# DM Nephropathy

Shivinder S Jolly MD FRCPC FASN
Nephrology and Hypertension

Fax: 519 743 2792
Pager 519 244 0130
Office 519 743 2573

# Definitions

**Albuminuria**

Increased excretion of albumin in the urine

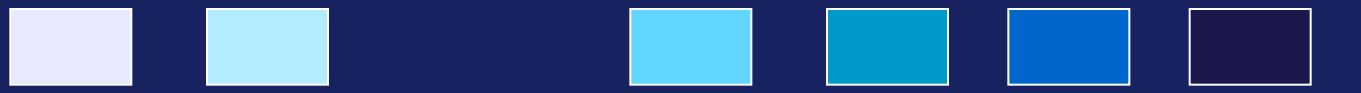
**Proteinuria**

Increased excretion of albumin, other specific proteins, or total protein in the urine

National Kidney Foundation. NKF KDOQI Guidelines. Available at: www.kidney.org

# How NOT to Measure Microalbuminuria

## Dipstick



NEG TRACE 0.3 g/L 1.0 g/L 3.0 g/L 20 g/L

- Dipsticks only measure urinary concentration of protein
- They can overestimate proteinuria in a concentrated urine
- They can underestimate proteinuria in a dilute urine
- They are typically insensitive to microalbuminuria
- Do not do 24 hour urine collections for MAU

# UACR

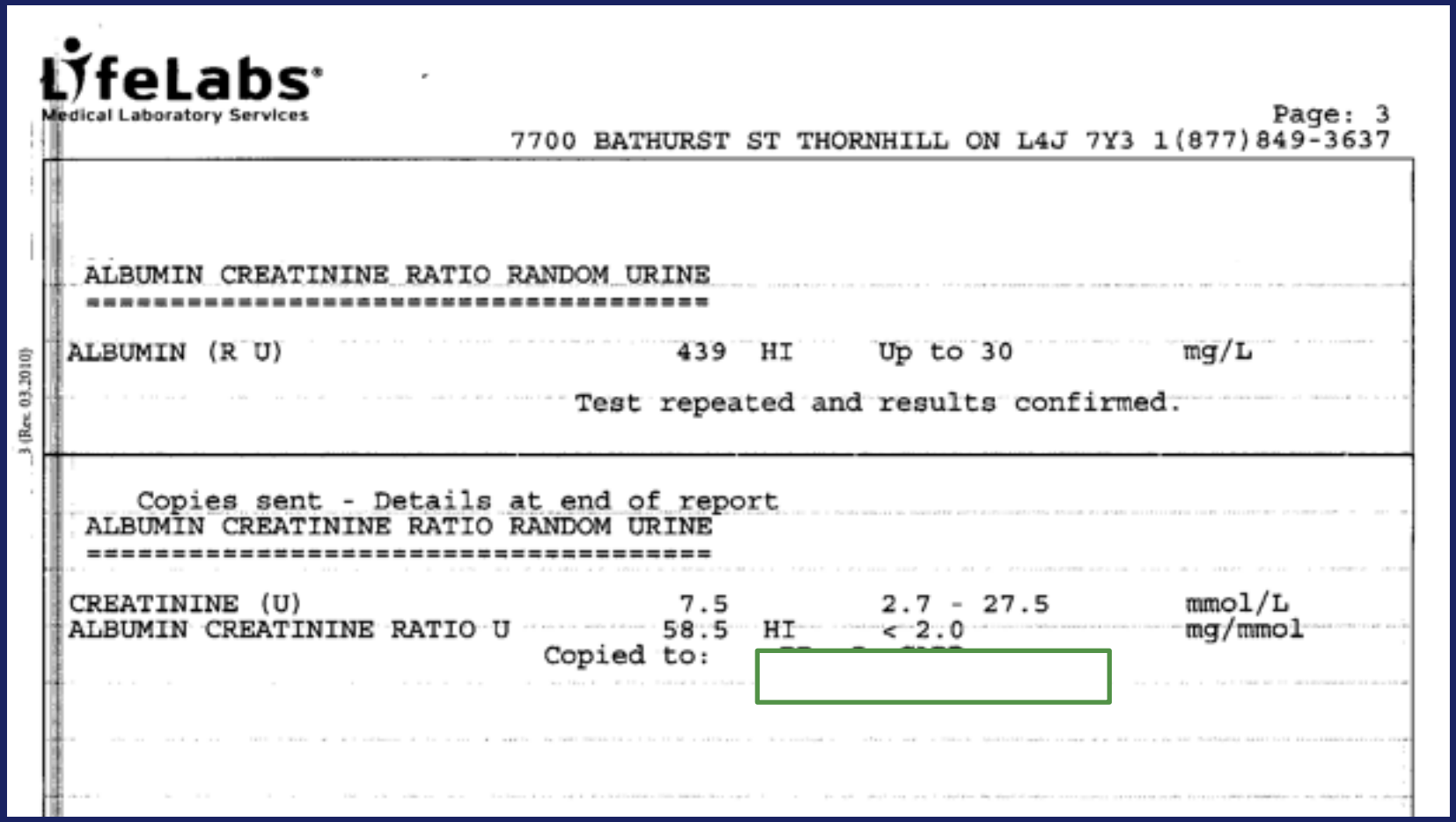
$$\text{UACR} = \frac{\text{mg}}{\text{mmol}}$$

Normal values
- UACR < 2.2 for men
- UACR < 3.0 for women

- Use of the UACR removes the effect of urinary dilution/concentration
- Creatinine and albumin are equally concentrated
- Therefore volume is irrelevant

UACR = urine albumin:creatinine ratio; NB = *nota bene*

# UACR



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ALBUMIN CREATININE RATIO RANDOM URINE

| | | | | |
|---|---|---|---|---|
| ALBUMIN (R U) | 439 | HI | Up to 30 | mg/L |

Test repeated and results confirmed.

Copies sent - Details at end of report

ALBUMIN CREATININE RATIO RANDOM URINE

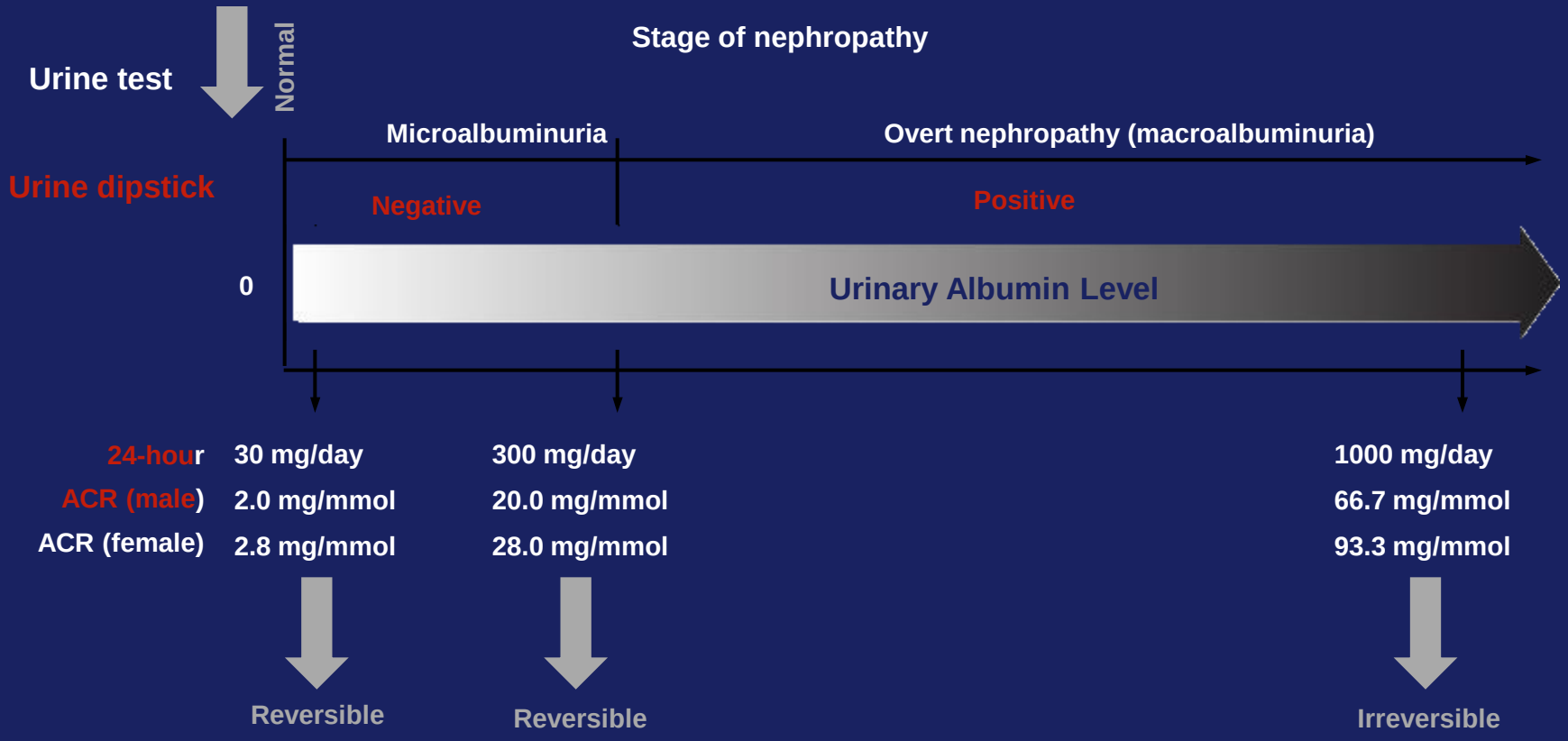
| | | | | |
|---|---|---|---|---|
| CREATININE (U) | 7.5 | | 2.7 - 27.5 | mmol/L |
| ALBUMIN CREATININE RATIO U | 58.5 | HI | < 2.0 | mg/mmol |

Copied to:

3 (Rev. 03.2010)

UACR = urine albumin:creatinine ratio

# Stage of Diabetic Nephropathy by Level of Urinary Albumin by Various Test Methods

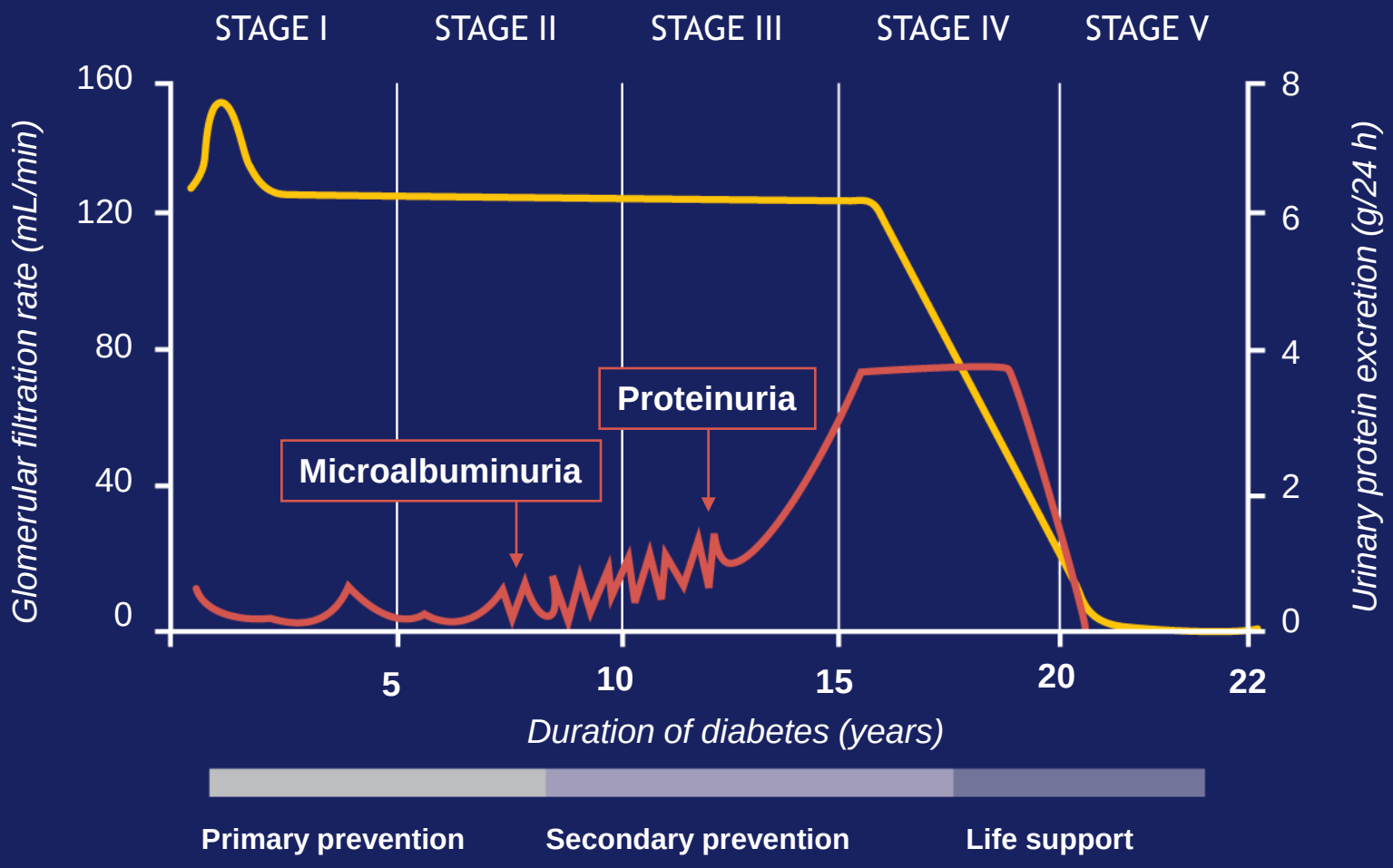



ACR: albumin-creatinine ratio

Adapted from:

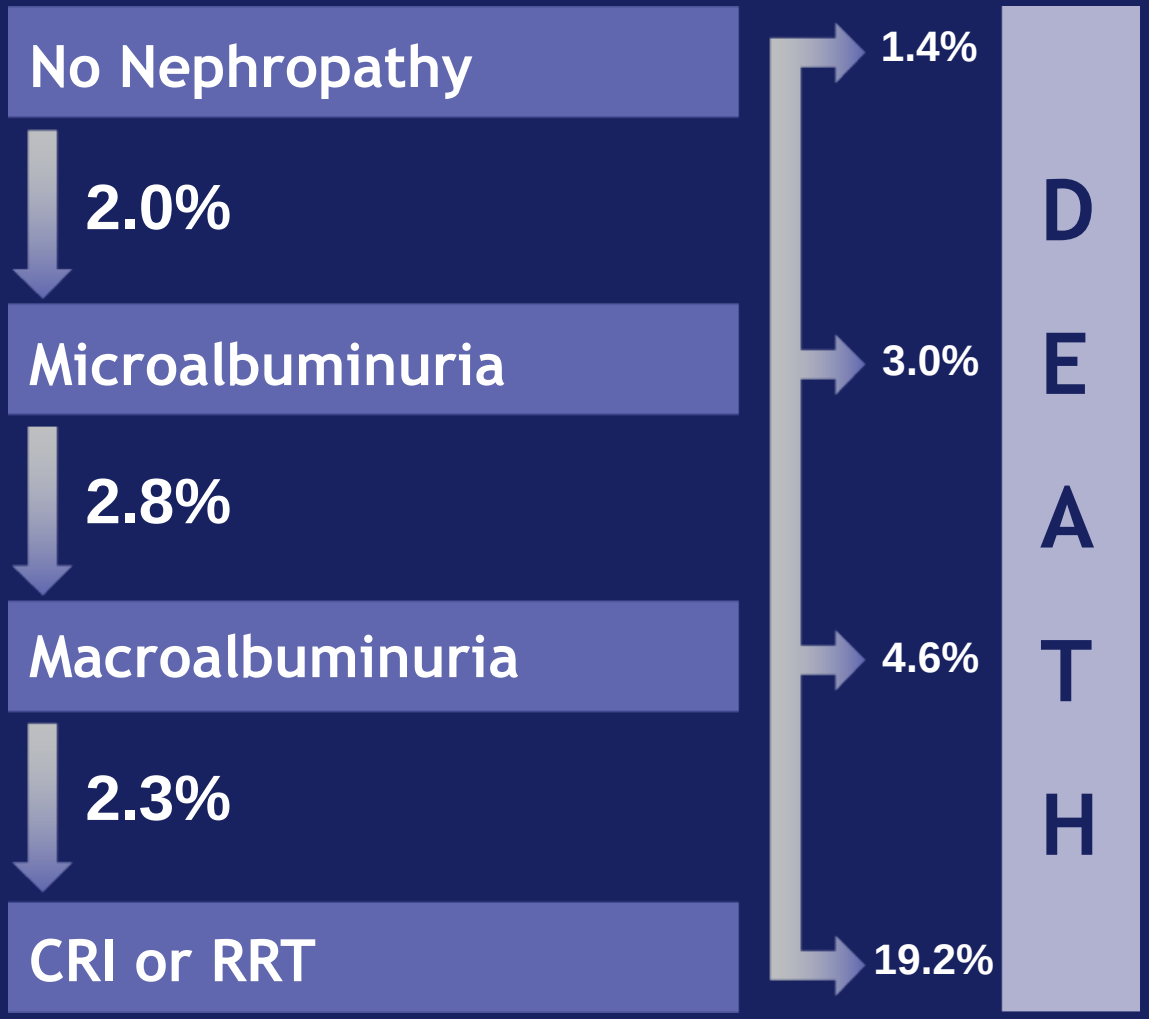
Warram JH, et al. *J Am Soc Nephrol* 1996; 7:930-937. Mathiesen ER, et al. *Diabet Med* 1995; 12:482-7.
Lemley KV, et al. *Kidney Int* 2000; 58:1228-37. Laplante L: Microalbuminuria: A Physician Handbook, 3rd ed., 2002.

# Natural History of Diabetic Nephropathy




Adapted from Pylypchuk GB, Beaubien E. C*an Fam Physician* 2000;46:636-42.

# UKPDS: Annual Transition Rates through the Stages of Nephropathy in Patients with Type 2 Diabetes




CRI = chronic renal insufficiency
RRT = renal replacement therapy

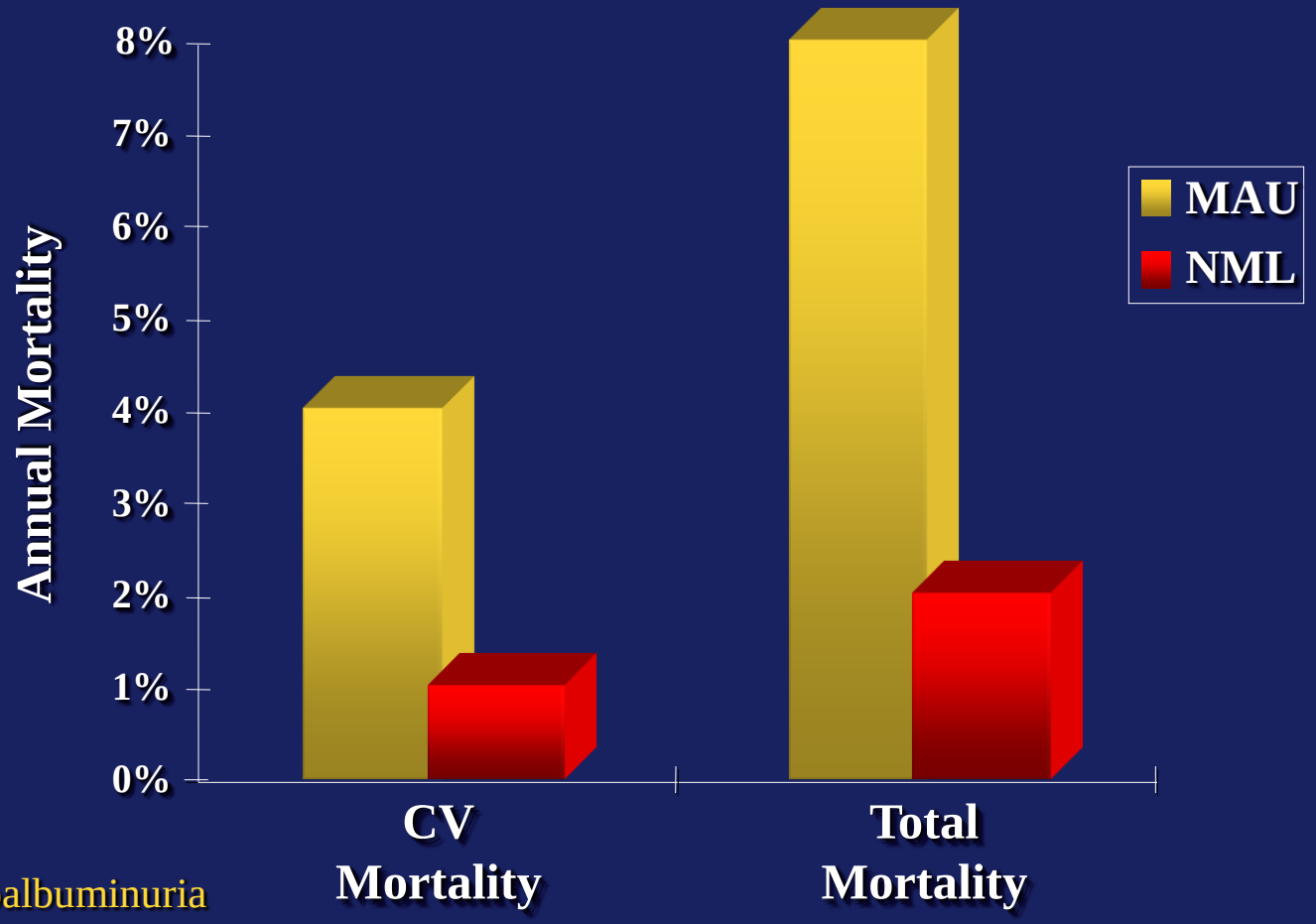
Adler AI *et al*. *Kidney Int* 2003;63:225-32.

# Why Screen for Proteinuria?

- The presence of protein in the urine is usually a marker of kidney damage
- To delay or prevent loss of renal function through early detection and initiation of effective therapies
- To manage complications in those identified with renal disease
- Screening may also identify people with increased vascular risk

K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease. Available at : www.kidney.org.
CDA 2008 Clinical Practice Guidelines. Can J Diabetes 2008; 32(suppl 1):S126-S133.

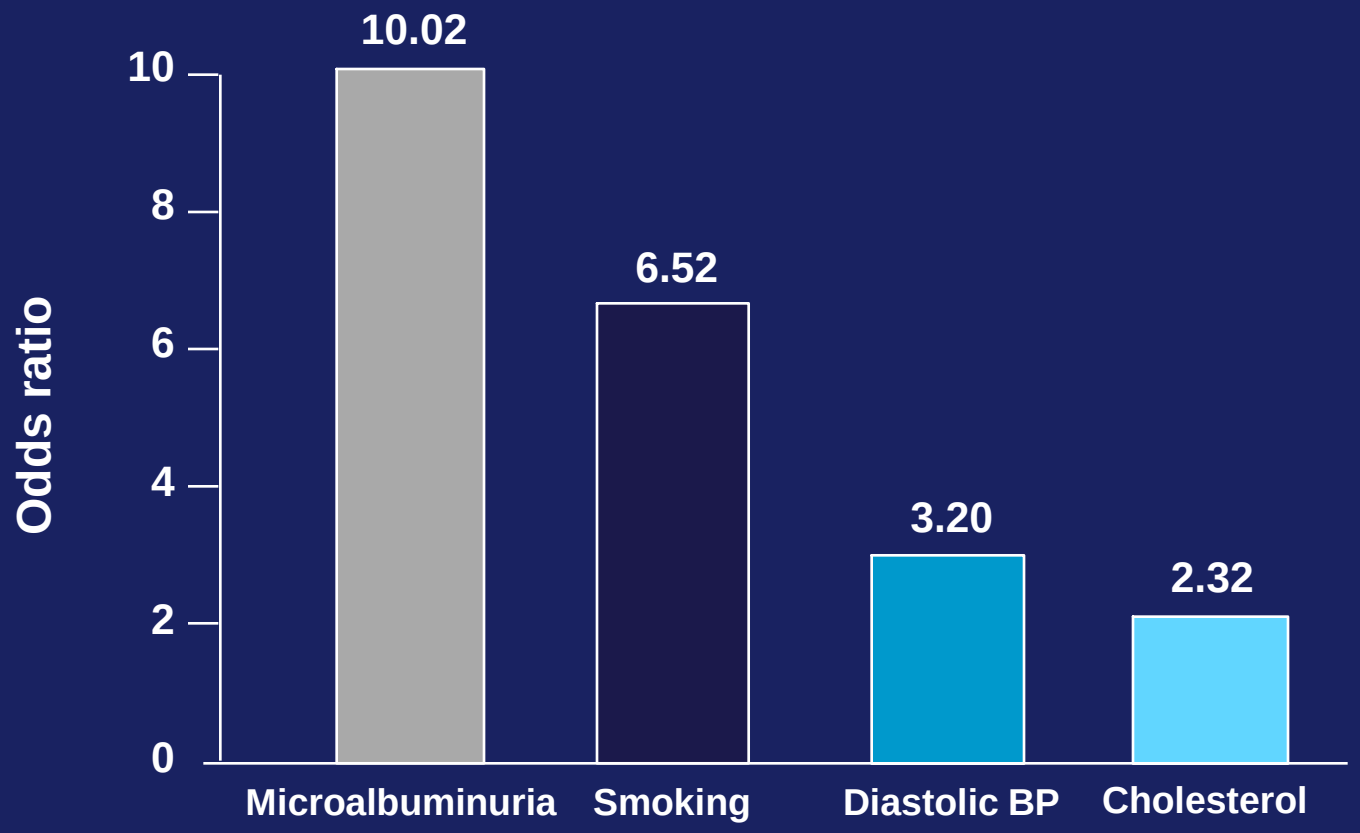
# Impact of Microalbuminuria




MAU = Microalbuminuria
NML = Normal

Ref : Neil,A. A prospective population-based study of MAU as a predictor of mortality in NIDDM. *Diabetes Care* 1993;16:996-1003

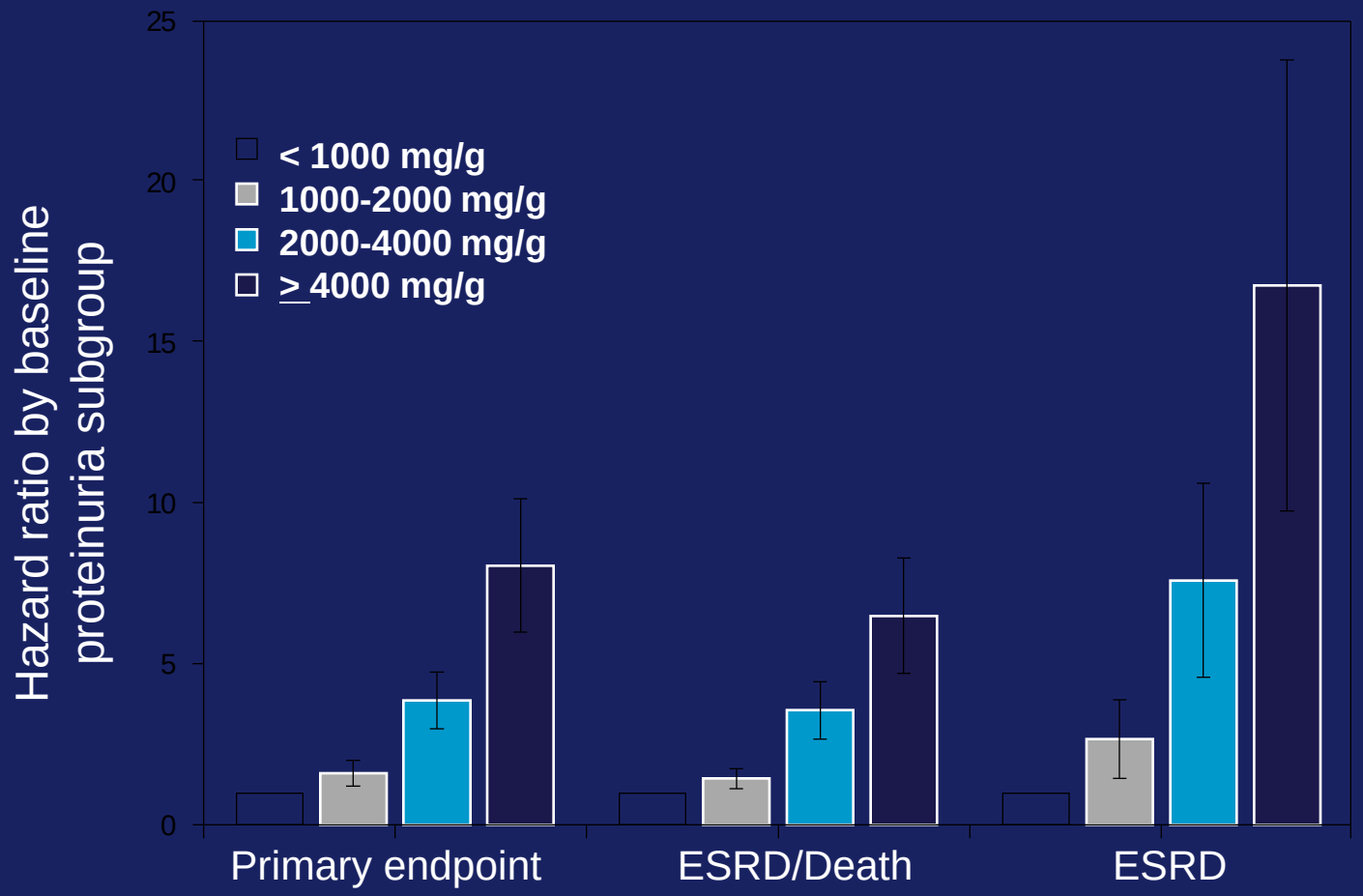
# CHD Mortality in Diabetes: Odds Ratios for Selected Risk Factors




CHD: coronary heart disease

Eastman RC, et al: Lancet 1997; 350 Suppl 1:SI29-32.

# Albuminuria: Factor Predicting Renal Events




n=1513
ESRD = end-stage renal disease
Zhang Z, et al. J Am Soc Nephrol 2005; 16(6):1775-80.

# Proteinuria and Renal End Points

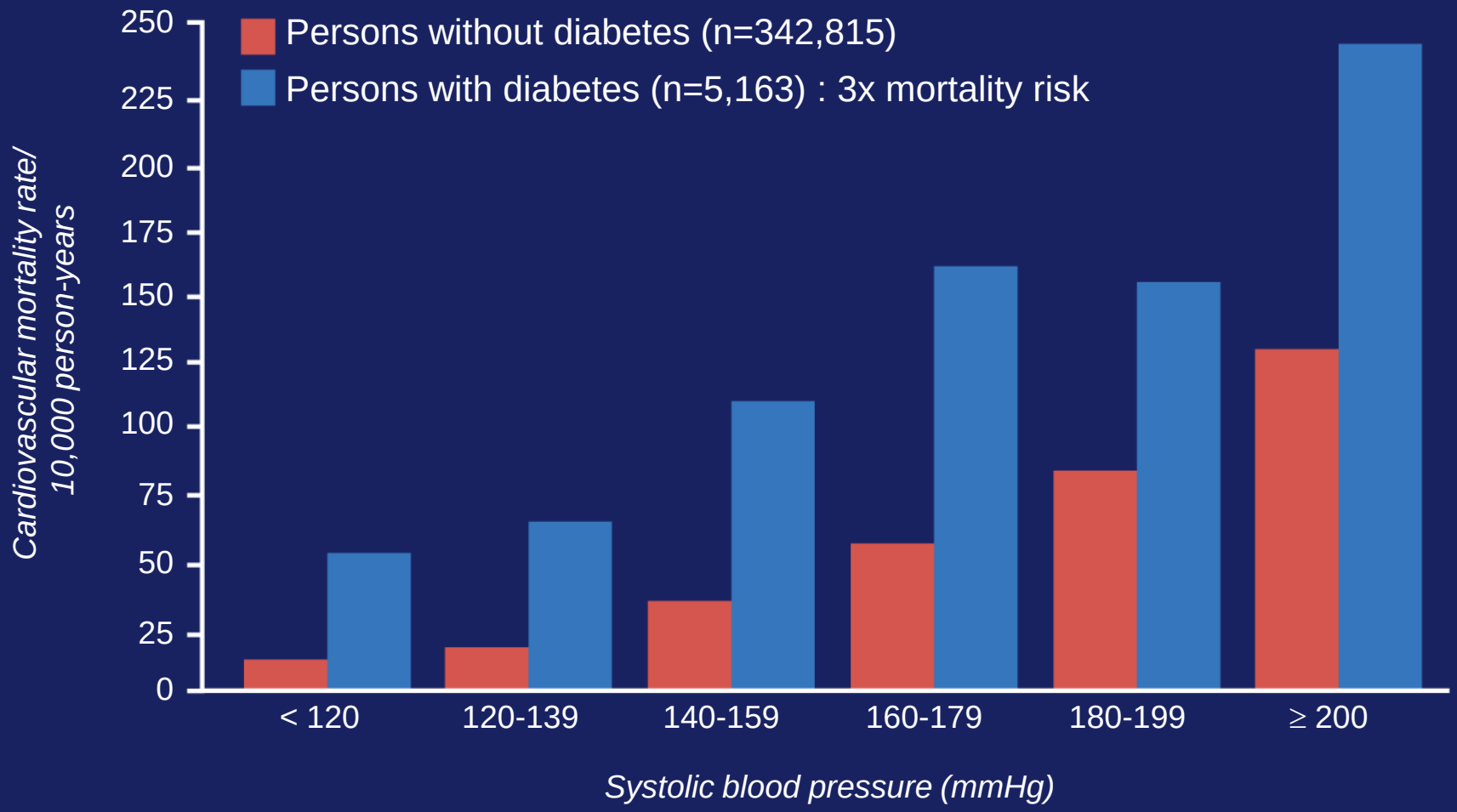
- The key point is not how much proteinuria you start with, it's how much you finish with
- For each halving of proteinuria, the relative risk of a renal endpoint was reduced during follow-up
- There was an 18 percent decrease in risk of a cardiovascular event for every 50 percent decrease in the rate of albumin excretion

# Blood Pressure Targets

- General < 140/90 mmHg
- Diabetes mellitus < 130/80 mmHg
- Chronic kidney disease < 130/80 mmHg

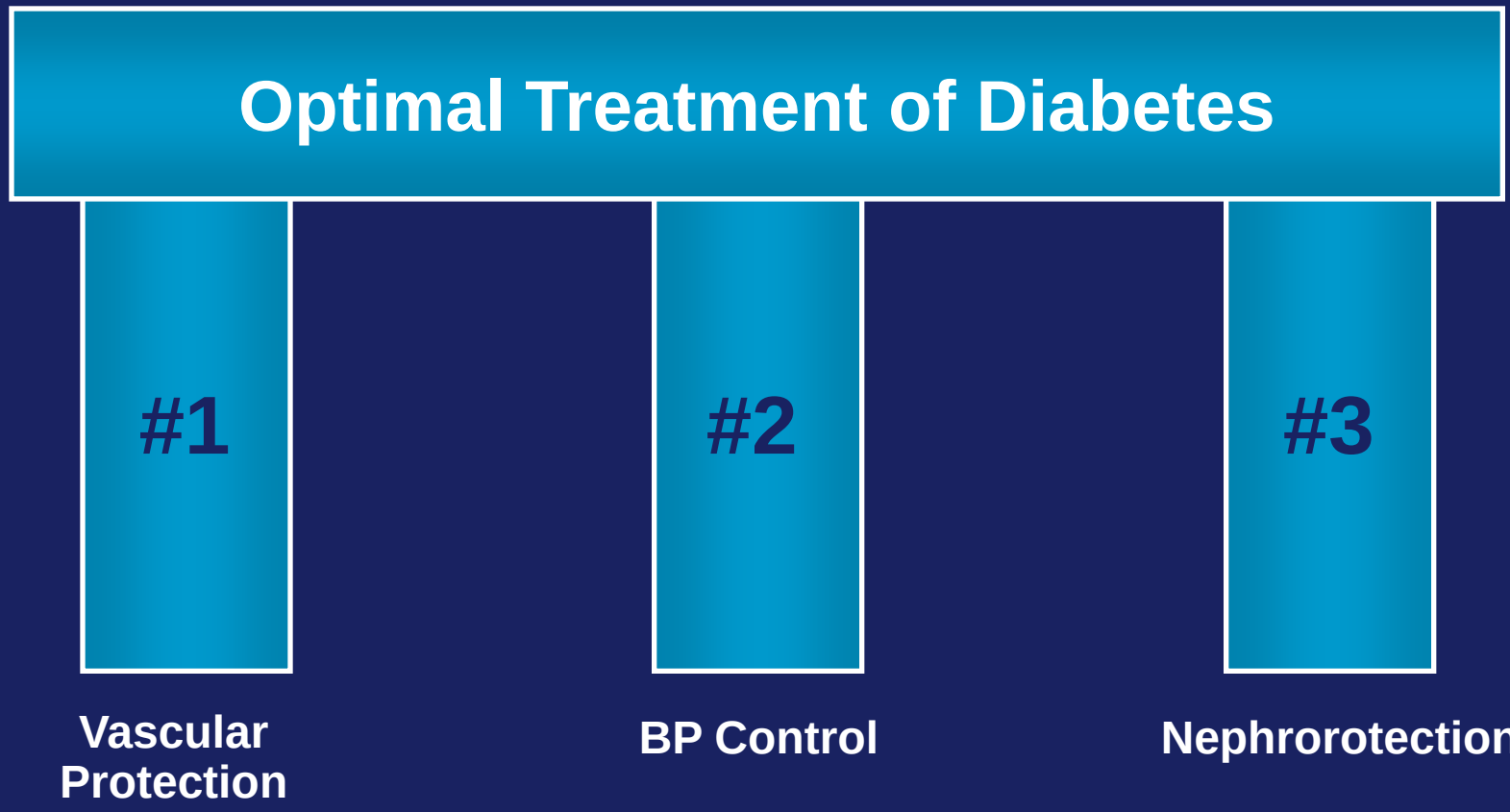
**CHEP 2009 Recommendations.**

# Association of Systolic BP and Cardiovascular Death in Type 2 Diabetes




**Stamler J *et al*. *Diabetes Care* 1993;16:434-44.**

# Priorities for Treatment in Diabetes: The Three Pillars of Protection




Adapted from: CDA Clinical Practice Guidelines Expert Committee. Can J Diabetes 2008;32(suppl 1):S1-S201

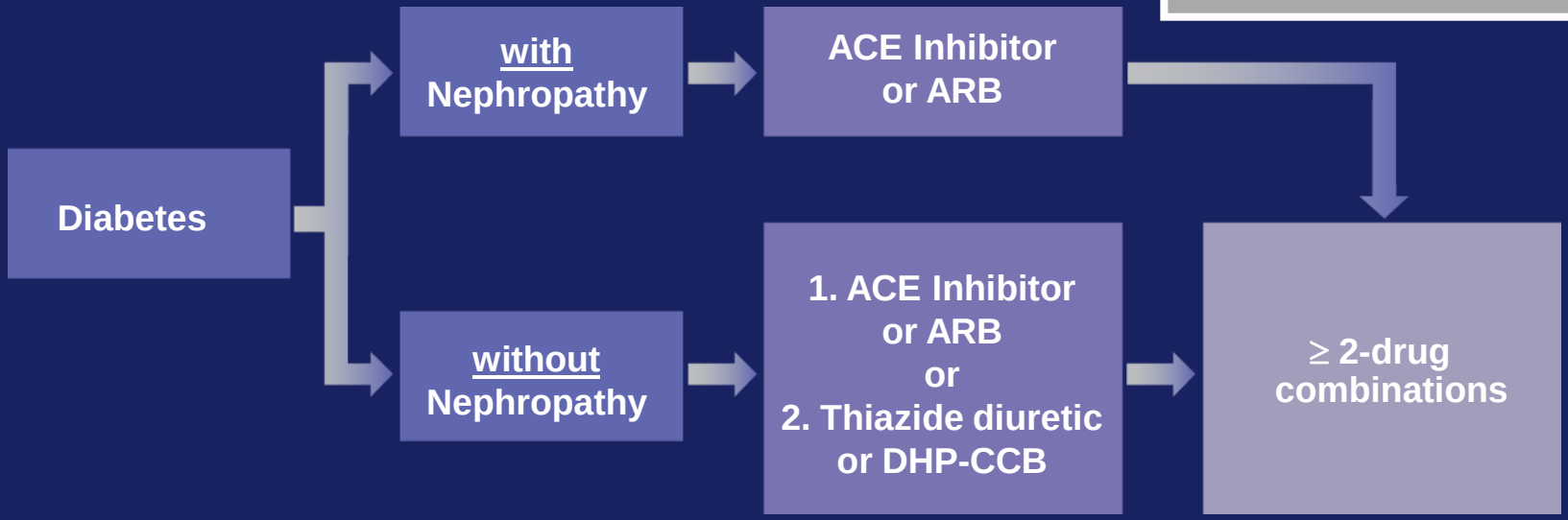
# Two Goals in Protecting a Diabetic Kidney

- Lower BP to target
- Decrease proteinuria

# Treatment of Hypertension in Association with Diabetes Mellitus

A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target

THRESHOLD EQUAL OR OVER 130/80 mmHg
AND TARGET BELOW 130/80 mmHg



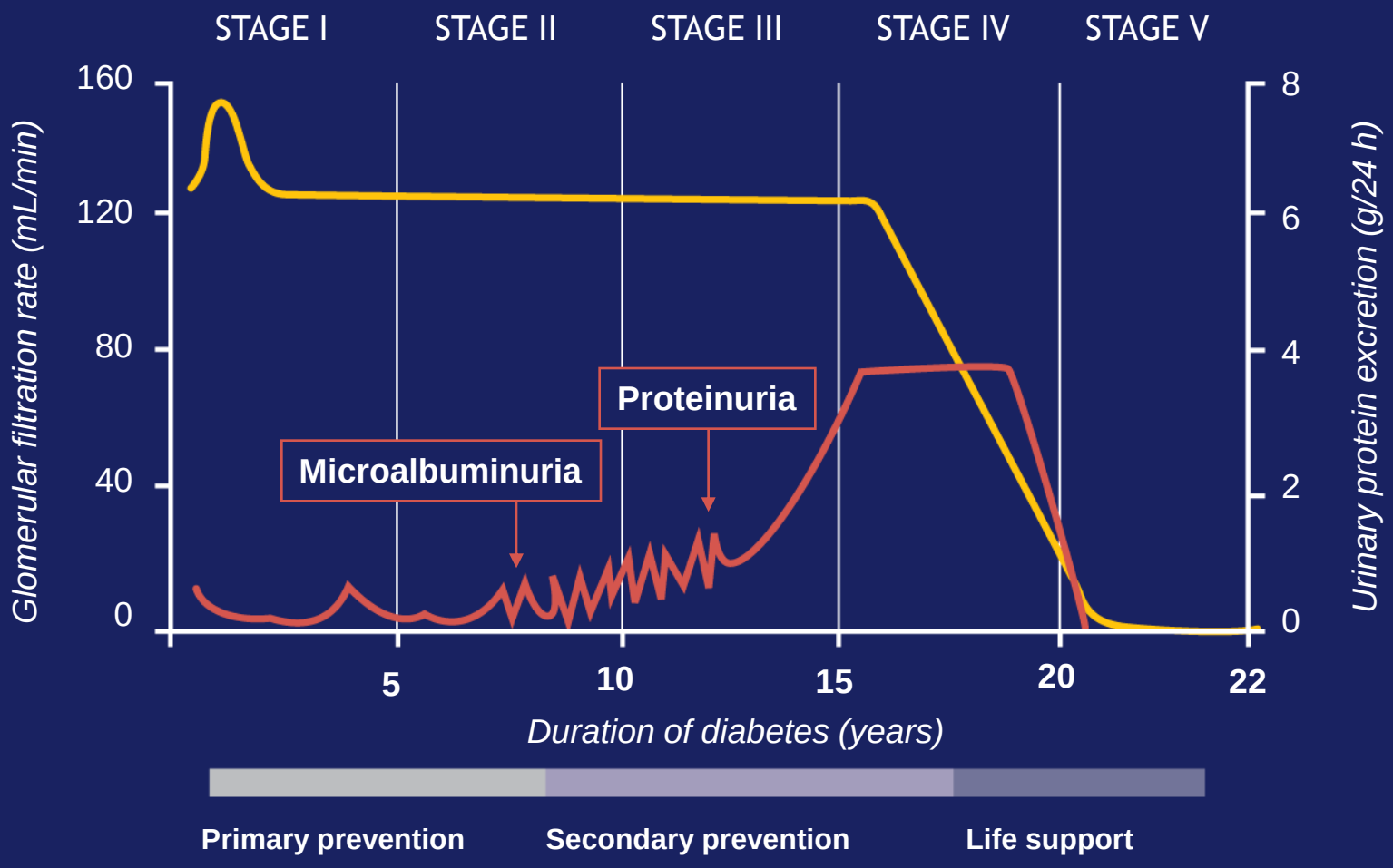

Monitor potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB. Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria.

**More than 3 drugs may be needed to reach target values for patients with diabetes**

If Creatinine over 150 µmol/L or creatinine clearance below 30 ml/min ( 0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired

**CHEP 2010 Recommendations**

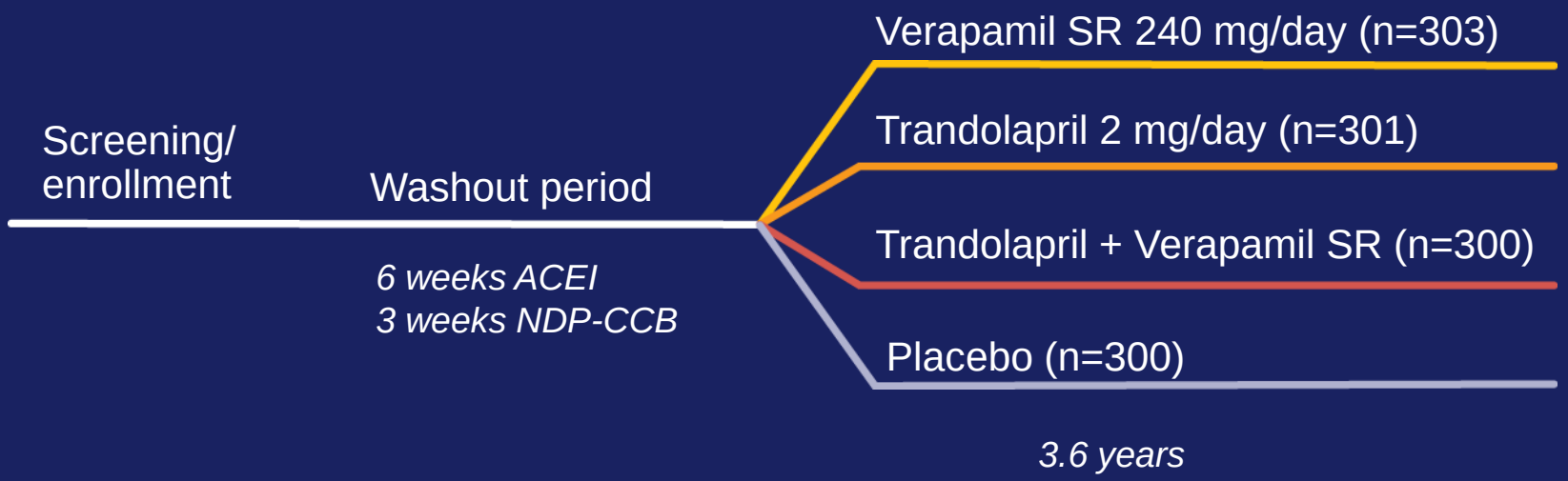
# Natural History of Diabetic Nephropathy




Adapted from Pylypchuk GB, Beaubien E. C*an Fam Physician* 2000;46:636-42.

# Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)

**1,209 patients with type 2 DM, normoalbuminuria, serum creatinine <133 µmol/L, and BP >130/85 mmHg**

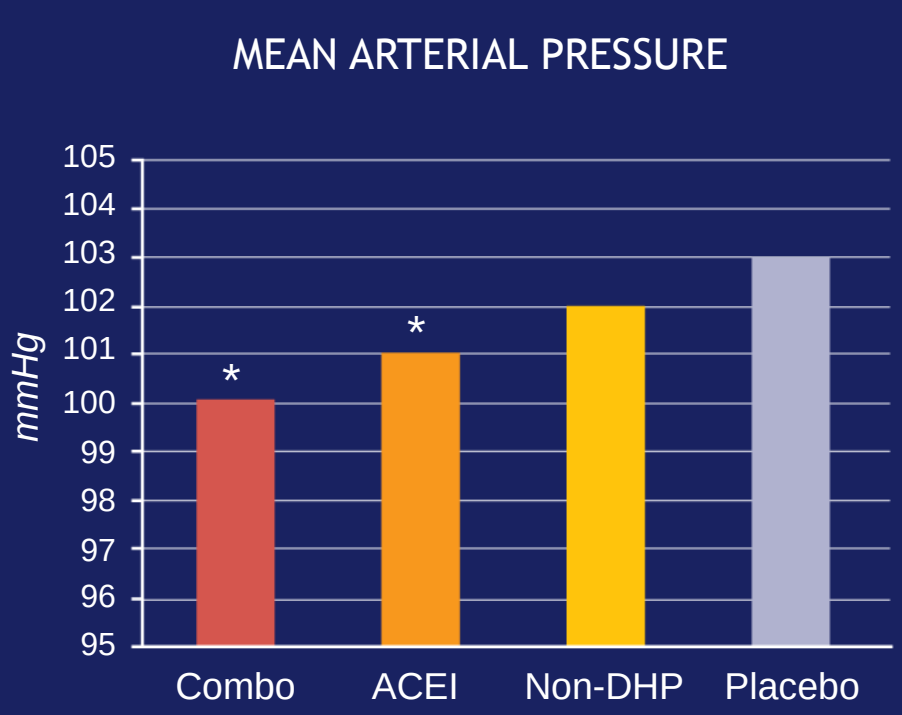


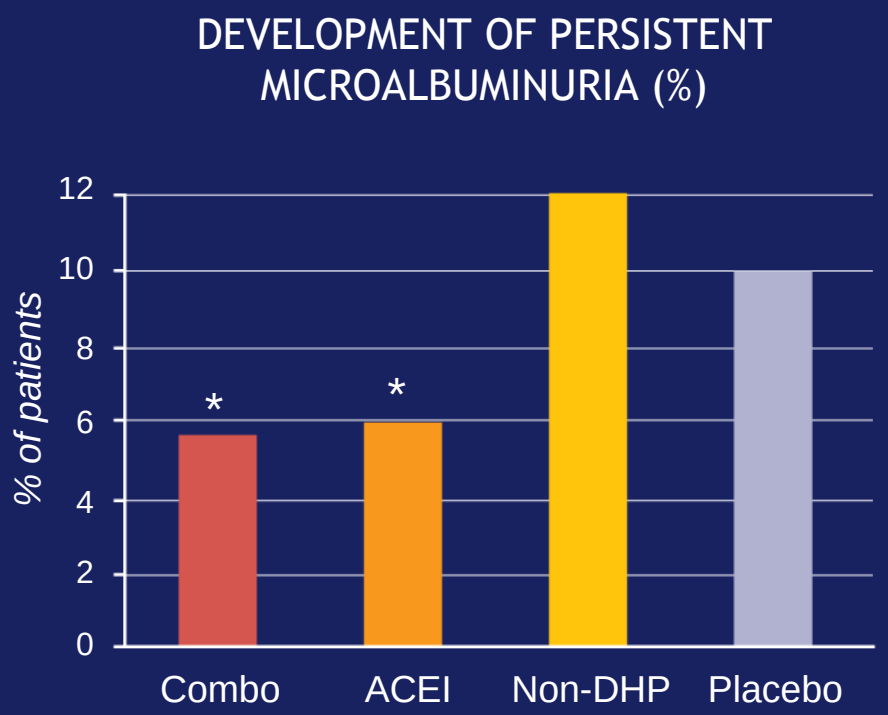

Target BP <120/80 mmHg and target A1C <7.0%

Primary endpoint: development of persistent MAU

**Ruggenenti P *et al*. *N Engl J Med* 2004;351:1941-51.**

# Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)

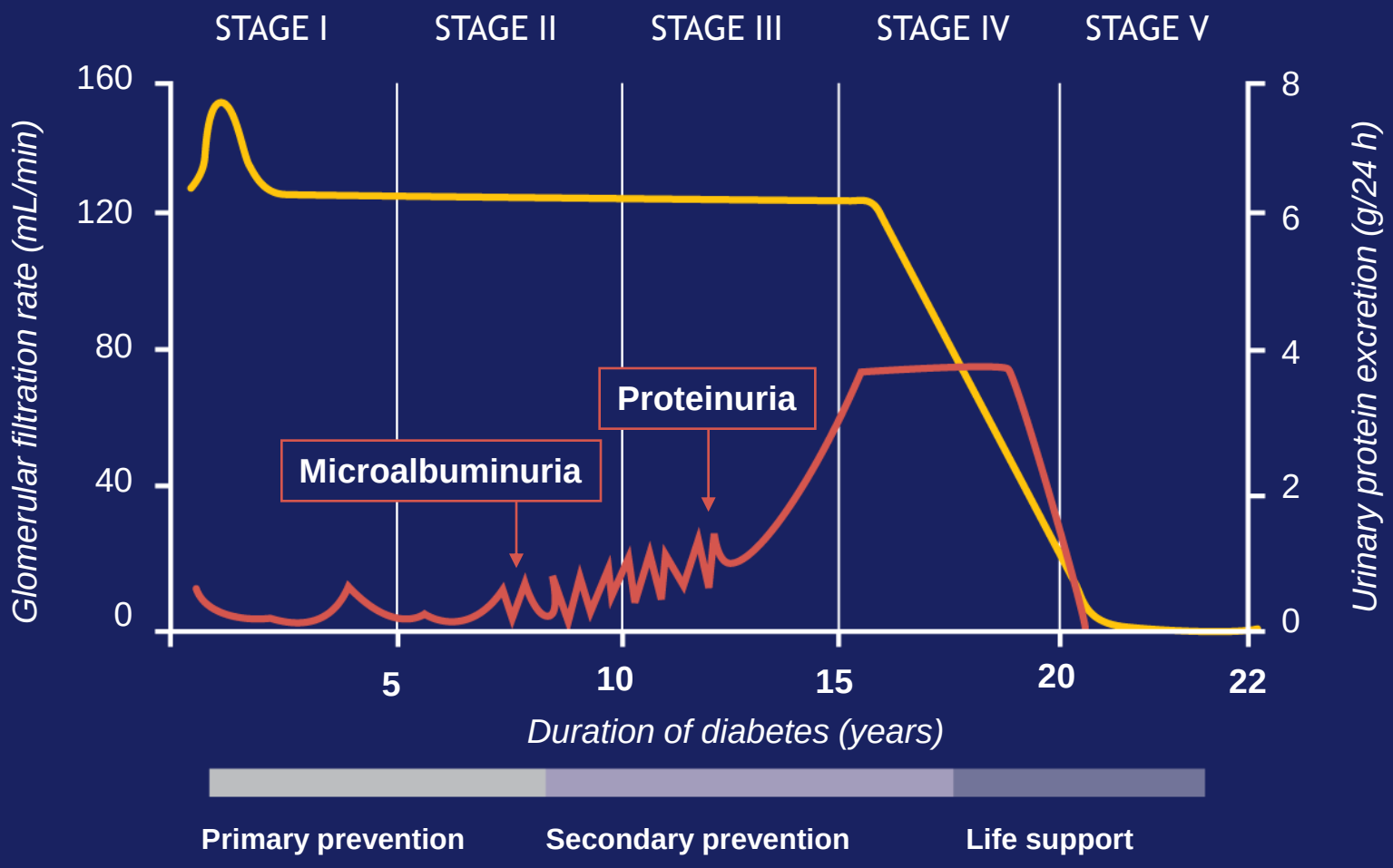



* Significant vs. placebo

**Ruggenenti P *et al. N Eng J Med* 2004;351:1941-51.**

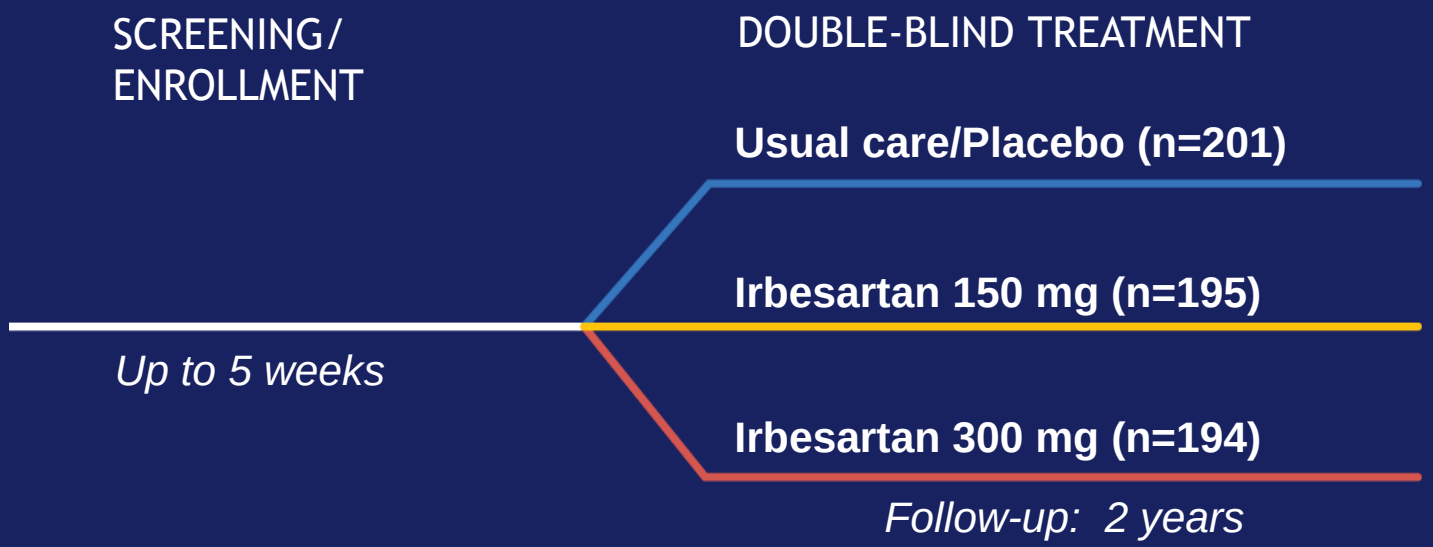
# Natural History of Diabetic Nephropathy




Adapted from Pylypchuk GB, Beaubien E. C*an Fam Physician* 2000;46:636-42.

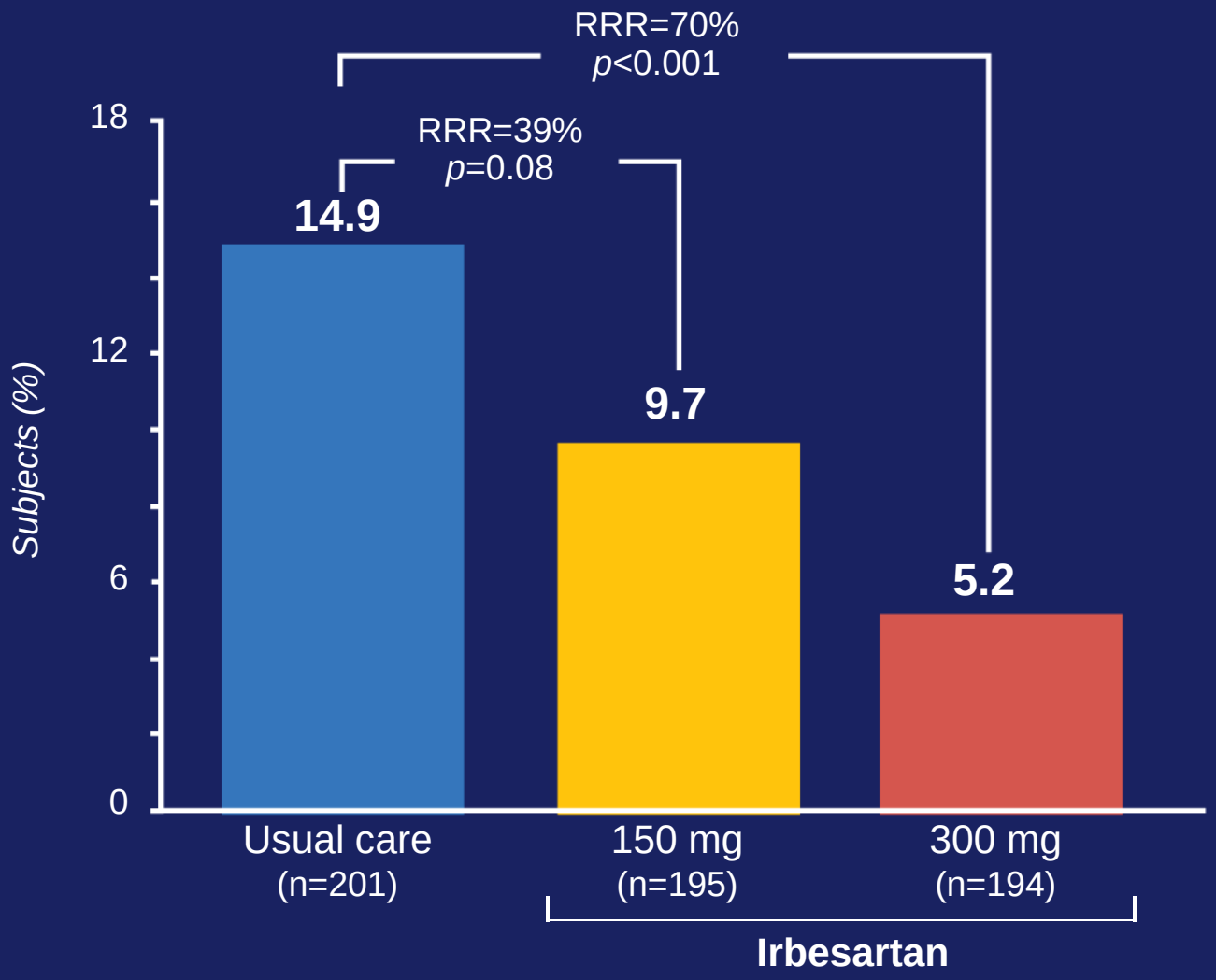
# IRMA 2: Study Design

590 patients with type 2 diabetes, microalbuminuria (albumin excretion rate: 20-200 µg/min), normal renal function, and hypertension



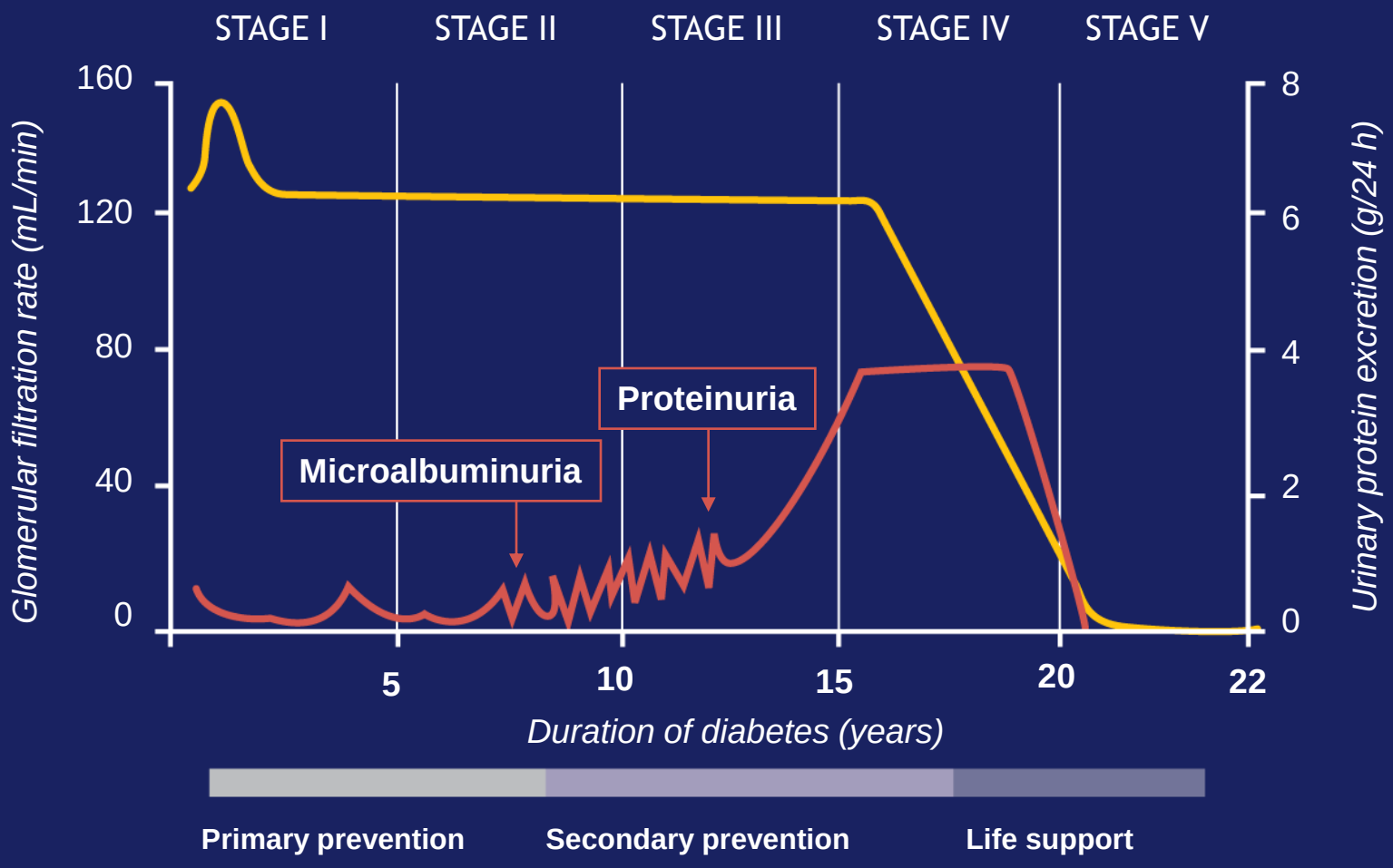

Parving HH *et al*. *N Engl J Med* 2001;345:870-8.

# IRMA 2:
# Development of Overt Proteinuria




Parving HH *et al*. *N Engl J Med* 2001;345:870-8.

# Natural History of Diabetic Nephropathy




Adapted from Pylypchuk GB, Beaubien E. C*an Fam Physician* 2000;46:636-42.

## IDNT

### Population
n = 1,715
NIDDM with albuminuria and HTN
(900 mg/24 hrs)

### Treatment
Irbesartan vs. Amlodipine vs. Placebo
(+non-ACEI, non-CCB agents)
2.6 years average

### Primary Endpoints
Doubling sCr/ESRD/death

### Secondary Endpoints
CV morbidity/mortality
Proteinuria

Lewis EJ *et al*. *N Engl J Med* 2001;345:851-60.

## RENAAL

### Population
n = 1,513
NIDDM with albuminuria and HTN
(300 mg/g creatinine)
Serum creatinine ≥115-265 µmol/L

### Treatment
Losartan vs. Placebo
(+ non-ACEI agents)
3.4 years average

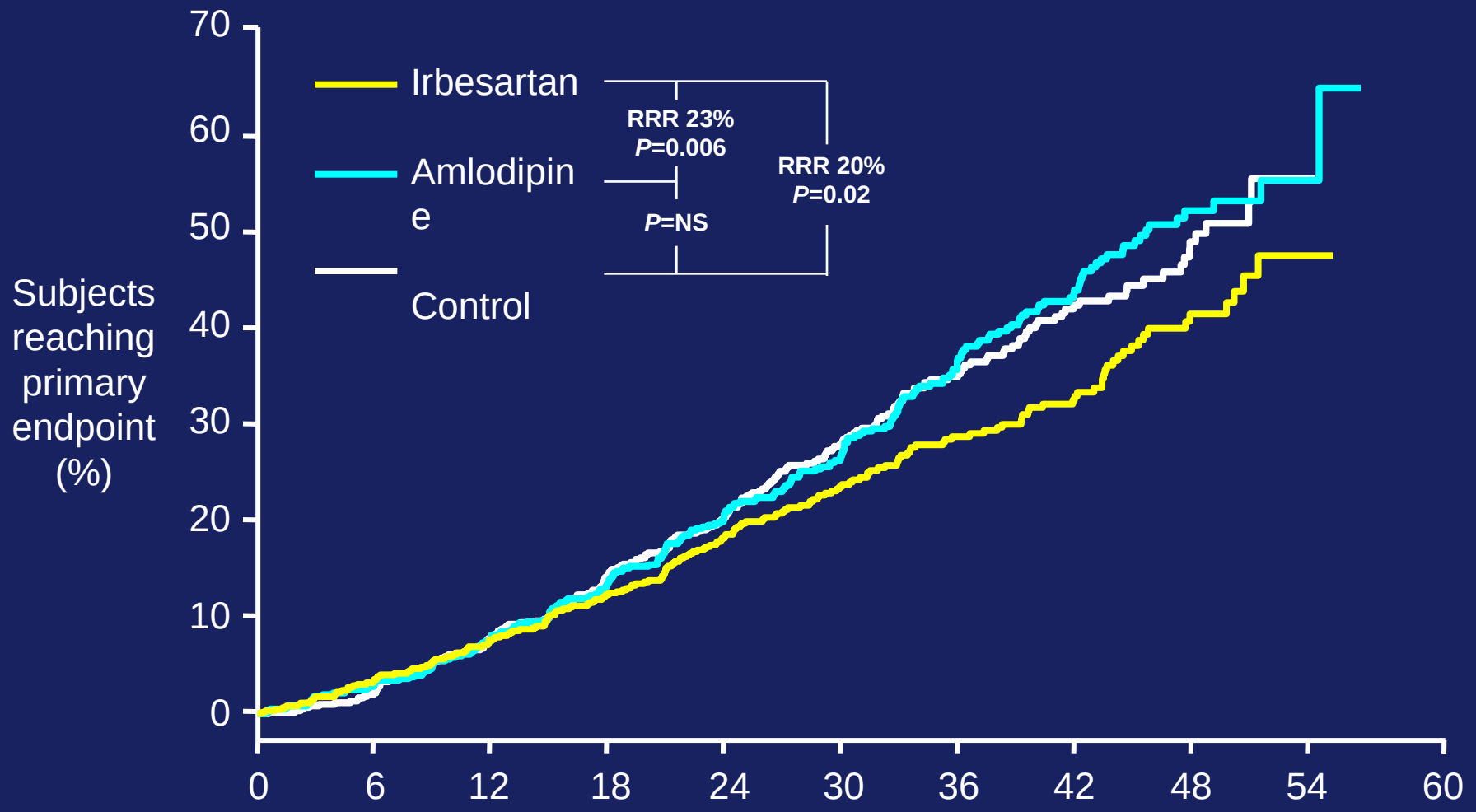
### Primary Endpoints
Doubling sCr/ESRD/death

### Secondary Endpoints
CV morbidity/mortality
Proteinuria

Brenner BM *et al*. *N Engl J Med* 2001;345:861-9.

# IDNT Primary Endpoint

## Time to Doubling of Serum Creatinine, ESRD, or Death



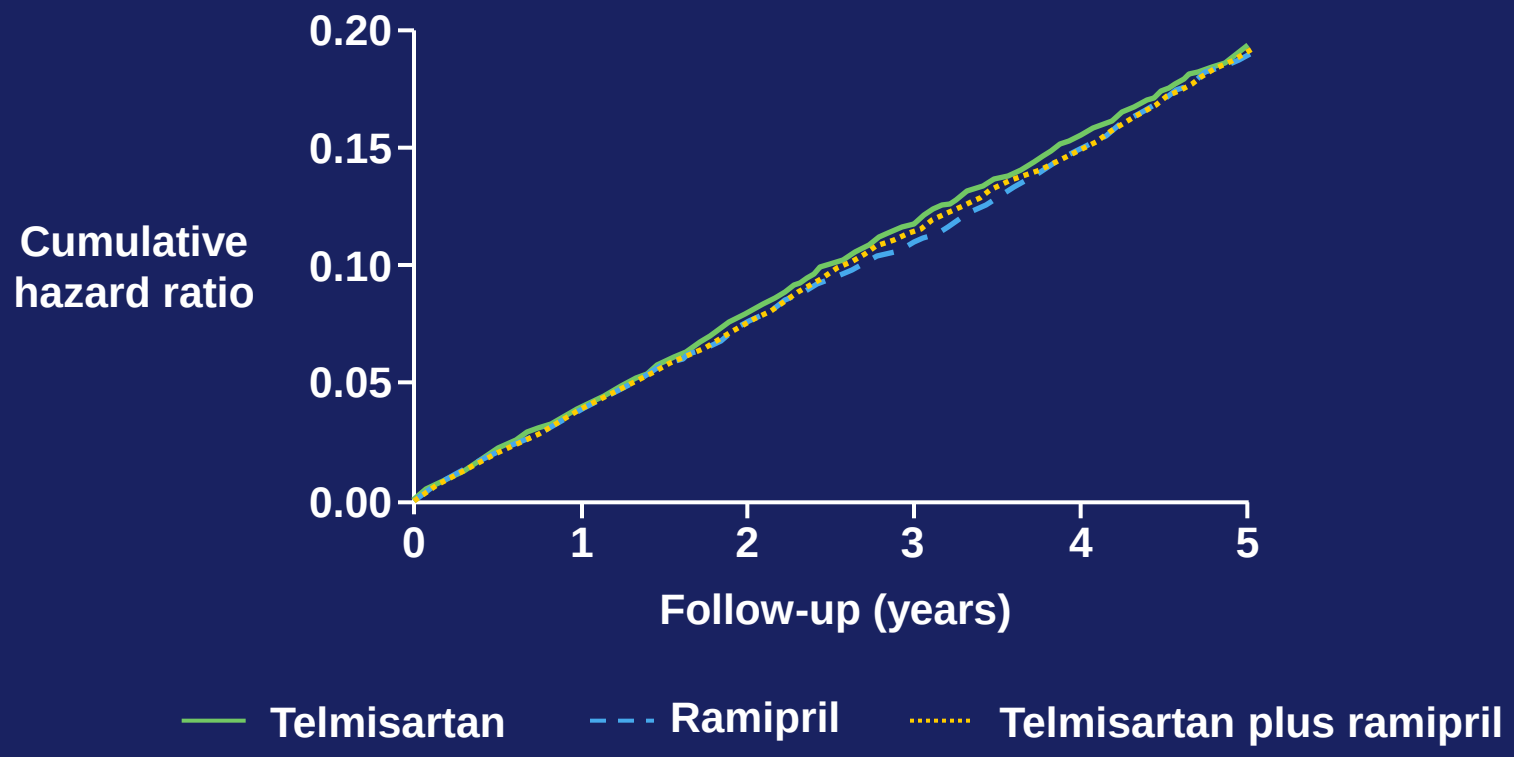

Lewis EJ et al. *N Engl J Med* 2001;345:851-860.

PRIME
IRBESARTAN MORTALITY/MORBIDITY EVALUATION

# Public Health Implications of RENAAL

- **For diabetic patients at risk over a 3.5 year period, it is estimated:***
  - one case of ESRD can be prevented for every 16 treated
  - losartan reduces days with ESRD by 32%
- **Extrapolating these results to the 595,000 Type 2 diabetic patients with proteinuria in the US:****
  - 37,500 fewer new ESRD patients
  - $3.1 billion reduction in the cost of ESRD alone (savings increase $4.4 billion at 4 years)
  - **Delay the need for dialysis in a diabetic by 2 years**

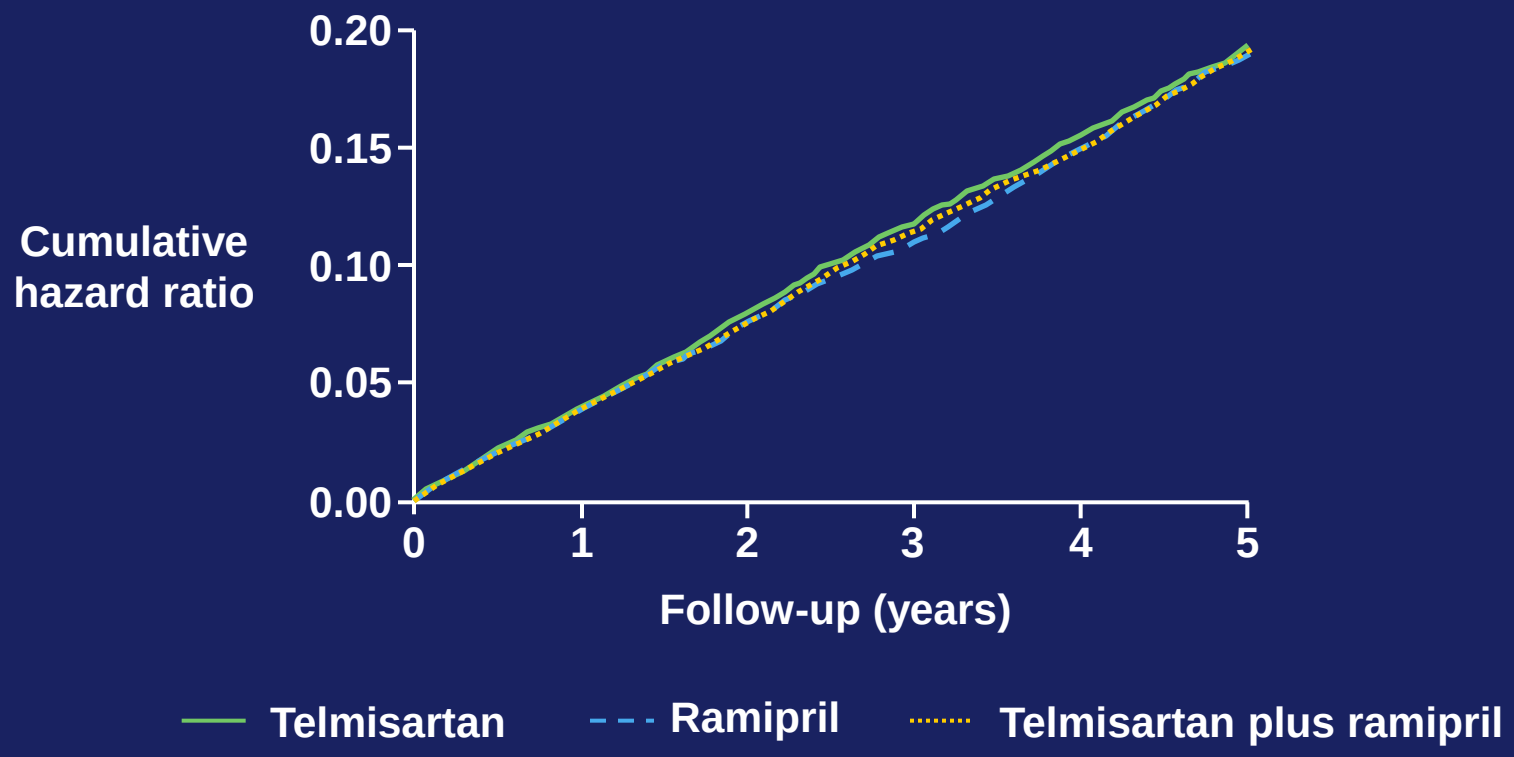
# ONTARGET: results




- no significant difference in primary or secondary outcomes
- combination showed no additional benefit

ONTARGET Investigators *et al*. *NEJM* 2008;358:1547-59.

# ONTARGET: results




- no significant difference in primary or secondary outcomes
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ONTARGET Investigators *et al*. *NEJM* 2008;358:1547-59.

"Combinations of an ACEI with an ARB are specifically not recommended except in patients who have CHF"

**- CHEP 2010 Guidelines**

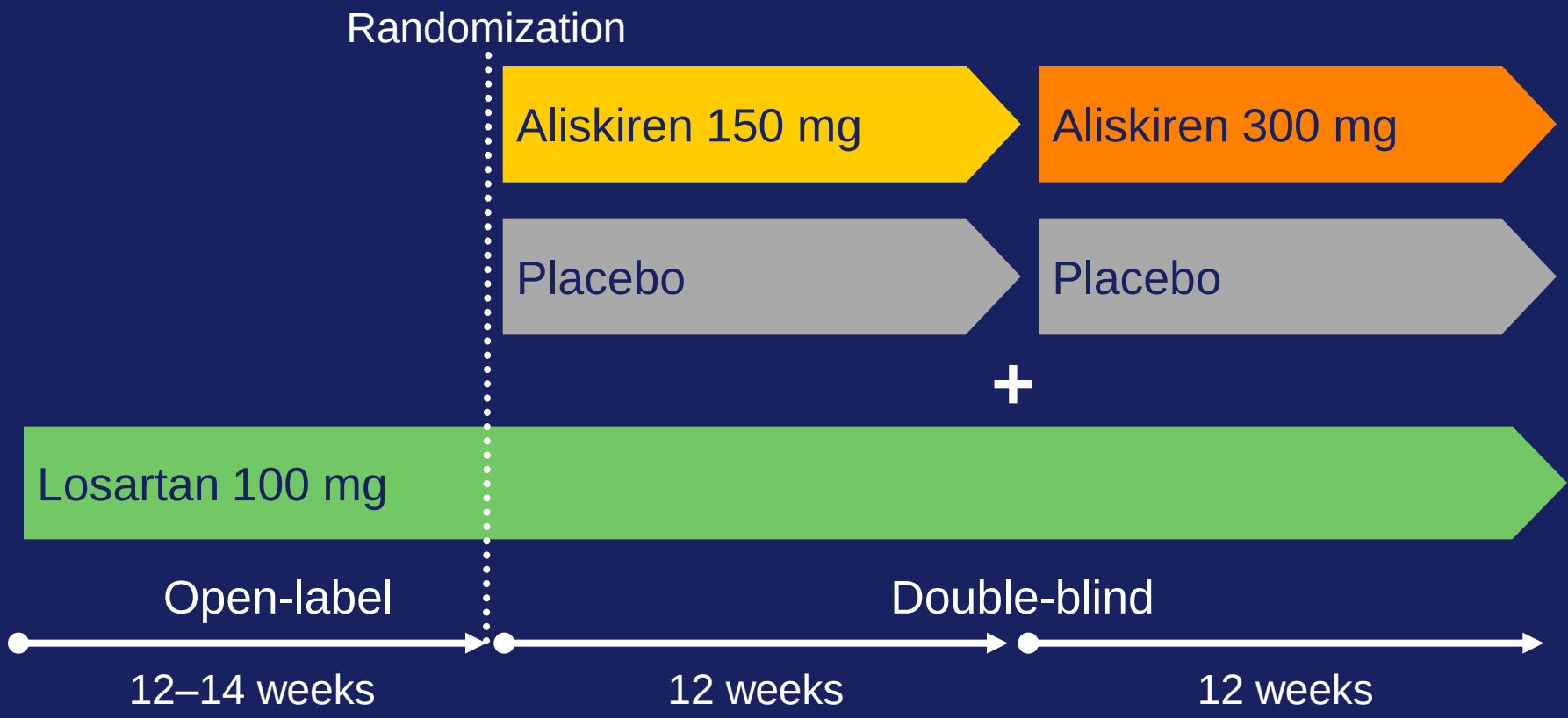
# Aliskiren in the EValuation of PrOteinuria In Diabetes AVOID study – Design

| | |
|---|---|
| Study design: | Double-blind, randomized, placebo-controlled |
| Study population: | 496 patients |
| Inclusion criteria: | Mild-to-moderate hypertension<br>Type 2 diabetes<br>Proteinuria |
| Treatment period: | 24 weeks |
| Study status*: | Completed |

*Study status as of May 2007

Clinicaltrials.gov 2006; Data on File, Novartis 2007

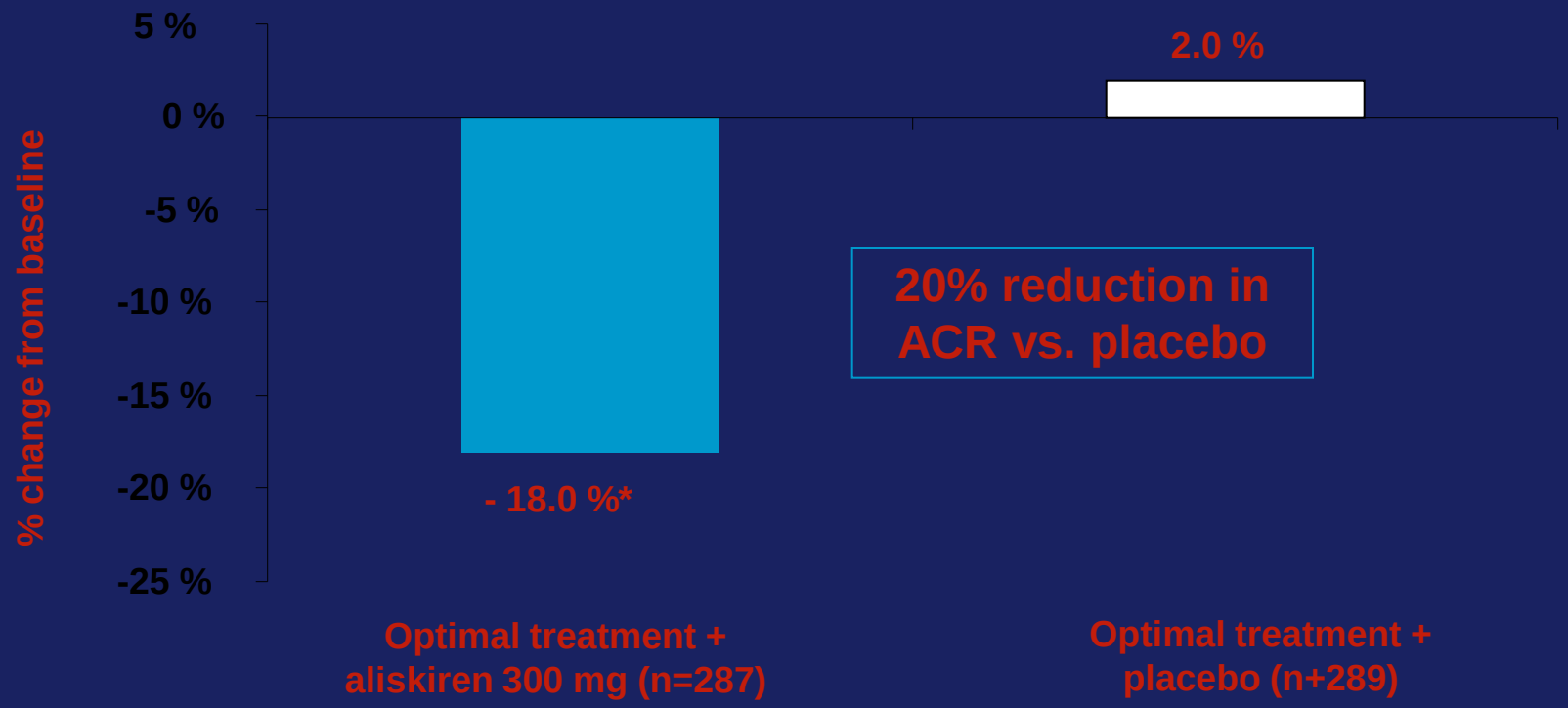
# AVOID study – Design overview




- All patients continue to receive open-label losartan 100 mg and optimal antihypertensive therapy during the double-blind period
- Patients force-titrated after 12 weeks
- All treatments administered once daily

Clinicaltrials.gov 2006; Data on File, Novartis 2007

# DRI or Placebo + Optimal Treatment Including ARB (The AVOID study): Mean Change in ACR




*$p$ < 0.001 vs. optimal care + placebo

Parving HH, *et al*: *N Engl J Med* 2008; 358:2433-46.

Blockers of the RAAS
delay the onset of MAU and
slow the progression of diabetic
nephropathy to ESRD

# Vascular Protection: Summary

## Non-pharmacological

- Smoking cessation
- Exercise
- BMI <25 kg/m$^2$
- Alcohol <2 drinks/day
- Low salt diet

## Pharmacological

- ASA 81 mg/day
- A1C <7%
- LDL-C ≤2.0 mmol/L
- BP <130/80 mmHg
- Blockers of the RAAS

**CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008;32(Suppl 1):S1-201.**