DIABETIC NEPHROPATHY

PRESENTED BY

CASEY LIGHT
RENAL NURSE PRACTITIONER
ARMADALE HEALTH SERVICE

INTRODUCTION

DIABETIC NEPHROPATHY is the leading cause of ESKD in Australia and worldwide

Over 4.5 million people in Aust are at risk of developing CKD due to presence of diabetes or hypertension (AIHW 2002)

ESKD is costly for patients , their families and the taxpayers

* Has 2nd worst Quality of Life (after lung cancer)

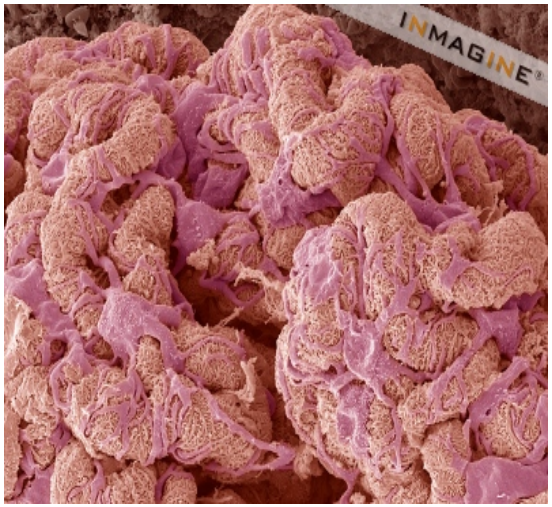
In 2010, cost of dialysis and transplant services was close to $1b

By 2020 : projected cost around $ 12b

Patients commencing ESKD treatment with diabetes is expected to increase from 45% to 64% (AIHW 2011)

DEFINITION

Diabetic Nephropathy is a progressive kidney disease characterised by:



- Histopathologically:
  - Angiopathy of glomerular capillaries
  - Diffused glomerulosclerosis

- **Late** clinical stages associated with
  - Persistent albuminuria
  - Progressive decline in the glomerular function
  - Elevated blood pressure

EPIDEMIOLOGY

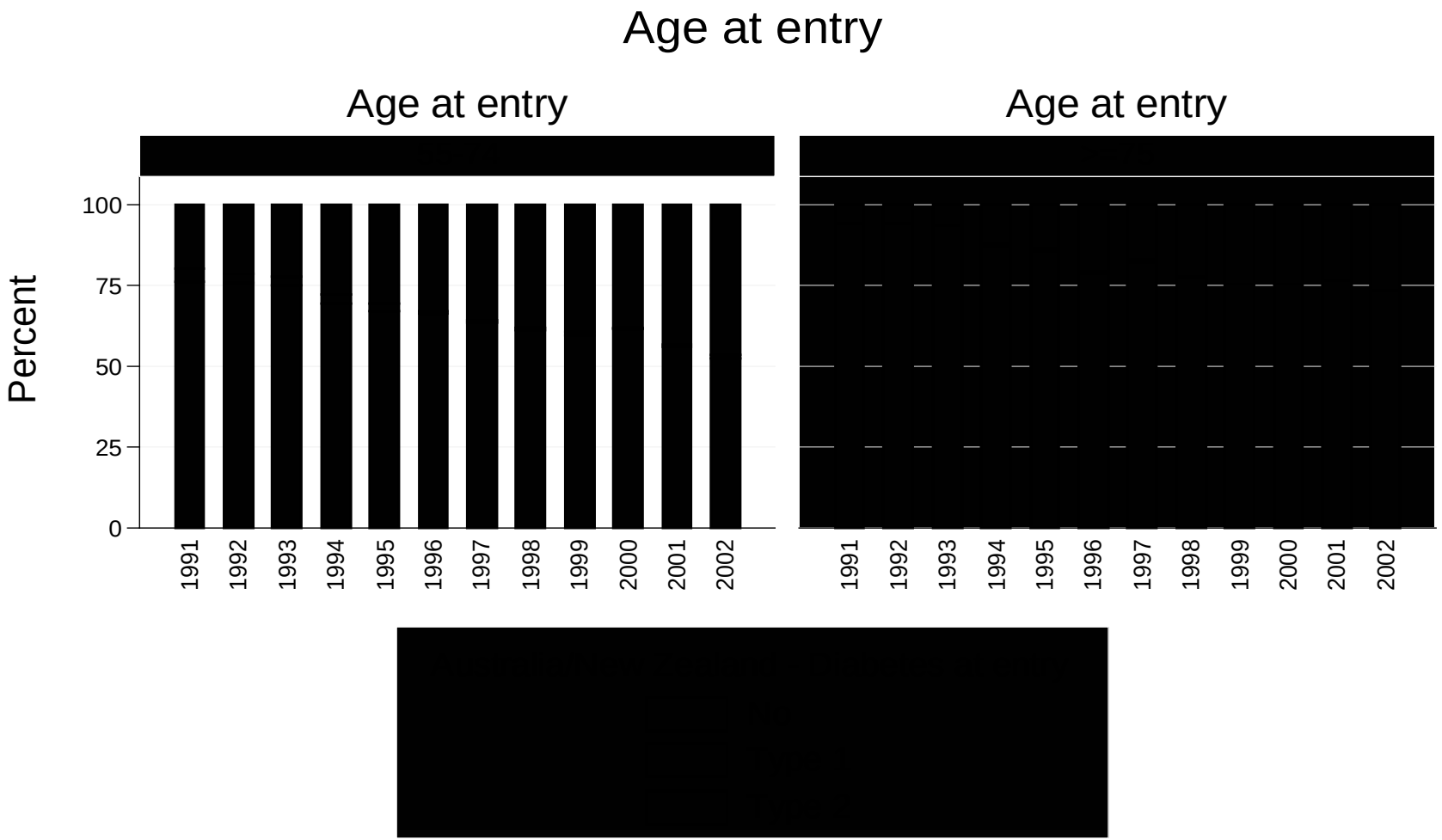
Most common cause of ESKD

- Common microvascular complication of diabetes
- **Early DN is reversible, and probably preventable**

- More common in T1DM patients
  - Well defined clinical course regarding progression

- Accounts for ~40% of patients starting DIALYSIS
- Indigenous 3.4 x higher than non-indigenous
- Male > Female

Age of patients with diabetes at entry to RRT



Graphs by Age category at entry

RISK FACTORS

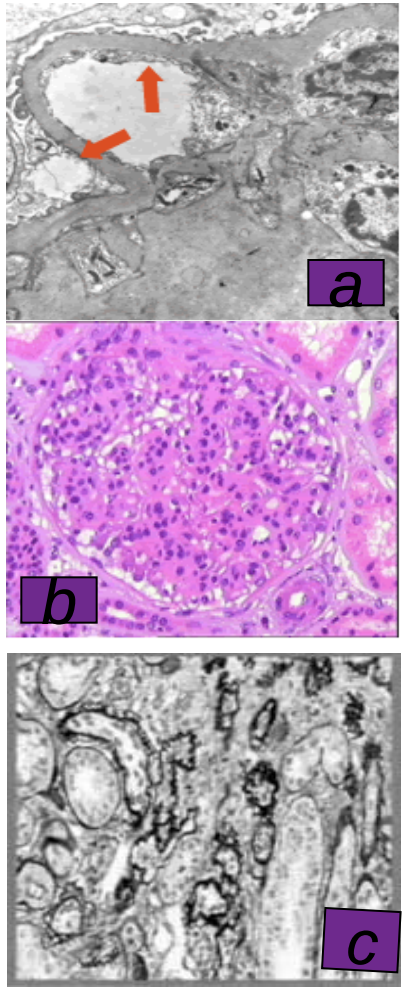
- Duration of diabetes
- Poor control of diabetes
- Smoking
- Metabolic syndrome: Overweight, Hypertension, dyslipidemia
- Associated micro-vascular complications as retinopathy, neuropathy
- Genetic susceptibility
- Gender M>F

CHARACTERISTICS OF DN

Diabetic milieu → hyperglycaemia→ AGEs
(mediators for functional and structural abnormalities of DN)

Structural

- hypertrophy of the kidney
- increased GBM thickness (*a*)
- Nodular and diffuse glomerulosclerosis (*b*)
- Tubular atrophy
- Interstitial fibrosis (*c*)



Functional

- Early increase in glomerular filtration rate
- Intraglomerular hypertension
- Subsequent proteinuria
- Eventual loss of renal function

5 STAGES OF DN

Stage 1 – **early hypertrophy**

increase in renal plasma flow and GFR

Stage 2 – **silent stage**

Subtle morphological changes

Thickening of GBM

Glomerular hypertrophy

mesangial and tubulointerstitial expansion

Stage 3 – **incipient DN (+/- Abnormal Creatinine/ BP)**

Microalbuminuria (U ACR: 5-25 mg/mmol)

Stage 4 – **Overt DN (High BP +/- Abnormal Creatinine)**

Macroalbuminuria (U ACR >25 mg/mmol)

Stage 5 – **ESRD with uraemia**

Natural History of DN and classifications of CKD stages

Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300	Type 1 normal Type 2 normal	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>300 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

Classifications of CKD stages

Table 3. Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73m^2)	Action*
	At increased risk	≥90 (with CKD risk factors)	Screening CKD risk reduction
1.	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment Treatment of comorbid conditions, slowing progression, CVD risk reduction
2.	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3.	Moderate ↓ GFR	30-59	Evaluating and treating complications
4.	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5.	Kidney Failure	<15 (or dialysis)	Replacement (if uremia present

Clinical evidence of DN

Earliest biochemistry abnormality –albuminuria

- **Without interventions,** 80% with T1DM have urinary albumin excretion increase at 10-20% per year to **overt nephropathy** over a period of 6-15 yrs

- Once overt nephropathy occurs , **with/ without interventions,** GFR falls over a period of several years.

- Eventually,
  - 50% of T1DM individuals develop ESRD within 10 yrs
  - 75% of T1DM individuals develops ESRD by 20 years

What about T2DM ?

Progression of Diabetic Nephropathy in Type 2 DM

	Australia
Type 2 DM	950,000 (1)
30% ↓	
Microalbuminuria	225,000 (2)
30% ↓	
Proteinuria	32,000 (2)
30% ↓	
(but 70% have CV death first)	
End Stage Renal Disease	2,000 (3)

Dunston et al Diabetes Care 2002
Atkins R KI 2004
ANZDATA 2004

DIAGNOSIS

- Patients history
- Physical examination
- Laboratory evaluations
- Imaging of the kidneys
- Positive microalbuminuria:
  - Spot urine, confirmed 2 out of 3, 3-6 mths
- Elevated creatinine urea
  (as kidney damage progress)
- Diabetic retinopathy
  - Long term T1D > 10yrs
  - Proteinuric T2D

DIAGNOSIS CONT...

Proteinuria is the hallmark of DN

Although characteristics of DN are :

- Thickening of GBM
- Mesangial expansion

These changes do not explain development of proteinuria

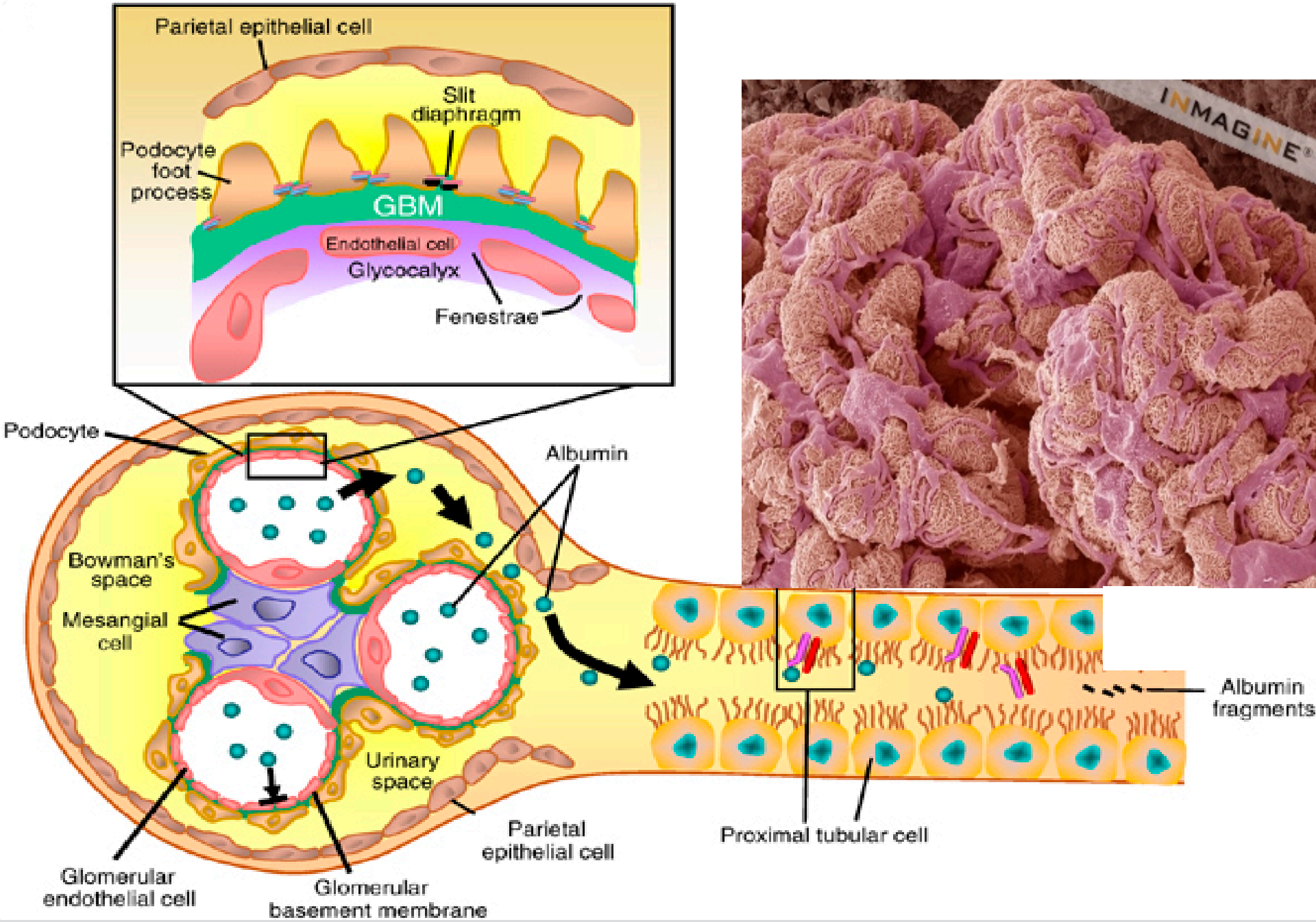
Recent advances in **podocytes** cell biology may be early markers of DN

Hyperglycemia → AGEs → podocytes cell deaths → protein leakage

Dead podocytes cells excreted in the urine

Strong evidence of podocytes injury very early in the course of DN → ?? Podocyte numbers : early marker

Wolf, G (2007). Nephron Physiology, 106(2): 26-31


Parietal epithelial cell
Slit diaphragm
Podocyte foot process
GBM
Endothelial cell
Glycocalyx
Fenestrae
INMAGINE
Podocyte
Albumin
Bowman's space
Mesangial cell
Albumin fragments
Urinary space
Parietal epithelial cell
Proximal tubular cell
Glomerular endothelial cell
Glomerular basement membrane

SCREENING FOR MICROALBUMINURIA

- ✓ **Screening for microalbuminuria provides early intervention opportunity**
- ✓ **performed annually from the onset of T2DM , 5 yrs after onset of T1DM**
- ✓ **morning spot urine for albumin : creatinine ratio (ACR) is most reliable**

ACR Result	Test Results Range	Recommended Follow -up
Normal	*Females* <3.5 mg/mmol *Males* <2.5 mg/mmol	Re-test annually
Microalbuminuria	*Females* 3.5 – 35 mg/mmol *Males* 2.5 – 25 mg/mmol	Repeat 2 times over 3 months – confirm microalbuminuria if 2 out of 3 tests is positive
Macroalbuminuria (also called proteinuria)	*Females* >35 mg/mmol *Males* >25 mg/mmol	Do a protein :creatinine ratio (PCR) or 24 hour urine protein (to quantify protein excretion)

NHMRC Guidelines 2009

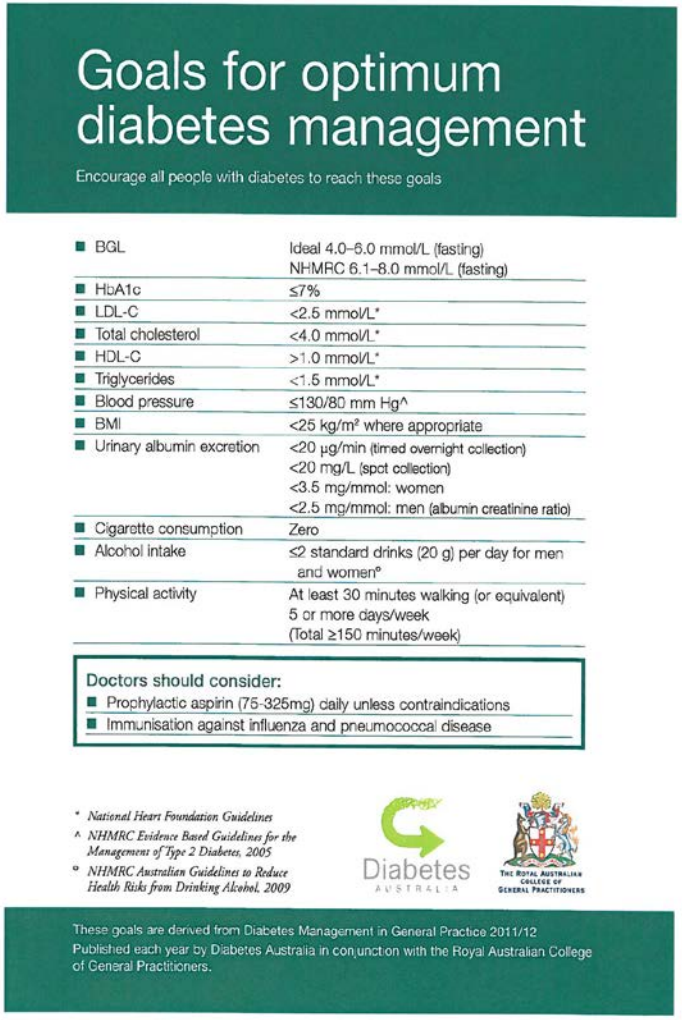
MANAGEMENT

MANAGEMENT GOALS:

Slow down progression of kidney damage

Target
Proteinuria
Hypertension
Hyperglycaemia

MULTIFOCAL TREATMENT APPROACH



Goals for optimum diabetes management

Encourage all people with diabetes to reach these goals

BGL	Ideal 4.0–6.0 mmol/L (fasting) NHMRC 6.1–8.0 mmol/L (fasting)
HbA1c	≤7%
LDL-C	<2.5 mmol/L*
Total cholesterol	<4.0 mmol/L*
HDL-C	>1.0 mmol/L*
Triglycerides	<1.5 mmol/L*
Blood pressure	≤130/80 mm Hg^
BMI	<25 kg/m² where appropriate
Urinary albumin excretion	<20 µg/min (timed overnight collection) <20 mg/L (spot collection) <3.5 mg/mmol: women <2.5 mg/mmol: men (albumin creatinine ratio)
Cigarette consumption	Zero
Alcohol intake	≤2 standard drinks (20 g) per day for men and women°
Physical activity	At least 30 minutes walking (or equivalent) 5 or more days/week (Total ≥150 minutes/week)

Doctors should consider:

- Prophylactic aspirin (75-325mg) daily unless contraindications
- Immunisation against influenza and pneumococcal disease

* *National Heart Foundation Guidelines*

^ *NHMRC Evidence Based Guidelines for the Management of Type 2 Diabetes, 2005*

° *NHMRC Australian Guidelines to Reduce Health Risks from Drinking Alcohol, 2009*

Diabetes AUSTRALIA

THE ROYAL AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS

These goals are derived from Diabetes Management in General Practice 2011/12
Published each year by Diabetes Australia in conjunction with the Royal Australian College of General Practitioners.

SLOW DOWN PROGRESSION OF DN

A. **Optimal glycemic control –**
   A. Hb A1c < 7%

B. **Intensive antihypertensive control**
   A. BP <130/80 for people with Proteinuria < 1g/day
   B. BP <120/75 for people with Proteinuria >=1g/day

C. **Blockade of RAS**
   A. ACEi OR ARB

A. Optimal glycemic control

Effects of Hyperglycaemia

- acutely increases membrane permeability to macromolecules
- raises BP by inducing sodium retention and extravascular sodium and fluid shift
- Generation of AGE leading to podocytes effacement
- leads to development and progression of DN

A. Optimal glycemic control

Tight glycaemia control delays onset /progression of DN

DCCT: 1441 IDDM , 1983-1993

Intensive (Insulin => tds)

Vs conventional (insulin 1 or 2 daily)

Intensive group outcome:

(no retinopathy) – DN progression reduced by 76%

- Microalbuminuria reduced by 34%

(mild retinopathy) –DN progression reduced by 54%

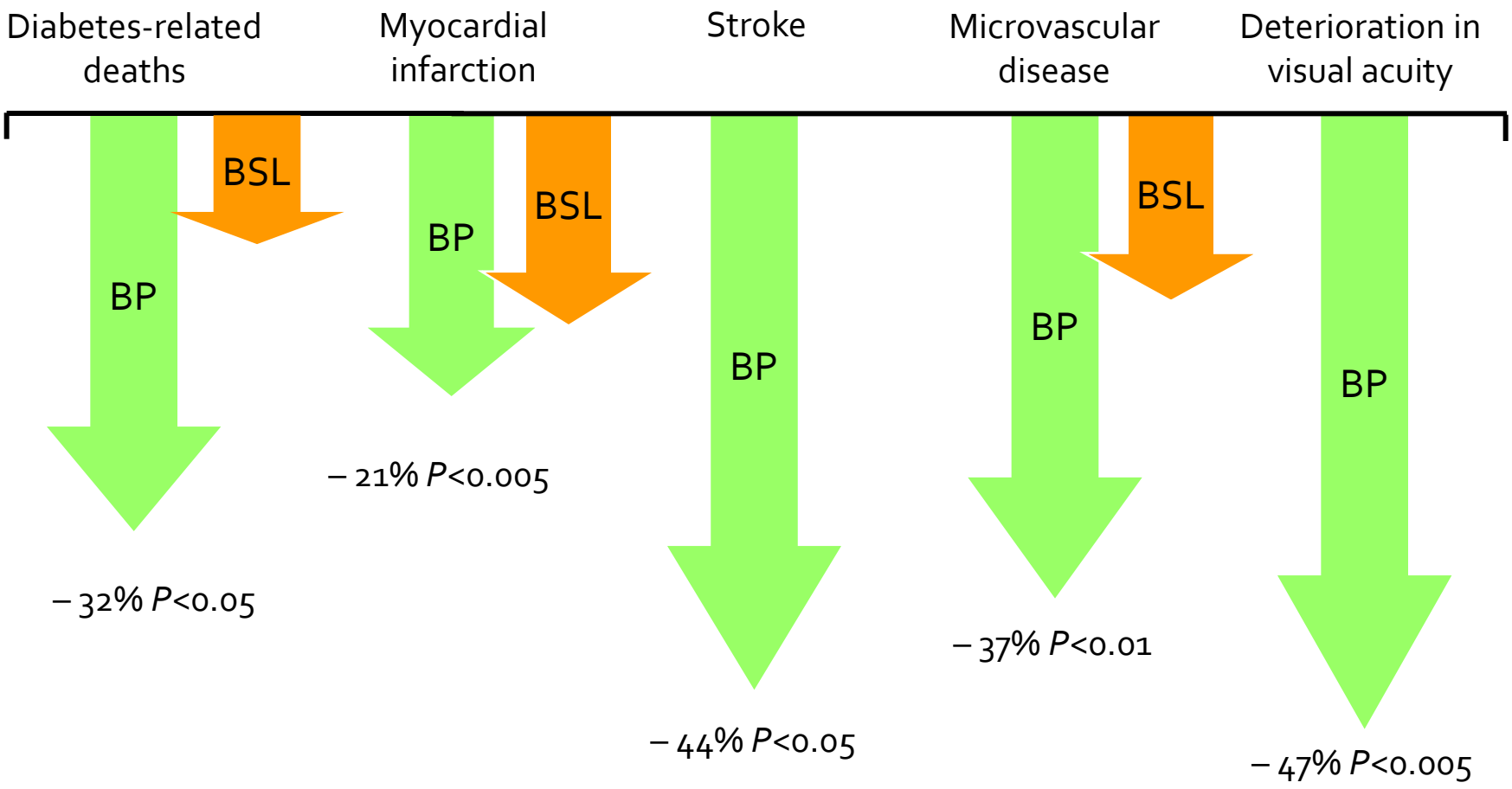
- Microalbuminuria reduced by 43%

Albuminuria reduced by 54%

Neuropathy reduced by 60%

B. Intensive antihypertensive control

UKPDS 38: RR reduction with tight vs less tight BP control (T2DM pts)

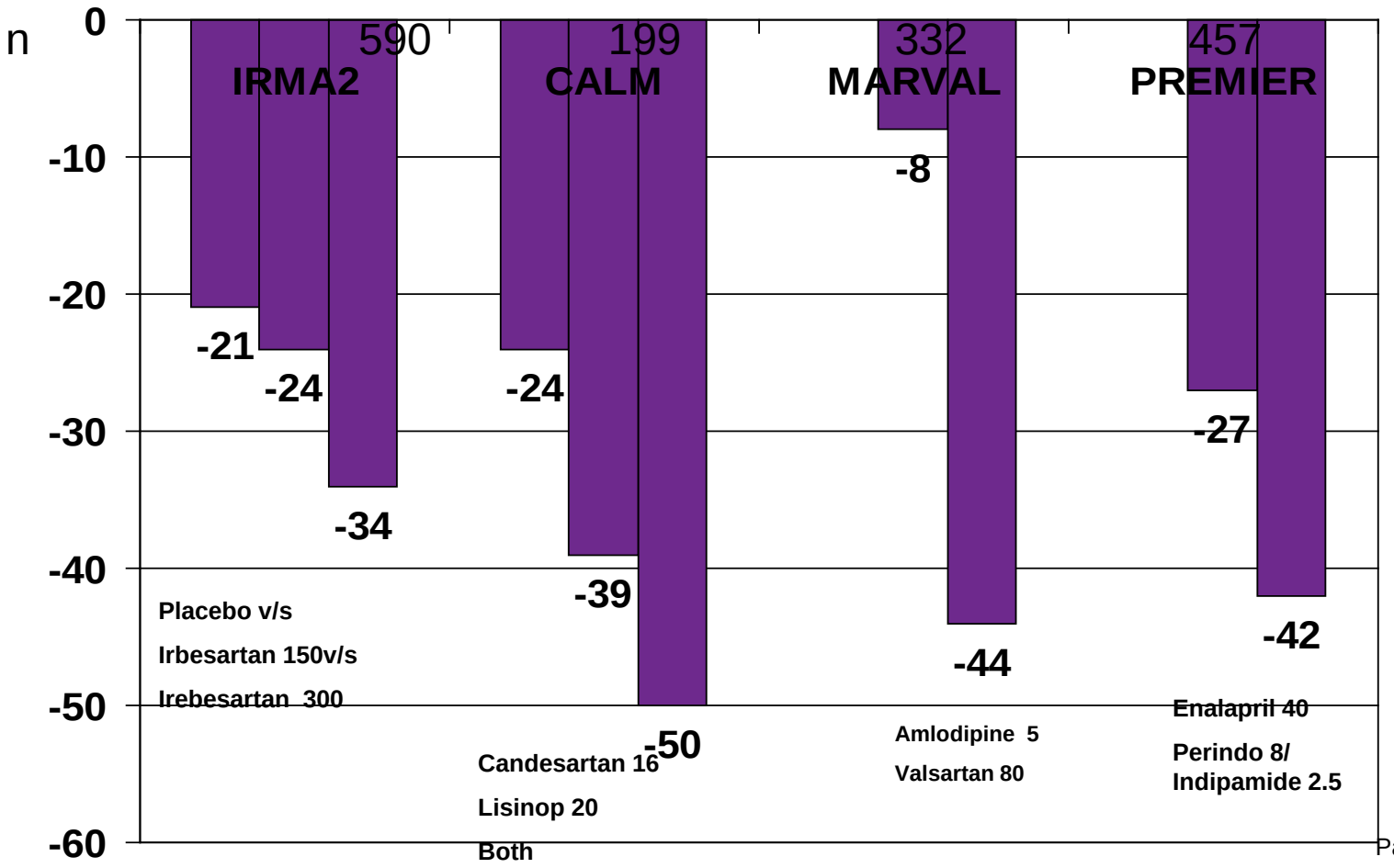


Tight BP (NOT BSL) control ↓ morbidity ,mortality in T2D patients

UKPDS Group. UKPDS 38. *BMJ* 1998;317:703–713.
UKPDS Group. UKPDS 33. *Lancet*. 1998;352:837-853.

B. Intensive BP control - Clinical Trials

Decrease in % albumin excretion rate in microalbuminuric with type 2 diabetes



Parving et al.. NEJM 2001

Mogenson BMJ 2000

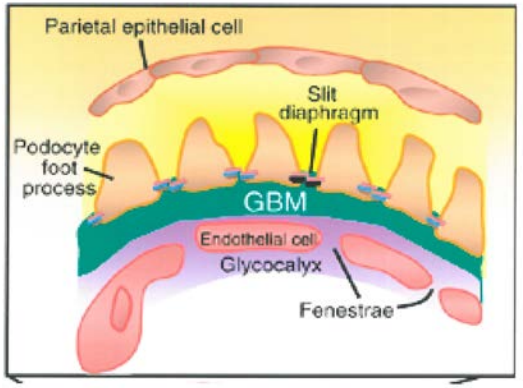
Viberti Circulation 2002

Mogenson Hypertension 2003

C. BLOCKADE OF RAS

ACE converts Angiotensin I to Angiotensin II (ANGII)

ANGII stimulates podocyte-derived VEGF, suppress nephrin expression , induces podocytes apoptosis → glomerular damage.



ANG II reduces insulin sensitivity , impairs insulin secretion

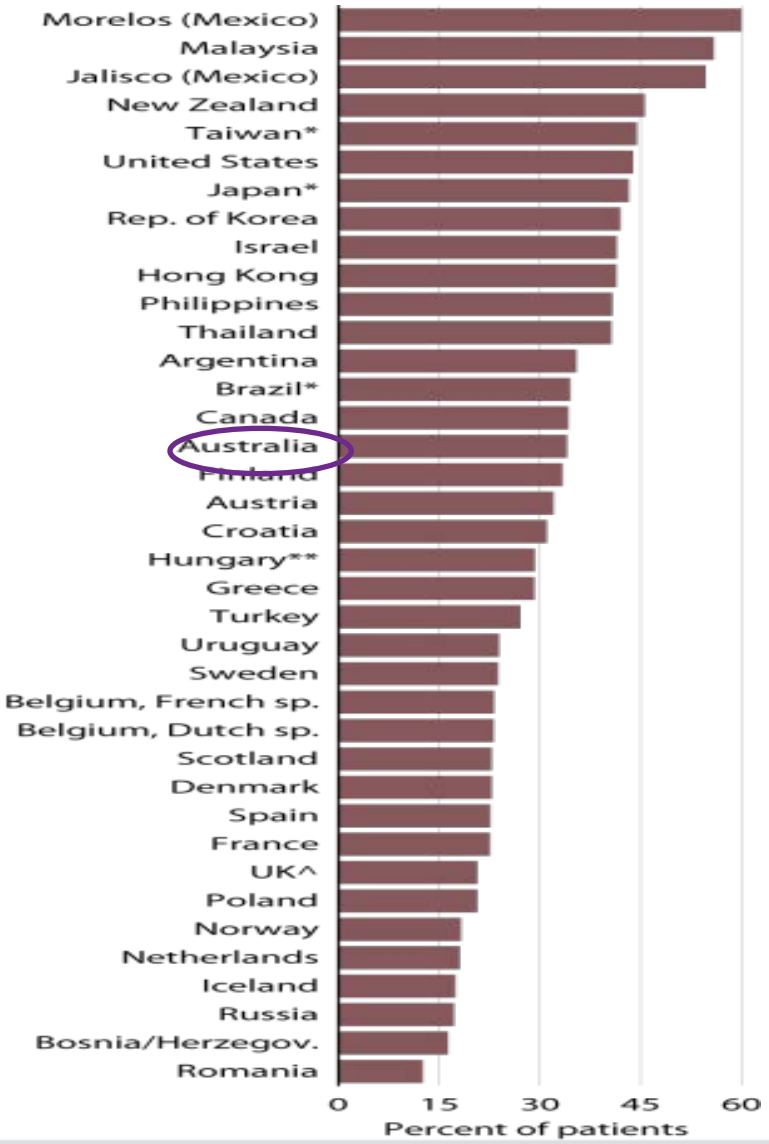
- Short tem effect –interferes with glucose-mediated insulin secretion
- Long term effect – causes degeneration and fibrosis of islet cells

Blockade of RAS has antidiabetogenic, antiproteinuric effects:

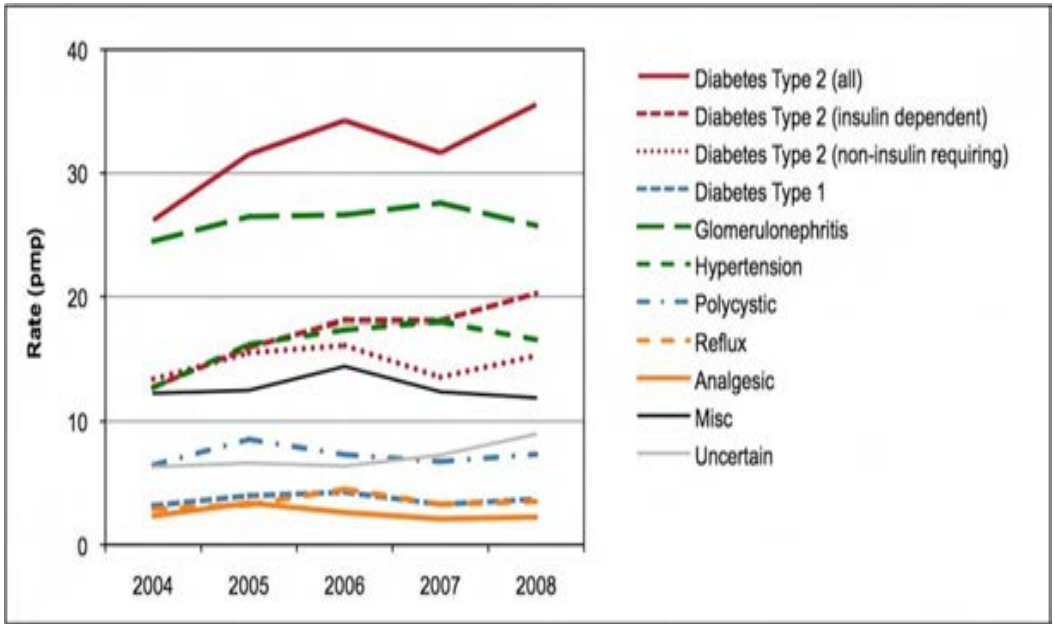
- preventing progression of DN
- Reducing progression from micro to macroalbuminuria

Diabetic Nephropathy and ESKD

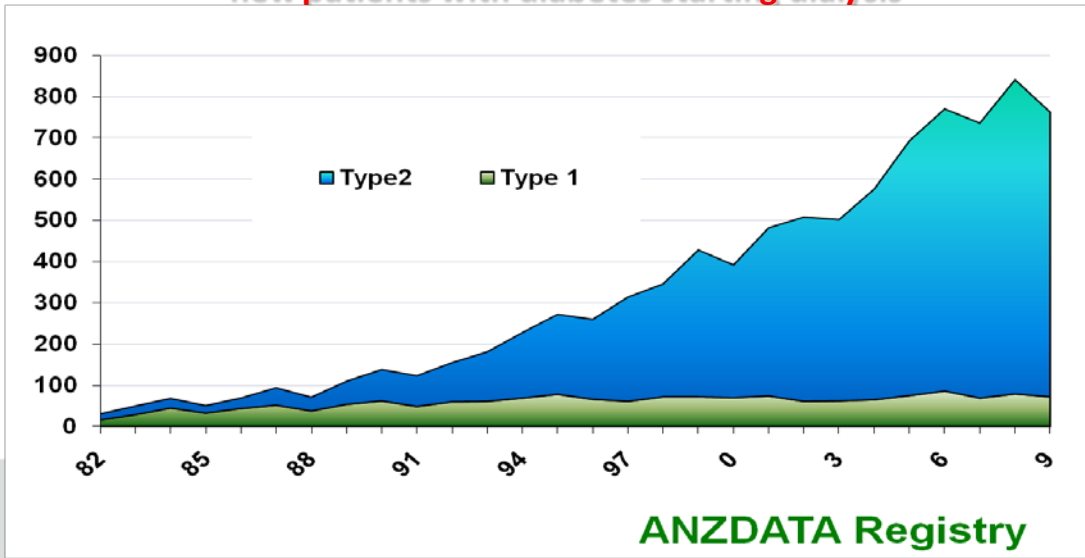
Percentage of patients with ESRD due to diabetes



DN is the major cause of ESRD requiring dialysis in Australia



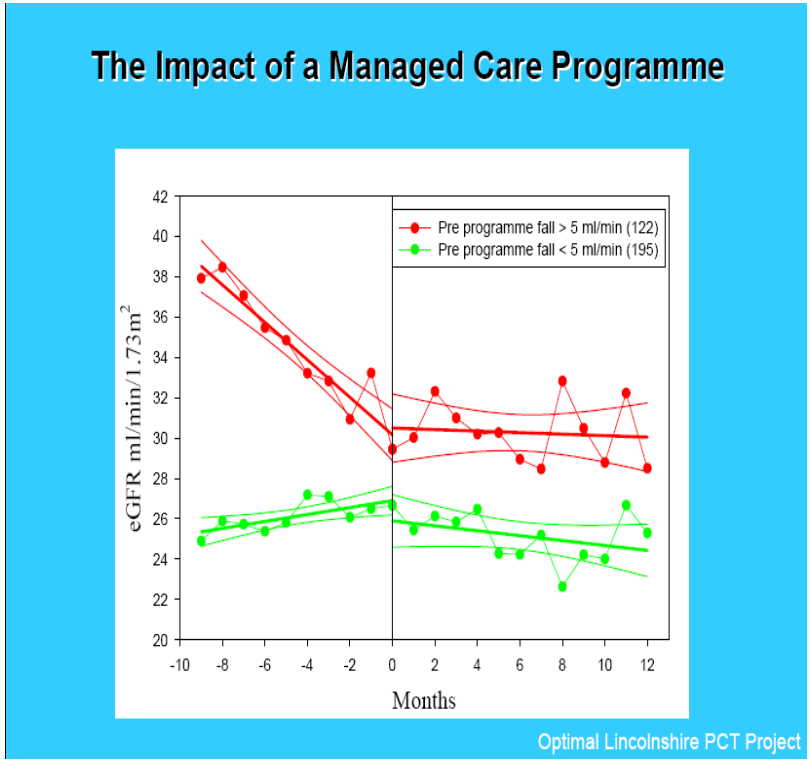
new patients with diabetes starting dialysis



ANZDATA Registry

EARLY REFERRAL

Early specialist renal referral reduces rate of progression of CKD, better management of complications better preparation for eventual RRT avoids complications related to LATE REFERRAL.



Consider referral when :

- **Diabetes with eGFR < 60mL/min/1.73m2**
  - **Proteinuria > 1g/24hrs**
  - **difficult to control Hypertension**
  - **Other un-usual clinical findings**
    - **Haematuria, rapid progression**
- eGFR < 30mL/min/1.73m2
- Unexplained decline in kidney function

  > 15% drop in eGFR over three months
- Abnormal findings:
  - Glomerular haematuria (particularly if proteinuria present)
  - Absence of albuminuria with abnormal creatinine
  - Resistant hypertension
  - Unexplained anaemia (Hb < 100 g/L)

SUMMARY

- DN is the leading cause of ESRD
- ESRD treatment is a costly health burden
- DN is potentially reversible with intense early treatment
- Intensive management of hyperglycaemia, hypertension and proteinuria is important to slow progression
- Blockade of RAS has beneficial effects on DN and other microvascular complications
- Annual screening for microalbuminuria is essential
- Timely specialist Nephrology referral has important role in multidisciplinary team approach to slow down DN

Government of Western Australia
Department of Health
Armadale Health Service

Free Kidney Health Checks

Kidney Health Week 2013

No appointments necessary

Monday 27 May to Friday 31 May

8.30am to 5pm

Armadale Kelmscott Memorial Hospital Foyer, 3056 Albany Highway, Armadale

Did you know?

- Every day 54 Australians die from kidney related disease
- 1 in 9 Australians over the age of 25 have Chronic Kidney Disease (CKD)
- 1 in 3 Australians is at an increased risk of developing CKD.

You are most at risk if you:

- ☑ are 60 years or older
- ☑ are of Aboriginal or Torres Strait Islander descent (ATSI)
- ☑ have diabetes
- ☑ have a family history of kidney disease
- ☑ had a heart failure or past heart attack
- ☑ had a stroke
- ☑ have high blood pressure
- ☑ are overweight or obese
- ☑ are a smoker.

Take 10 minutes out of your day for a check – it could save your life.


THANK
YOU