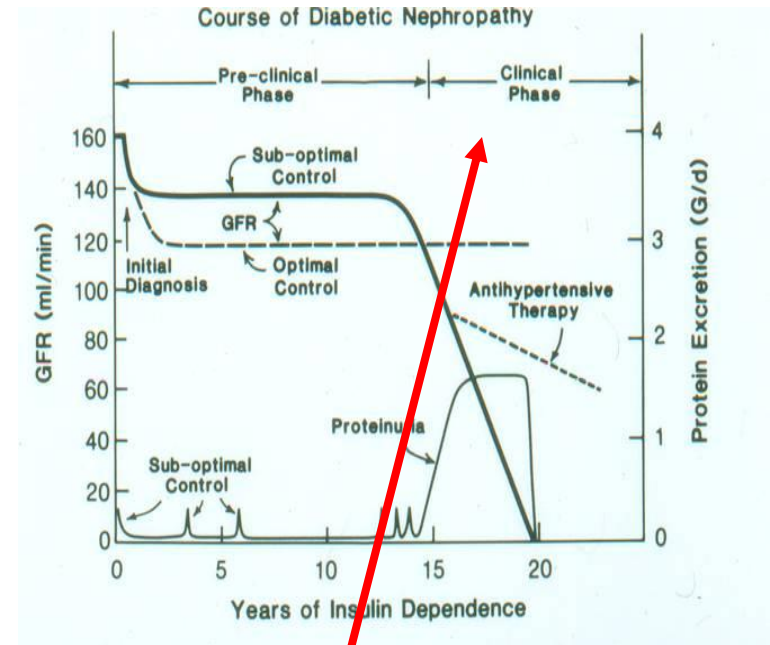

Course of Diabetic Nephropathy

Morgensen CE et al Diabetes 1983; 32 (suppl 2): 64-78

Time-course for Diabetic Nephropathy

Progression of Renal Disease in Patients with Type I Diabetes

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Adapted from Mogensen CE et al., Diabetes 1983;32(suppl 2):64-78.

Course of Diabetic Nephropathy

> 50% Type 2 DM will have proteinuria at time of diagnosis.

Parving et al. BMJ 1988; 296: 156-60
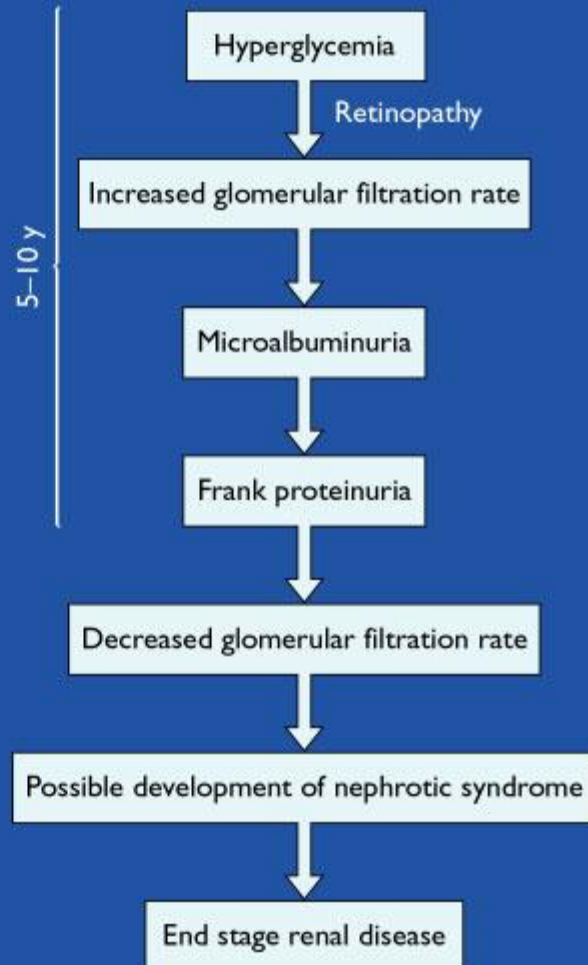
Risk of ESRD in type 2 diabetes

- Urine alb:creatinine HR 6.2 (4.4 –8.7)
- Serum creatinine. HR 2.1 (1.7 – 2.5)
- Serum albumin. HR 0.7 (0.61 – 0.8)
- Hemoglobin. HR 0.89 (0.84 – 0.95)
- Proteinuria most important risk for progressive kidney damage in type 2 diabetic nephropathy
- Proteinuria also marker of cardiovascular outcome.

RENNAL Study. 2003.

Microalbuminuria

- Type 1 Diabetes
  - Prevalence 12%
  - 40-50% by 30 years
  - Can be seen in first 5 years
  - Incidence 2% per year
  - Risk for progression:
    - High normal UACR
    - Poor glycaemic control
    - Increased BP
    - Presence of retinopathy

- Type 2 Diabetes
  - Prevalence 10-50% depending on population studied
  - Higher in Maori and PI Indigenous populations
  - Incidence 2-4% per year
  - 1/3 progress to clinical nephropathy over 5 years
  - Cholesterol also a risk factor for progression

Screening

- Microalbuminuria
  - False positive results: infection, exercise, DKA, poor glycaemic control, uncontrolled hypertension, obesity
  - 2 positive results several months apart
  - Urine albumin : creatinine ratio most convenient
  - Early morning least variability.

Definitions

Category	Albumin:creatinine ratio (mg/mmol)	24-h collection (mg/24 h)	Timed collection (µg/min)
Normal	M:<2.5 F:<3	<30	<20
Micro-albuminuria	M: 2.5-20 F: 3-30	30–299	20–199
Clinical albuminuria	M: >20 F: >30	>300	>200

Diabetic Nephropathy. Management issues.

- Target Blood Pressure?

- Drugs of choice?

- Does glycaemic control influence outcome?

- How long until renal replacement management required?

Management

- Diet, exercise
- Medication - blood pressure control, lipids
- Other risk factors?
- What will influence progression?
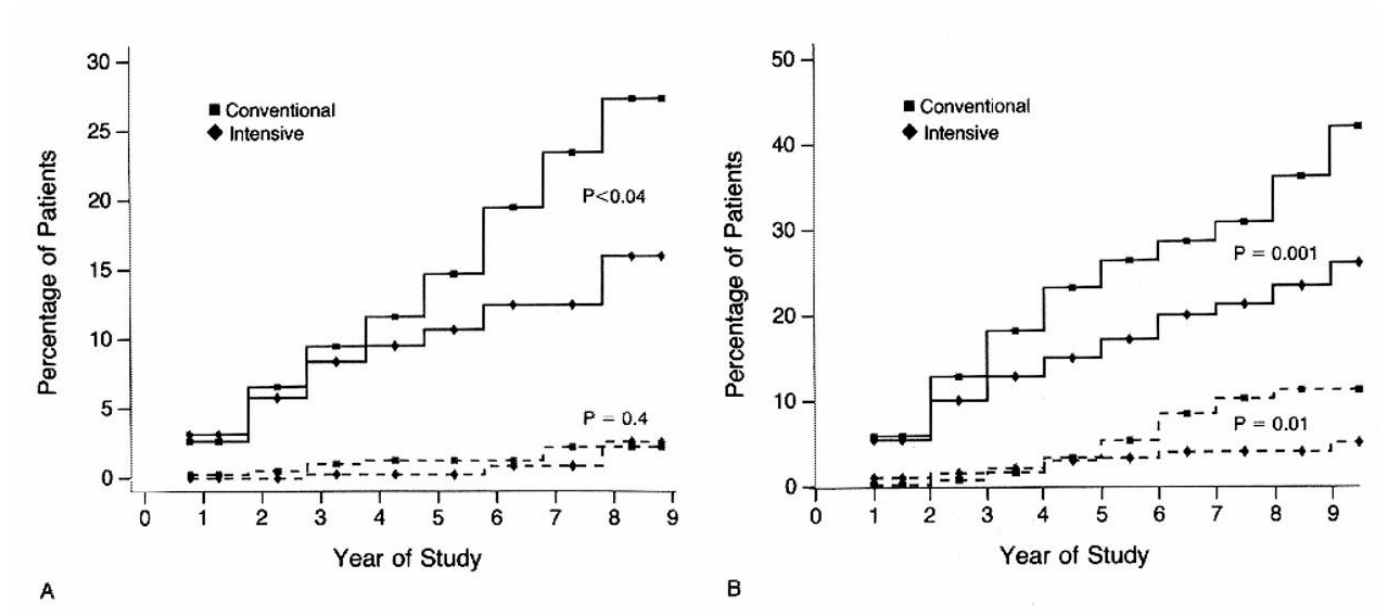- What are your markers for progression?
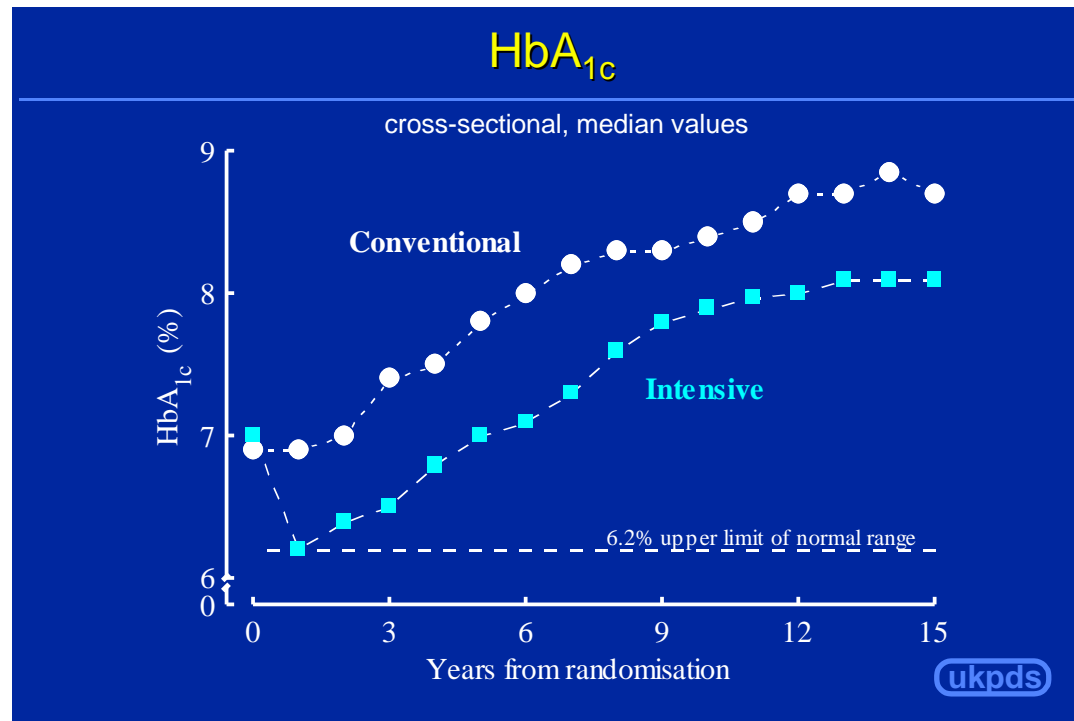
Management of Microalbuminuria

- Does glycaemic control reduce progression?
- Does blood pressure control reduce progression?
- Do ACEI's have additional renoprotective effects?
- Are any other interventions effective?

Management of Microalbuminuria

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Cumulative Incidence of Urinary Albumin Excretion [>=] 300 mg per 24 Hours (Dashed Line) and [>=] 40 mg per 24 Hours (Solid Line) in Patients with IDDM Receiving Intensive or Conventional Therapy

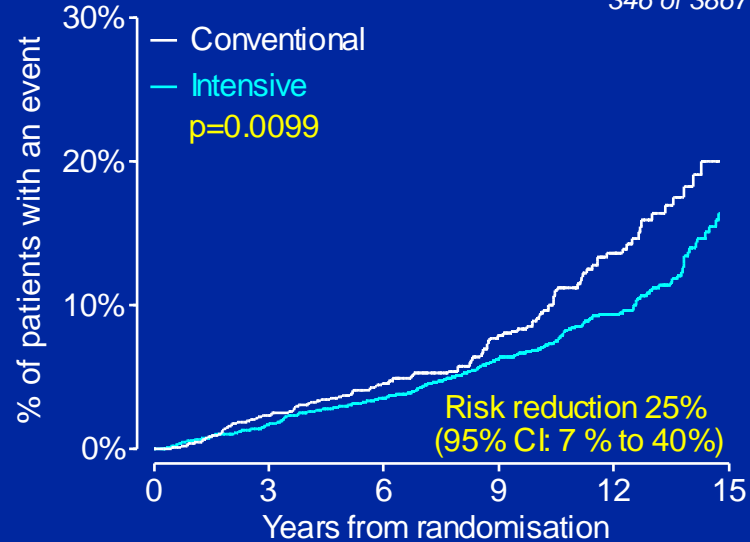**The Diabetes Control and Complications Trial Research Group, N Engl J Med 1993;329:977-986**

UKPDS 1

UKPDS 2

Microvascular Endpoints (cumulative)

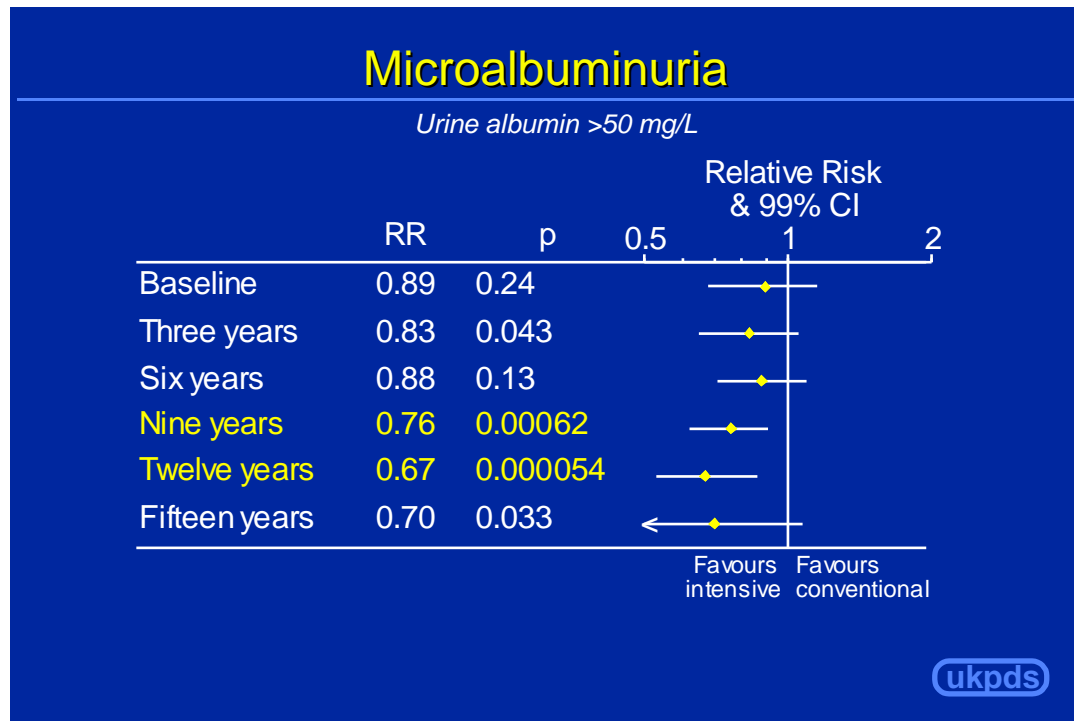*renal failure or death, vitreous haemorrhage or photocoagulation*
346 of 3867 patients (9%)

— Conventional
— Intensive
p=0.0099

Risk reduction 25%
(95% CI: 7 % to 40%)

% of patients with an event — 0%, 10%, 20%, 30%
Years from randomisation — 0, 3, 6, 9, 12, 15

ukpds

UKPDS 3

Mrs MH

- Commenced on Metformin

Date	HBA1c	UACR
July 09	12.1	22
August 09	11.3	8.5
Oct 09	9.1	-
May 10	5.9	11
Dec 10	6.3	4.0

Management of Microalbuminuria

- Does glycaemic control reduce progression?
- Does blood pressure control reduce progression?
- Do ACEI's have additional renoprotective effects?
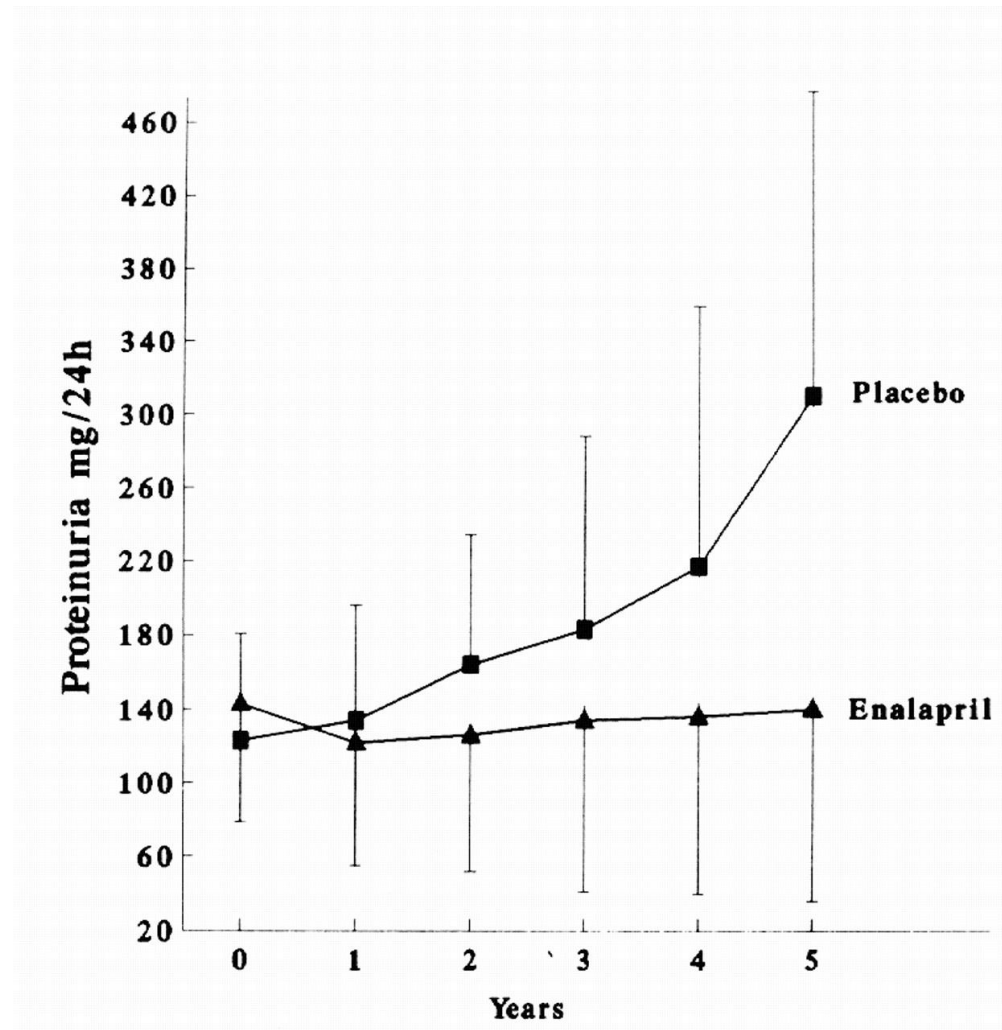- Are any other interventions effective?

UKPDS
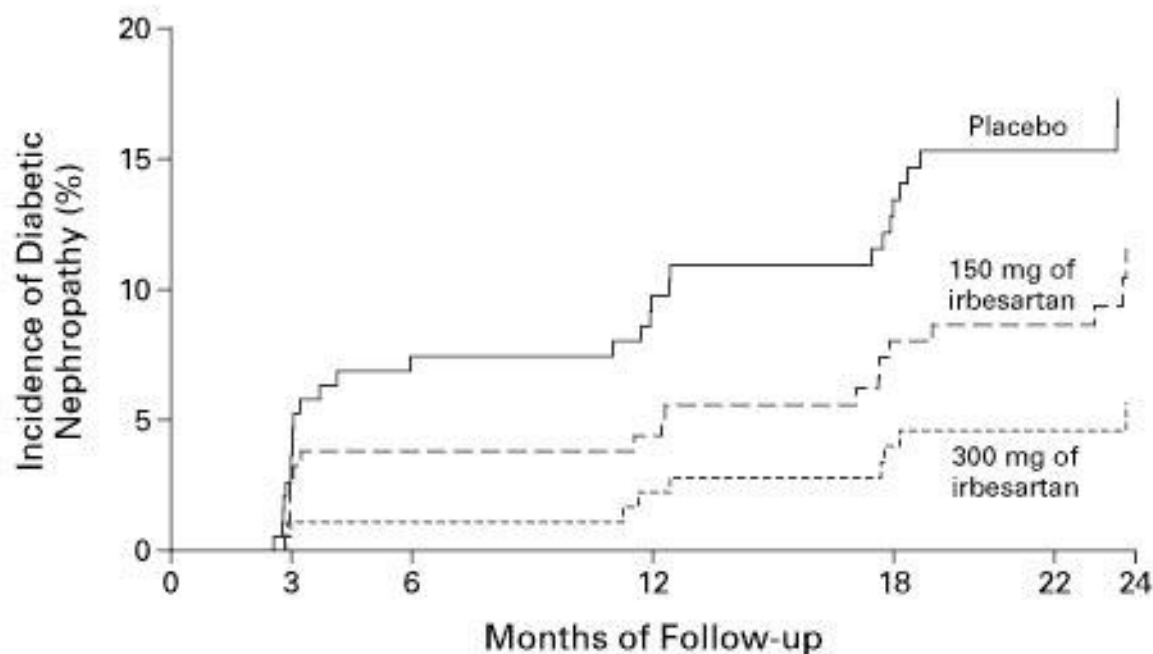
- No threshold for blood pressure
- The lower the better!
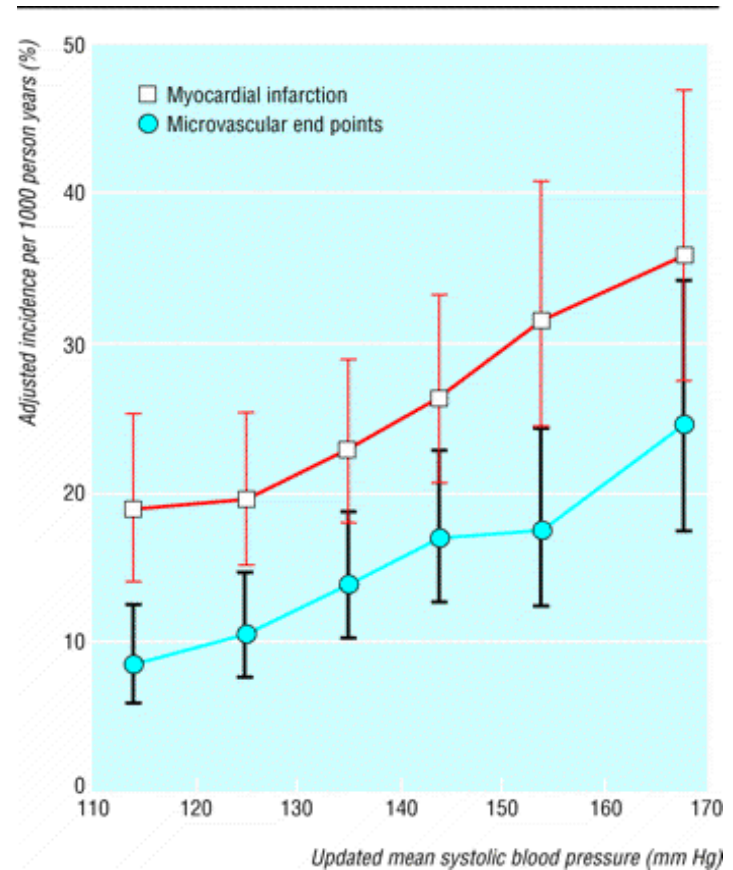
BMJ 1998;317;703-713

Proteinuria during 5-year follow-up in diabetics treated with enalapril or placebo

Parving, H.-H. et al. N Engl J Med 2001;345:870-878

Studies of treatment effect (angiotensin-converting enzyme [ACE] inhibitor and angiotensin II receptor blocker [ARB] trials) on regression to normoalbuminuria, compared with fixed-effects and random-effects models
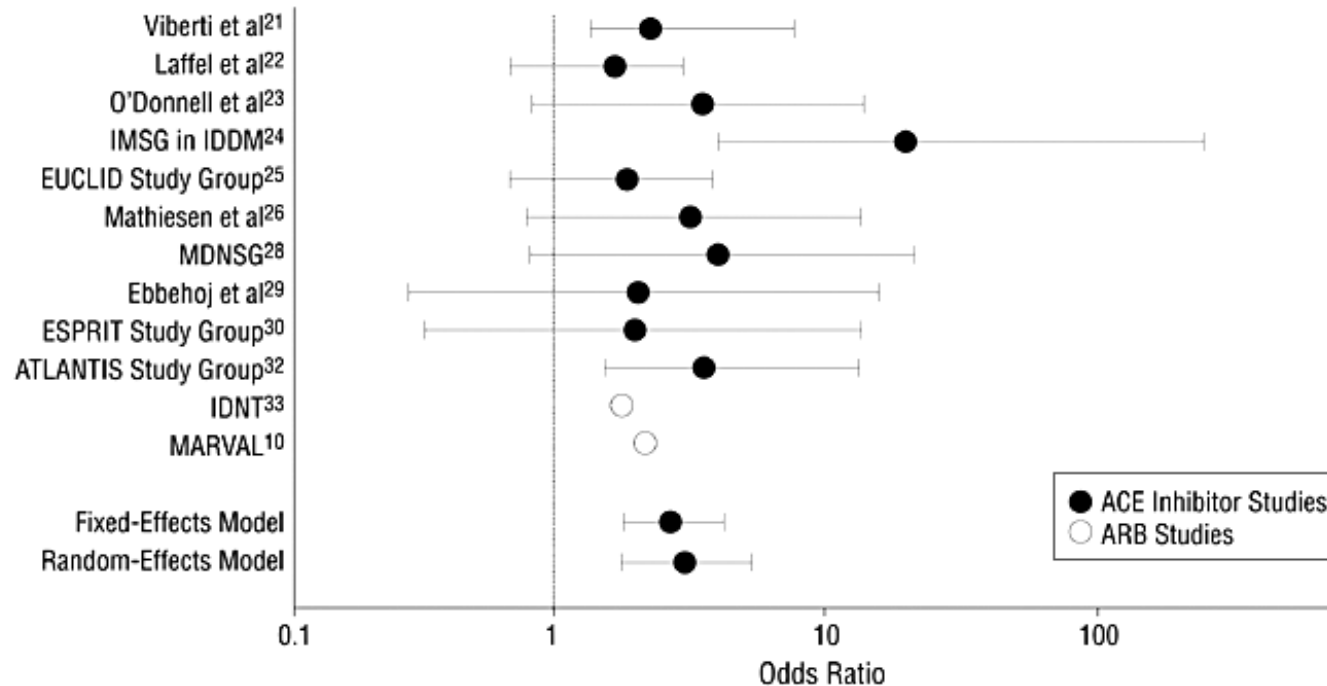
Hollenberg, N. K. Arch Intern Med 2004;164:125-130.

ARCHIVES OF
INTERNAL MEDICINE

Studies of treatment effect (angiotensin-converting enzyme [ACE] inhibitor and angiotensin II receptor blocker [ARB] trials) on risk of progression to macroalbuminuria, compared with fixed-effects and random-effects models
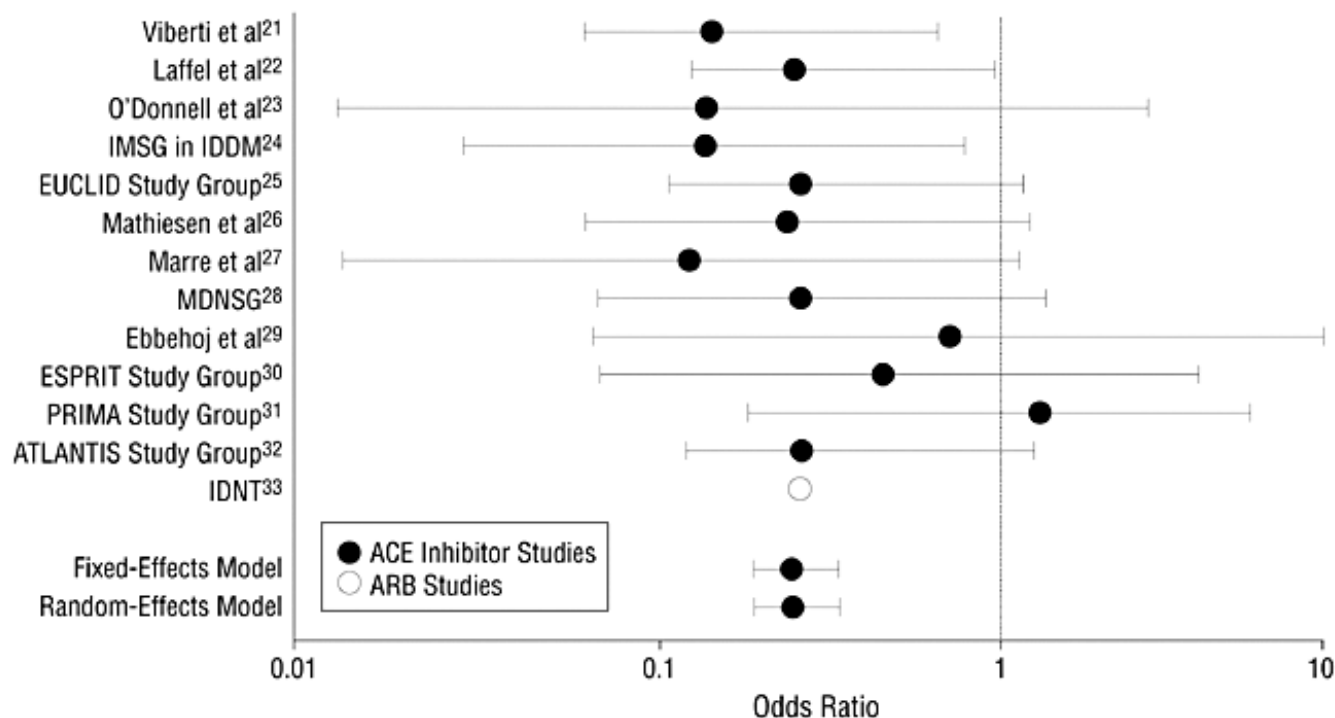
Hollenberg, N. K. Arch Intern Med 2004;164:125-130.

Interventions to slow progression of Clinical Nephropathy -1

- A2RB
  - Irbesartan
  - Losartan
- Increase time to doubling of creatinine
- Increase time to ESRF
- Effect over and above effect on blood pressure
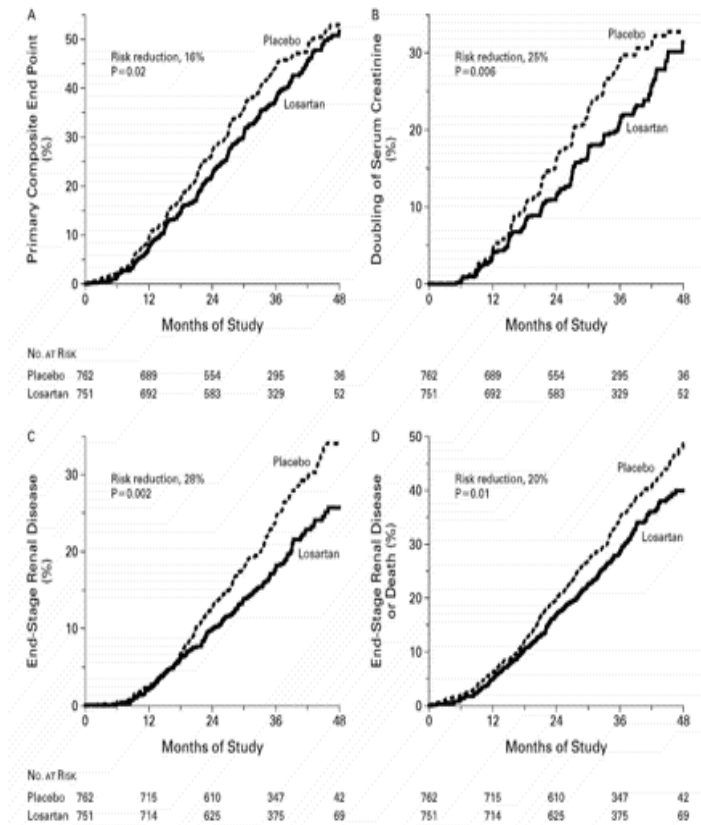
Prediction of Response to Therapy?

- Prospective studies have demonstrated the initial reduction in albuminuria (surrogate end point) predicted a beneficial long term effect on GFR decline (principal end point)

  (Rossing P. Diabetologia 1994, Breyer J. KI 1996)

Mrs MH

Date	Blood Pressure	Creatinine μmol/l	Medication
July 09	150/98	95	Cilazapril 2.5mg/day
October 09	140/96	115	Cilazapril 5mg/day
December 09	125/78	150 K+ = 5.6mmol/l	Cilazapril 5mg/day Candesartan 4mg

Do you stop the ACEI / ARB as renal function has declined?
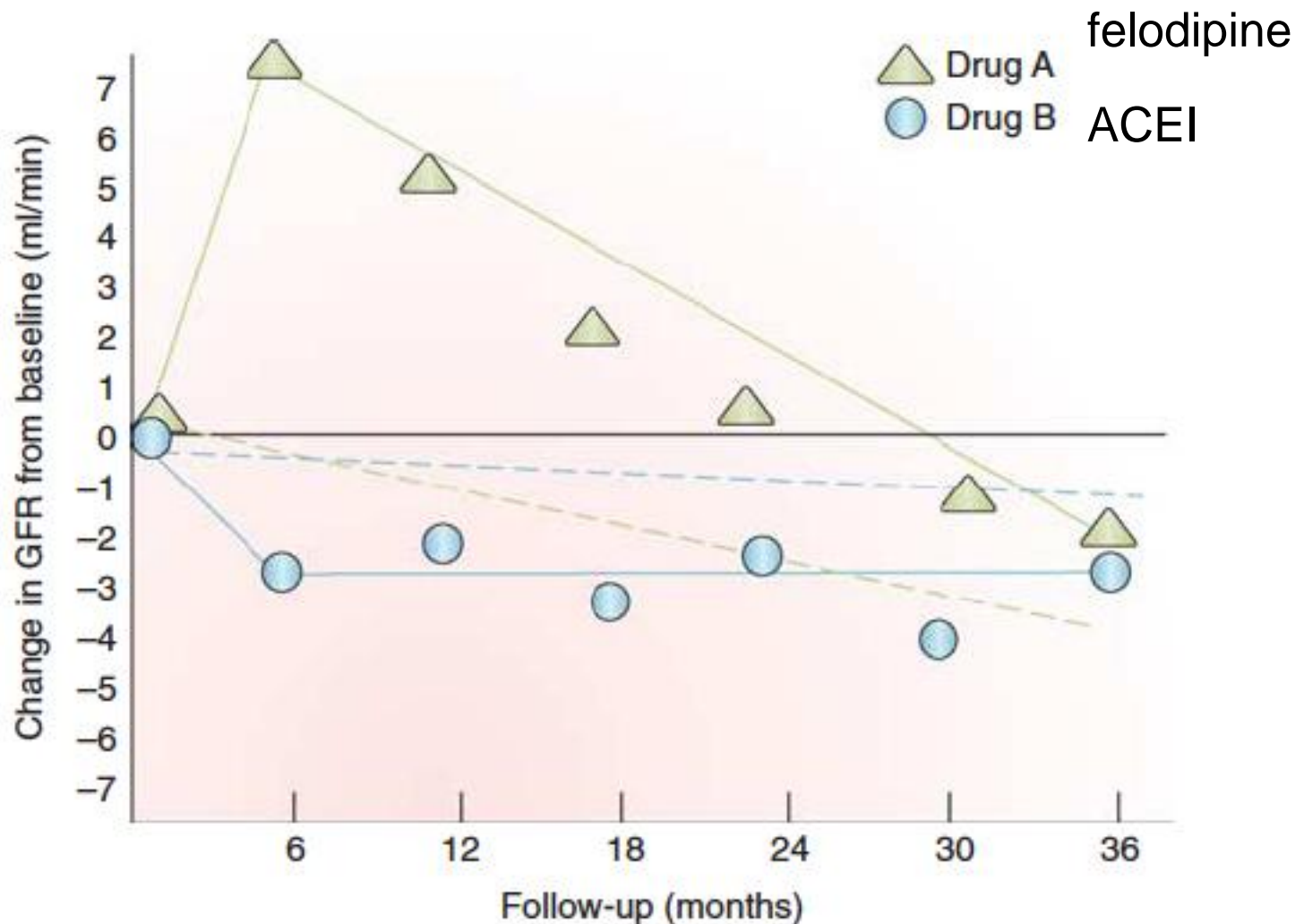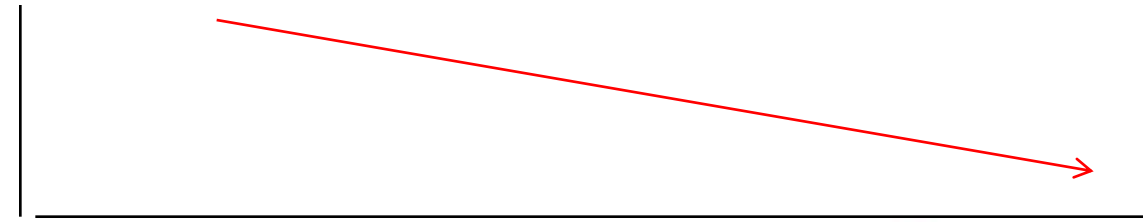
felodipine

ACEI

△ Drug A
○ Drug B

Figure 1 | Illustration of two different patterns of change in estimated GFR, calculated from baseline (solid line) versus 6 months (dashed line) for drug A (triangles) versus drug B (circles). GFR, glomerular filtration rate.

Weir M Kidney Int 2011; **80,** 235–237.

Δ GFR

$\downarrow$ AII
vasodilation

$\downarrow$ AII
vasodilation

SNGFR = Kf.NFP

Kf in
glomerulus

$P \propto 1/r^4$

Action of ACEI in
CKD
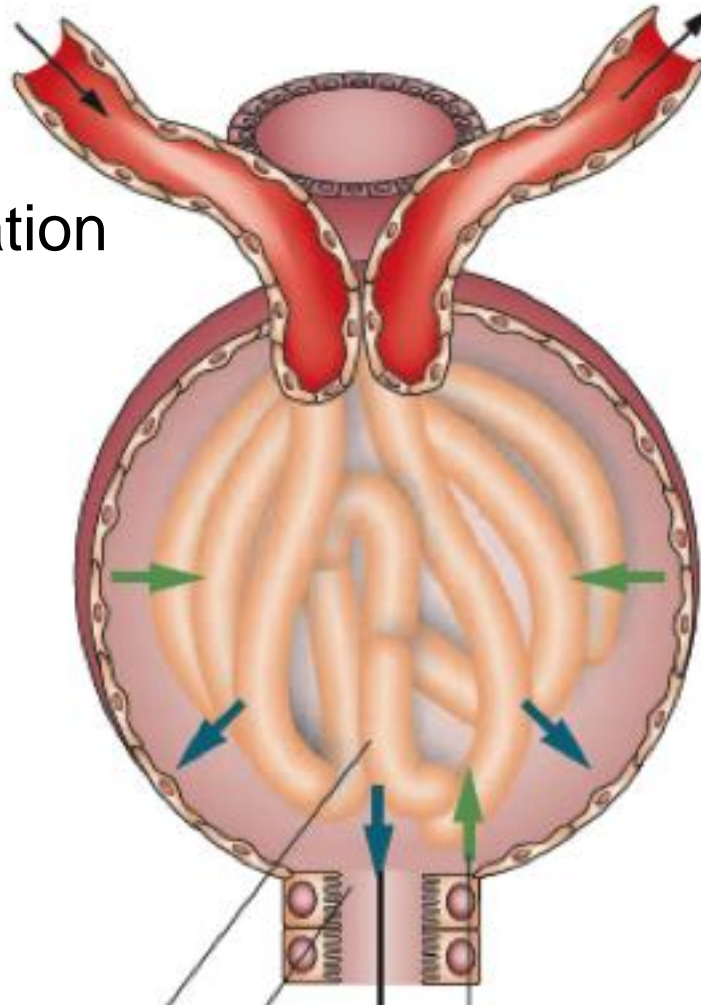
Mrs MH

- 2014
- Blood pressure – 130/80
- Wgt stable 88kg
- Creatinine 178umol/l, HB1Ac 6.8%, Cholesterol 4.5mmol/l, ACR 35
- Meds-Candersarten, cilazapril-hydrochlorthiazide, rosiglitazone, metformin. Simvastatin aspirin.

Slowing the Progression of Diabetic Nephropathy

High-risk patients with diabetic nephropathy

Seen in a specialist Diabetologist /Nephrologist combined clinic

High patients defined as
significant proteinuria,
hypertension,
a progressive rise in plasma creatinine or
diabetic complications.

Slowing the Progression of Diabetic Nephropathy

Follow up was defined as at least two data sets (over 12 months) prior to referral, and at least 18 months of follow up thereafter.

10 year audit.

Interventions

- Aggressive glycaemic control. HbA1c < 7

- Aggressive BP control < 130/80 anti-proteinuric therapy

- Lipid lowering therapy

- Endothelial protection

- "Fear factor" – nephrologist'

- HbA1c 7.3 (1.0)

- BP 132/70 (14/10)

- Alb/creat 112 (16)

- Chol. 4.01 (1.16)

Slowing the Progression of Diabetic Nephropathy

- At referral GFR decline -7.97 ml/min/year (95% CI 9.83 – 6.10) intervention -3.17 ml/min/year (95% CI 4.47 – 1.87)

- Estimated time to ESRF 6 yrs to 15 yrs
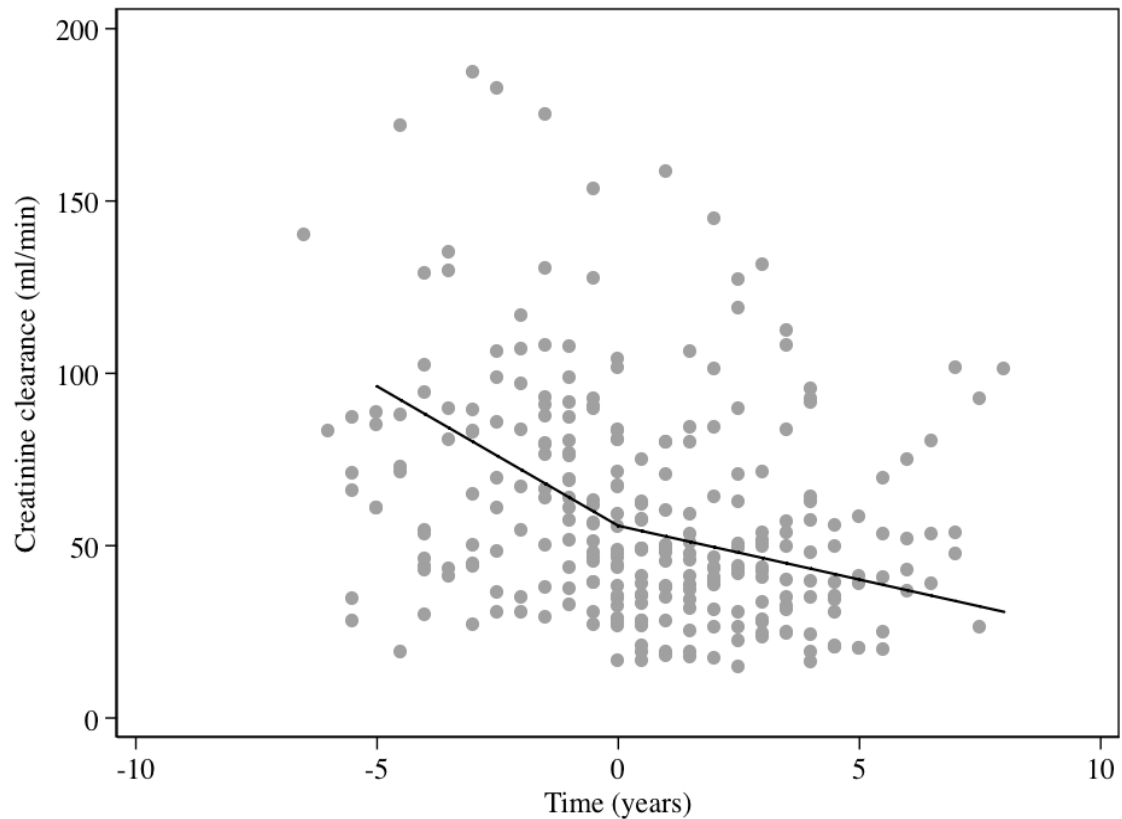
Slade H et al. Diabetes Research and Clinical Practice 2011

Atherosclerosis Is Common
in *Newly Diagnosed* Diabetes Mellitus

- Cardiovascular diseases are common causes of morbidity
  and mortality in people with diabetes
- >50% of patients with newly diagnosed type 2 diabetes show evidence of cardiovascular disease
- Atherosclerosis is a major cause of death among patients with diabetes mellitus
  - 75% from coronary atherosclerosis
  - 25% from cerebral or peripheral vascular disease
- >75% of hospitalizations for individuals with diabetes are for atherosclerotic disease

Adapted from Amos AF et al *Diabet Med* 1997;14:S7-S85; Hill Golden S *Adv Stud Med* 2002;2:364-370; Haffner SM et al
N Engl J Med 1998;339:229-234; Sprafka JM et al *Diabetes Care* 1991;14:537-543.
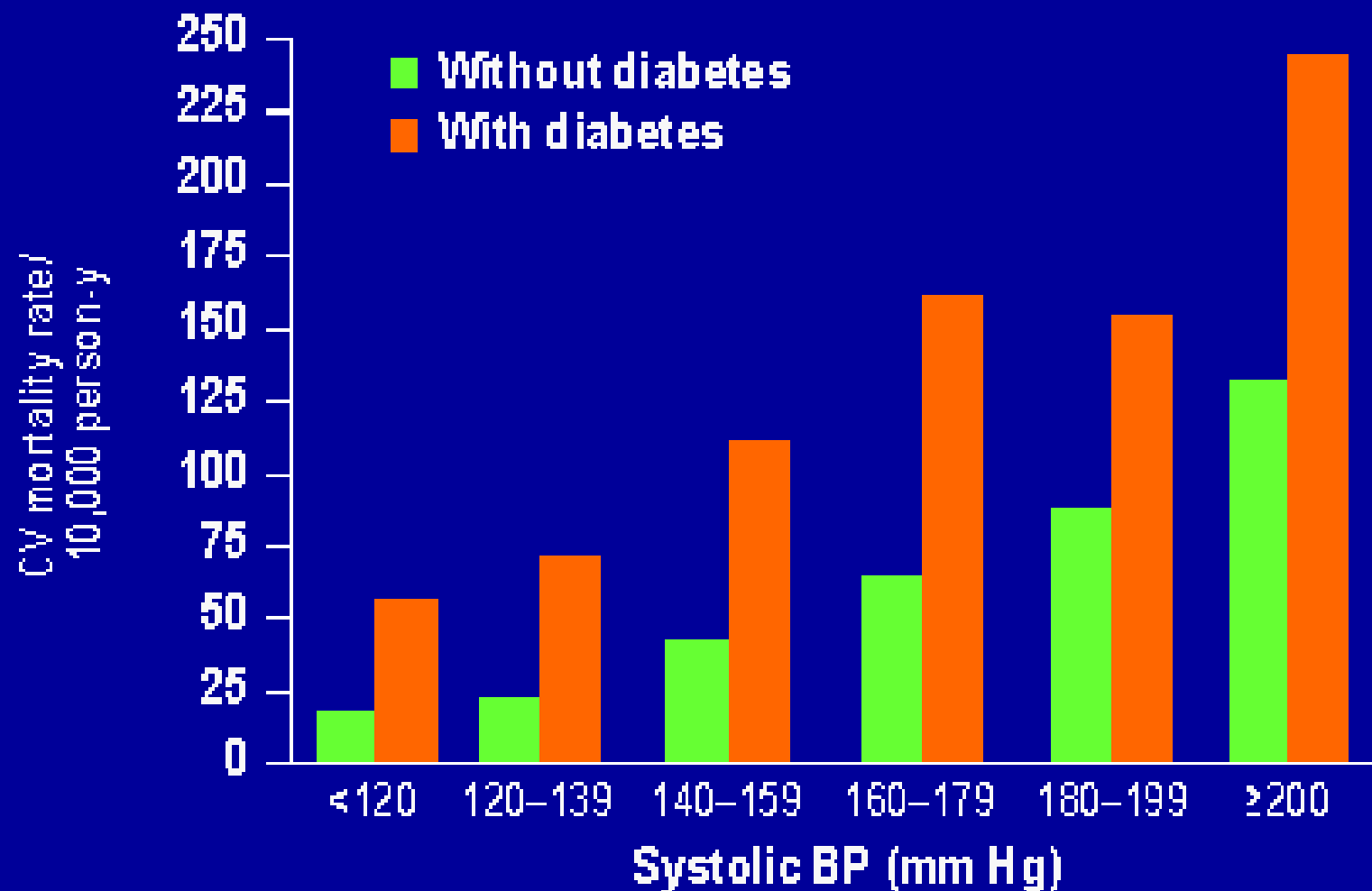
Two-Thirds of People with Diabetes Die of Cardiovascular Disease

- Among people with diabetes, macrovascular complications, including CHD, stroke, and peripheral vascular disease, are the leading causes of morbidity and mortality.

Causes of mortality in people with diabetes

67%

CHD, stroke, and peripheral vascular disease

Other

Adapted from Alexander CM, Antonello S *Pract Diabet* 2002;21:21-28.
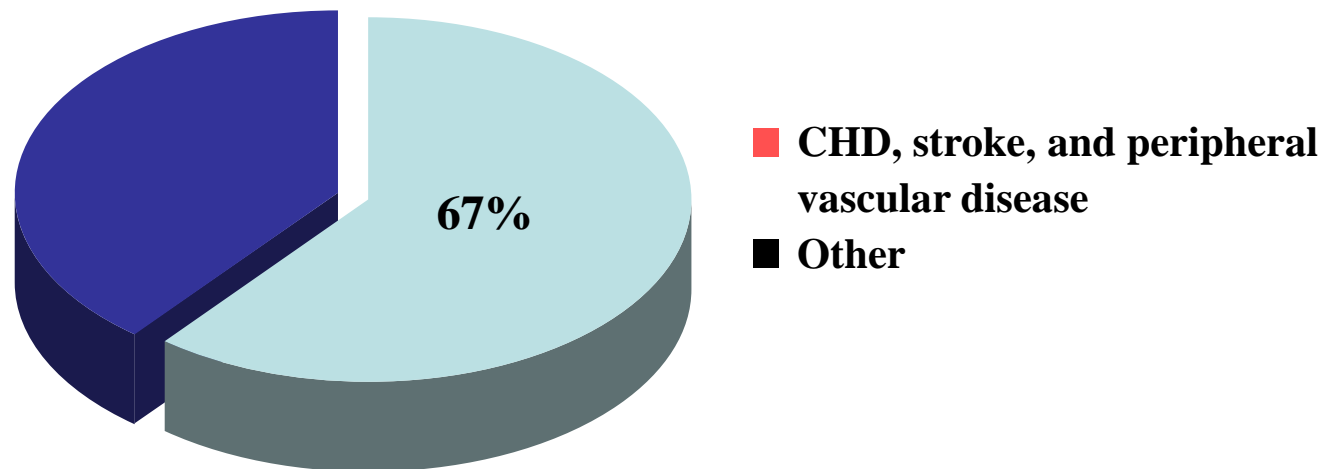
Association of Systolic BP and CV Death in Type 2 Diabetes

Stamler et al. *Diabetes Care.* 1993;16:434.

# Treatment Strategies for Patients with Diabetes

Treatment goals for diabetes should include
- Optimum glycemic control and elimination of hyperglycemia-related symptoms
  - Dietary and lifestyle changes
  - Exercise
  - Medication
- Prevention of microvascular complications
  - Control of glycemia
  - Control of blood pressure
  - Monitoring and screening
- Prevention of CHD, MI, and other macrovascular complications
  - Control dyslipidemia: ↓ LDL-C, ↑ HDL-C, ↓ TG
    - Dietary and lifestyle changes and exercise
    - Drug therapy with statins

Adapted from Powers AC. In *Harrison's Principles of Internal Medicine*. 15th ed. New York: McGraw-Hill, 2001:2109-2137; American Diabetes Association *Diabetes Care* 2002;25(suppl 1):S74-S77.

Interventions to slow progression of Clinical Nephropathy-2

- Lipid lowering therapy

- Low protein diet

- Glucose control

- Stopping smoking

- New approaches
  - Aldosterone inhibition
  - Anti-fibrotic agents
  - Multi-Drug approaches
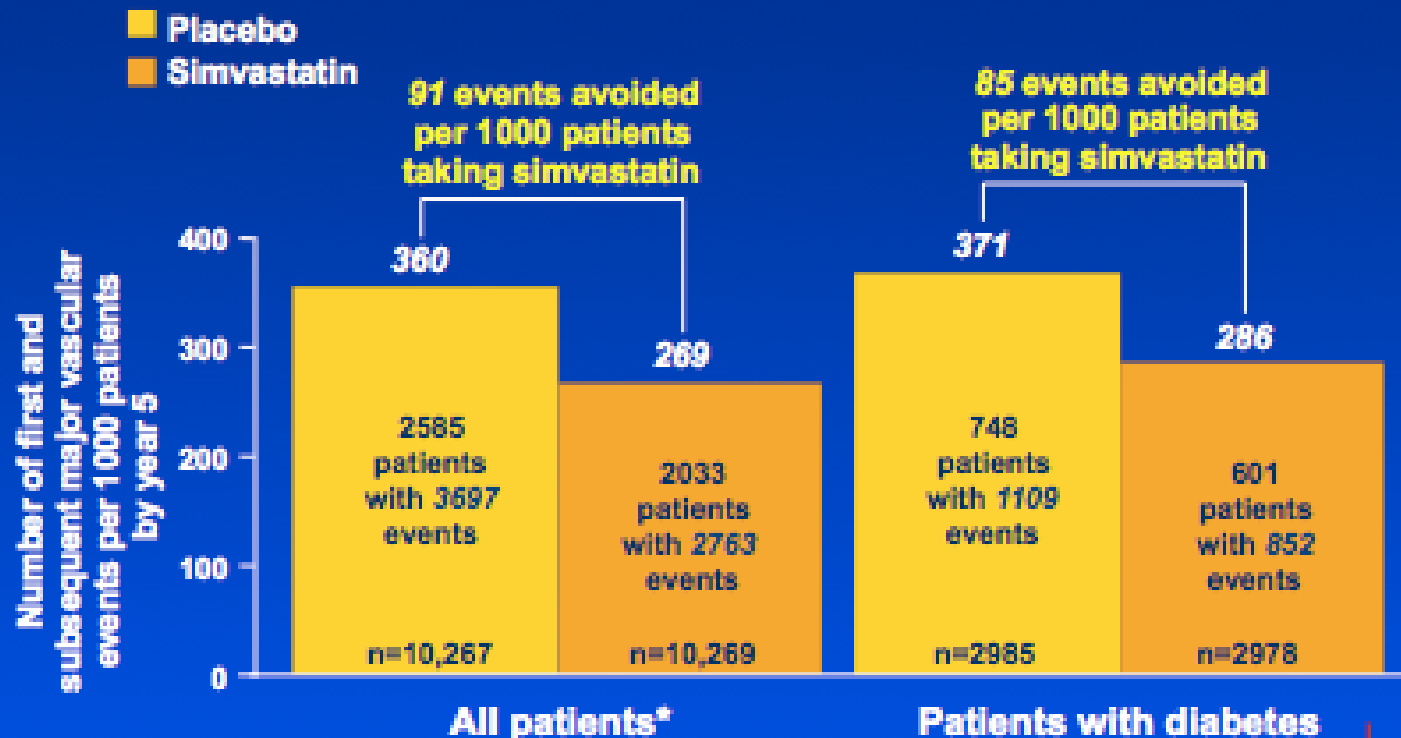
Summary

- Diabetic nephropathy – epidemic
- Early aggressive intervention required
- Glycaemic control important
- BP – ACEI and /or ARB first line targeting a normal blood pressure
- CV protection – statins and aspirin.

ASIAN PACIFIC SOCIETY OF NEPHROLOGY

"Once in a while
You may come across a place
where everything
is as close to perfection
as you will ever need"

"Place" Brian Turner