Microalbuminuria in Type 2 Diabetics

AN IMPORTANT BUT OVERLOOKED RISK FACTOR

INTRODUCTION AND DEFINITIONS

- Increased urinary protein excretion may be an early clinical manifestation of diabetic nephropathy.
- The **normal** rate of albumin excretion is less than 30 mg/day (20 mcg/min);
- Persistent albumin excretion between 30 and 300 mg/day (20 to 200 mcg/min) is called **moderately increased albuminuria** (formerly "**microalbuminuria**").

Nationla Kidney foundation. 2020. Available from https://www.kidney.org/kidneydisease/siemens_hcp_acr. Accessed on 25-05-2020

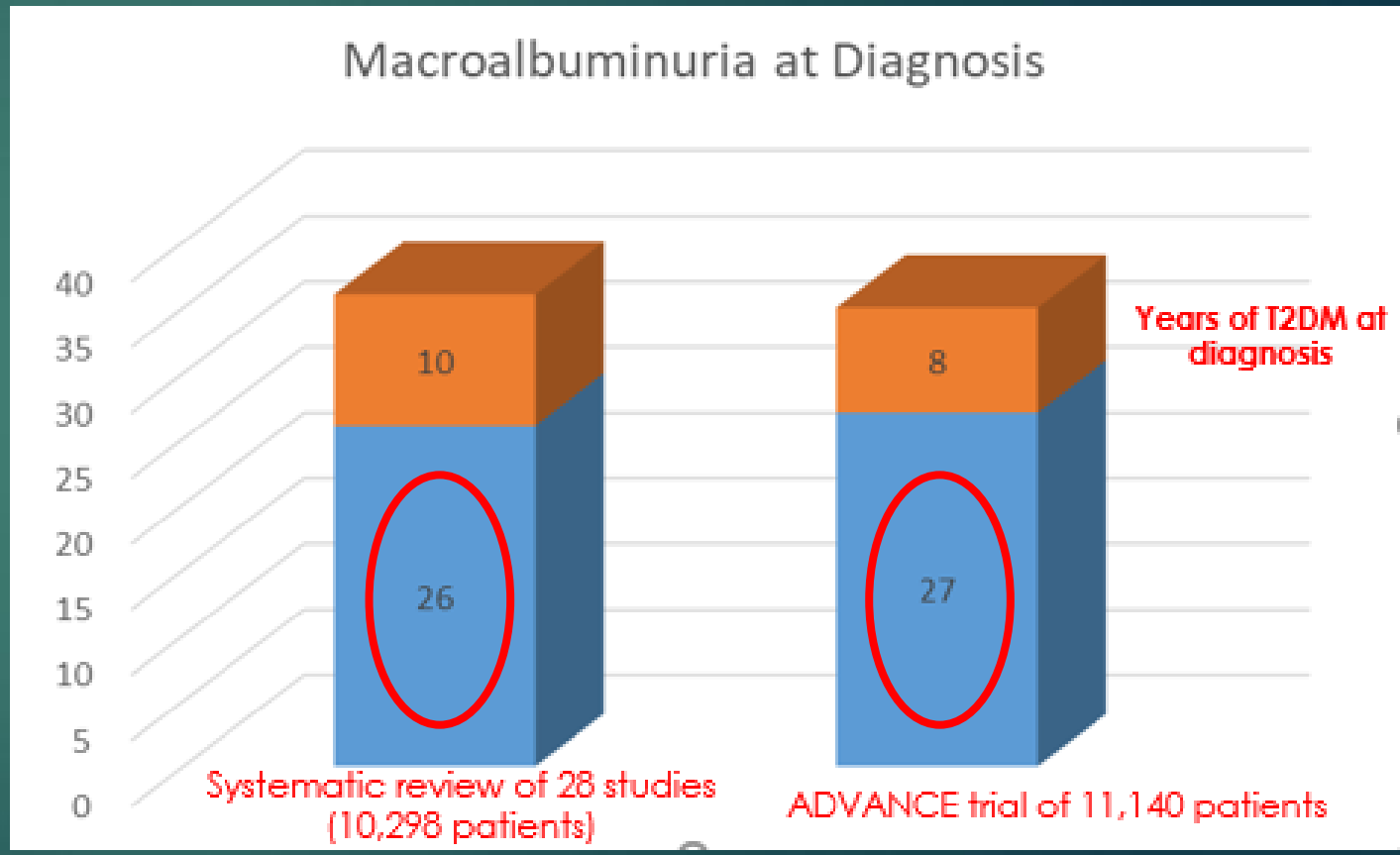
INTRODUCTION AND DEFINITIONS

- Albumin excretion above 300 mg/day (200 mcg/min) is considered to represent **severely increased albuminuria** (formerly "**macroalbuminuria**")
- Also called by the names:
  - **Overt proteinuria,**
  - **Clinical renal disease,** or
  - **Dipstick positive proteinuria**.

Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011) 2013; 3:19.
Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK). Am J Kidney Dis 2003; 42:617.

Prevalence

- The reported prevalence of moderately increased albuminuria among patients with type 2 diabetes approximately 10 years after the diagnosis ranges from 25 to 40 percent.



Newman DJ, Mattock MB, Dawnay AB, et al. Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess 2005; 9:iii.
ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560.

Ethnicity

- Prevalence higher in Asians and Hispanics than in whites.
- Illustrated in an international cross-sectional study of over 24,000 patients with type 2 diabetes without known albuminuria.
- At a mean duration of diabetes of almost eight years, the rate of moderately increased albuminuria was significantly higher in Asians and Hispanics (43% vs 33%).
- There are also racial and ethnic differences in the rate of progression to severely increased albuminuria

Young BA, Katon WJ, Von Korff M, et al. Racial and ethnic differences in microalbuminuria prevalence in a diabetes population: the pathways study. J Am Soc Nephrol 2005; 16:219.
Parving HH, Lewis JB, Ravid M, et al. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int 2006; 69:2057.

Albuminuria at DM diagnosis

- Some patients with type 2 diabetes have moderately increased albuminuria at the time of diagnosis.
- United Kingdom Prospective Diabetes Study (UKPDS)
  - Approximately 5100 patients with newly diagnosed type 2 diabetes
  - 6.5 percent had moderately increased albuminuria
  - 0.7 percent had severely increased albuminuria at the time of diagnosis [23].
  - The annual rate of progression from normal albumin excretion to moderately increased albuminuria was 2.0 percent.
  - Higher in older patients.

Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens 1993; 11:309.

Mykkänen L, Haffner SM, Kuusisto J, et al. Microalbuminuria precedes the development of NIDDM. Diabetes 1994; 43:552.

Albuminuria at DM diagnosis

- Two possible explanations for the presence of moderately increased albuminuria at the time of diagnosis of type 2 diabetes:
  - The patients had previously undiagnosed diabetes or
  - Some other disease (eg, benign nephrosclerosis) was responsible for the moderately increased albuminuria.

Mogensen CE, Vestbo E, Poulsen PL, et al. Microalbuminuria and potential confounders. A review and some observations on variability of urinary albumin excretion. Diabetes Care 1995; 18:572.

DETECTION

- Establishing the diagnosis of moderately increased albuminuria requires the demonstration of an elevation in albumin excretion (30 to 300 mg/day) that persists over a three- to six-month period.
- Fever, exercise, heart failure, infections, and poor glycaemic control are among the factors that can cause **transient moderately increased albuminuria**

Mogensen CE, Vestbo E, Poulsen PL, et al. Microalbuminuria and potential confounders. A review and some observations on variability of urinary albumin excretion. Diabetes Care 1995; 18:572.

Approach to detection

- **Urine albumin-to-creatinine ratio in an untimed urinary sample is the preferred screening strategy.**
- If an abnormal result (30 mg/g or higher) is noted in previously normal patient - repeat the test twice more over a 3 to 6 months period to confirm moderately increased albuminuria.

Mogensen CE, Vestbo E, Poulsen PL, et al. Microalbuminuria and potential confounders. A review and some observations on variability of urinary albumin excretion. Diabetes Care 1995; 18:572.

Albumin-to-creatinine ratio

- Advantages of the urine albumin-to-creatinine ratio
  - Test gives a quantitative result that correlates with the 24-hour urine values over a wide range of protein excretion,
  - It is simple to perform and
  - Inexpensive,
  - Repeat values can be easily obtained.

Mogensen CE, Vestbo E, Poulsen PL, et al. Microalbuminuria and potential confounders. A review and some observations on variability of urinary albumin excretion. Diabetes Care 1995; 18:572.

Urine albumin concentration

- Although the 24-hour urine collection was the initial gold standard screening can be more simply achieved by a **timed urine collection or measurement of the urine albumin concentration on an early morning specimen**.
- Moderately increased albuminuria is unlikely if the albumin excretion rate is below 20 mcg/min in a timed collection or the urine albumin concentration is less than 20 to 30 mg/L in a random specimen.
- Higher values may represent false positive results and should be confirmed by repeated measurements.

Mogensen CE, Vestbo E, Poulsen PL, et al. Microalbuminuria and potential confounders. A review and some observations on variability of urinary albumin excretion. Diabetes Care 1995; 18:572.

Testing

Dipsticks

- Semiquantitative
- If urine albumin excretion cannot be directly measured.
- Guidelines on appropriate testing using dipsticks state that,

…of the available methods, the immunoturbidimetric assay is the most reliable and should be the standard for comparison because it has >95 percent sensitivity and specificity to detect very low levels of albuminuria.

Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2011; 34:e61
Gross JL, de Azevedo MJ, Silveiro SP, et al. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005; 28:164

Testing

- False negative and false positive results can occur with dipstick, since the urine albumin concentration is determined by the urine volume as well as the amount of albuminuria.
- Thus, at a particular rate of albumin excretion, a substantial increase or decrease in urine volume will respectively lower and raise the urine albumin concentration.
- The confounding effect of the urine volume can be minimized by repeated measurements on early morning specimens.

Schwab SJ, Dunn FL, Feinglos MN. Screening for microalbuminuria. A comparison of single sample methods of collection and techniques of albumin analysis. Diabetes Care 1992; 15:1581.

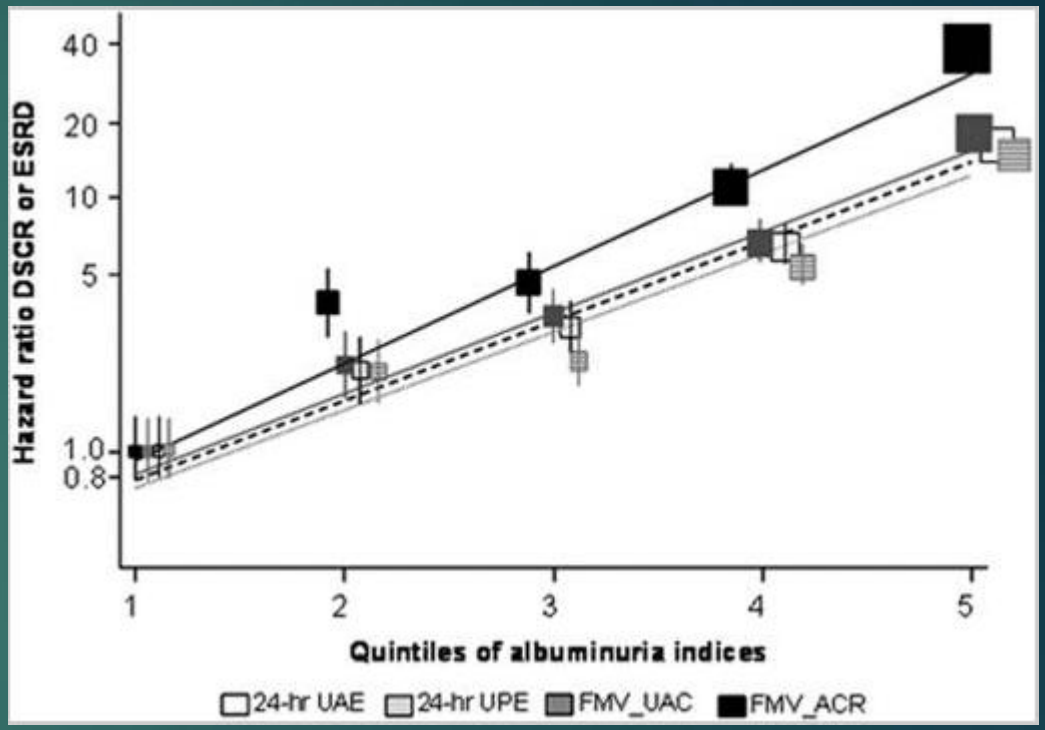
Urine albumin-to-creatinine ratio

- The confounding effect of variations in urine volume on the urine albumin concentration can be avoided by an untimed urine specimen.
- A value 30 to 300 mg/g of creatinine suggests that albumin excretion is between 30 and 300 mg/day and, therefore, that moderately increased albuminuria is probably present.
- Values above 300 mg/g (or 34 mg/mmol) are indicative of severely increased albuminuria.
- This classification system requires that at least two of three specimens fall within the moderately increased or severely increased albuminuria range over a three- to six-month period.

KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis 2007; 49:S12.

Predictive value

- The albumin-to-creatinine ratio from a first morning void sample appears to provide the best predictive value for renal disease progression.
- **RENAAL trial**
  - Methods of estimating protein excretion were compared
    - In their ability to predict renal outcomes,
    - the time of doubling of serum creatinine or end-stage renal disease.
  - Albumin-to-creatinine ratio from a first morning void demonstrated the strongest association with the risk for renal events.



- The superior predictive capability reflects both an increase in albumin and decrease in creatinine generation and excretion.

Lambers Heerspink HJ, Gansevoort RT, Brenner BM, et al. Comparison of different measures of urinary protein excretion for prediction of renal events. J Am Soc Nephrol 2010; 21:1355.

Limitations

- There are two major limitations of using random spot urine samples to quantify proteinuria:
  - The UPCR and UACR are heavily influenced by the urine creatinine concentration (the denominator of the ratio) and therefore by the total daily creatinine production.
  - Urine protein excretion can vary throughout the day (especially resulting from exercise and posture) and from day to day

Naresh CN, Hayen A, Craig JC, Chadban SJ. Day-to-day variability in spot urine protein-creatinine ratio measurements. Am J Kidney Dis 2012; 60:561.

Timing of collection

- The best correlation was found with the first morning void.
- There are no data about the timing of repeat measurements as the patient's course is being monitored.
- If possible, it seems preferable to obtain the samples at approximately the same time of day.

Witte EC, Lambers Heerspink HJ, de Zeeuw D, et al. First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am Soc Nephrol 2009; 20:436.

Accuracy

- Vigorous exercise can cause a transient increase in albumin excretion.
- As a result, patients should refrain from vigorous exercise in the 24 hours prior to the test.
- The accuracy of the urine albumin-to-creatinine ratio will be diminished if creatinine excretion is abnormal

Jefferson IG, Greene SA, Smith MA, et al. Urine albumin to creatinine ratio-response to exercise in diabetes. Arch Dis Child 1985; 60:305.

Accuracy

- Albumin excretion will be underestimated in a muscular man with a high rate of creatinine excretion and overestimated in a cachectic patient in whom muscle mass and creatinine excretion are markedly reduced.
- The ratio also varies with gender and with race/ethnicity in the United States, as creatinine excretion is significantly higher among non-Hispanic black and Mexican American patients than among non-Hispanic white patients.

Younes N, Cleary PA, Steffes MW, et al. Comparison of urinary albumin-creatinine ratio and albumin excretion rate in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Clin J Am Soc Nephrol 2010; 5:1235.
Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. J Am Soc Nephrol 2002; 13:1034.

Progression to severely increased albuminuria

- Severely increased albuminuria (also called overt proteinuria, clinical renal disease, or dipstick positive proteinuria) is defined as

"Abumin excretion greater than 300 mg/day or 200 mcg/min or a urine albumin-to-creatinine ratio greater than 300 mg/g of creatinine or, using standard (SI) units, 34 mg/mmol of creatinine."

Progression to severely increased albuminuria

- Other risk factors contributing to progression to severely increased albuminuria include:
  - Higher baseline levels of albuminuria,
  - Worse glycemic control as measured by HbA1c
  - Higher blood pressure
  - Cigarette smoking.

Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984; 310:356.
Klein R, Klein BE, Moss SE, Cruickshanks KJ. Ten-year incidence of gross proteinuria in people with diabetes. Diabetes 1995; 44:916.
Rossing K, Christensen PK, Hovind P, et al. Progression of nephropathy in type 2 diabetic patients. Kidney Int 2004; 66:1596.

Progression of CKD

- Severely increased albuminuria in patients with type 2 diabetes is typically associated with a progressive reduction in glomerular filtration rate (GFR).
- The mean rate of loss of GFR in patients with severely increased albuminuria was 0.93 mL/min per month.

Regression to normal albuminuria

- Regression to normal albuminuria — As with type 1 diabetes, some patients with moderately increased albuminuria and type 2 diabetes regress to normal albuminuria
- The following factors were independently associated with remission:
  - A short duration of moderately increased albuminuria,
  - Better glycemic (hemoglobin a1c less than 7 percent) and
  - Blood pressure control (systolic pressure less than 129 mmHg),
  - Use of ACE inhibitors or angiotensin II receptor blockers, which have been shown in clinical trials to promote regression of moderately increased albuminuria.

Araki S, Haneda M, Sugimoto T, et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. Diabetes 2005; 54:2983.

Mortality

- Moderately increased albuminuria appears to be associated with increased long-term mortality in patients with type 2 diabetes.
- The relative risk for all-cause mortality was 1.9 compared with patients who had normal albuminuria
- similar significant relative risks (2.0 and 2.3) were noted for cardiovascular and coronary heart disease mortality.

Newman DJ, Mattock MB, Dawnay AB, et al. Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess 2005; 9:iii.

Screening of Microalbuminuria in T2DM

- The availability of effective therapy led to the recommendation that patients with type 2 diabetes should be screened for moderately increased albuminuria.
- If not found at the initial screen, yearly screening for albuminuria is recommended

KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis 2007; 49:S12. ; Bennett PH, Haffner S, Kasiske BL, et al. Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis 1995; 25:107.

Screening of Microalbuminuria in T2DM

- If detected, treatment is aimed at correcting underlying disorders such as
  - Hypertension,
  - Hyperglycemia,
  - Dyslipidemia,
- Albuminuria should be assessed annually thereafter.

Bakris GL, Molitch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care 2014; 37:867.

Screening of Microalbuminuria in T2DM

- The KDIGO guidelines recommend use of the UACR on a spot urine sample for screening and that an elevated UACR should be confirmed in the absence of urinary tract infection with additional tests performed over at least a three-month interval.
- The diagnosis of moderately increased albuminuria requires an elevated ratio be persistent for at least three months.

Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011) 2013; 3:19.

EFFECT OF INTERVENTIONS ON ALBUMINURIA CASES

EFFECT OF INTERVENTIONS ON ALBUMINURIA

- Glycemic and blood pressure control
  - Particularly with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), renin inhibitors, and aldosterone receptor antagonists, reduce both microalbuminuria and progression to macroalbuminuria.
  - Nondihydropyridine calcium channel blockers (diltiazem and verapamil) may also reduce albuminuria in hypertensive patients
  - But ACE inhibitors and ARBs have not been shown to slow the progression of chronic kidney disease in hypertensive or normotensive individuals with moderately increased albuminuria

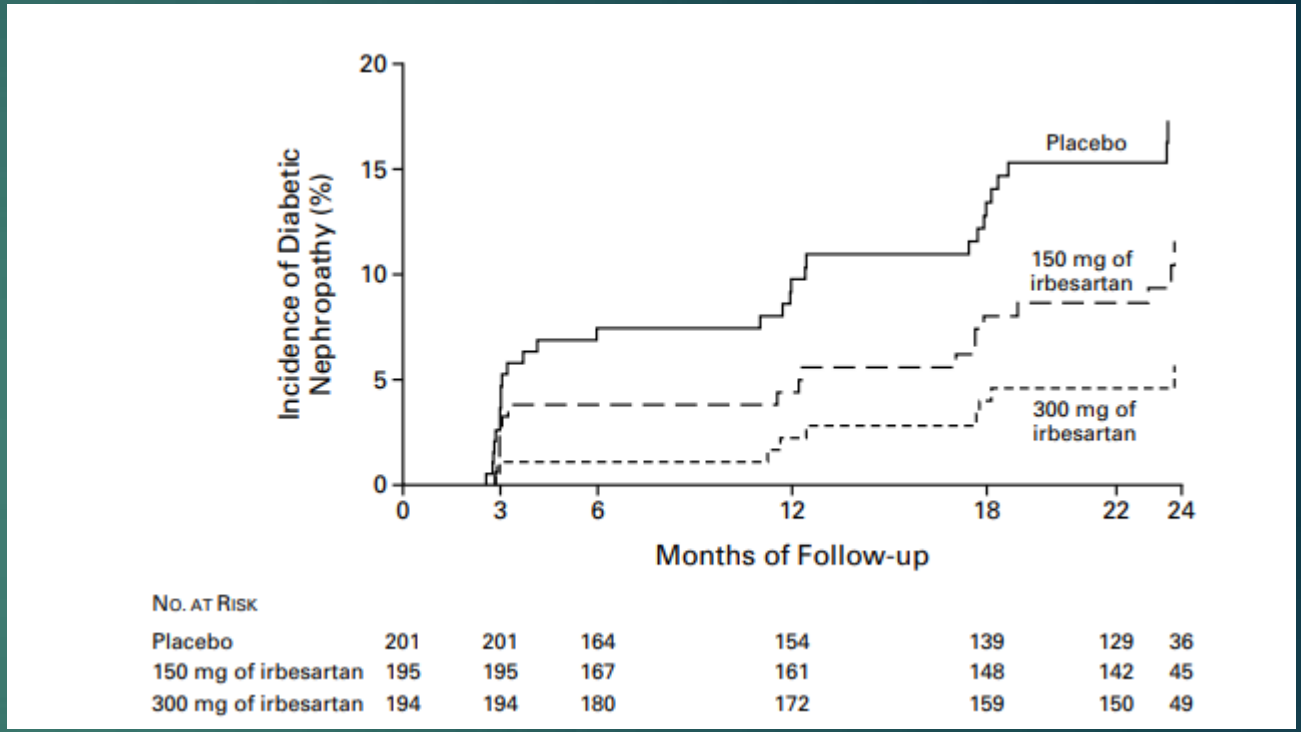
Bakris GL, Weir MR, Secic M, et al. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney Int 2004; 65:1991.

ACE inhibitors and ARBs

ACE inhibitors and ARBs

Parvaing et al. study:

- 590 hypertensive patients with type 2 diabetes and moderately increased albuminuria were randomly assigned to either Irbesartan (150 or 300 mg/day) or placebo and then followed for two years [40].

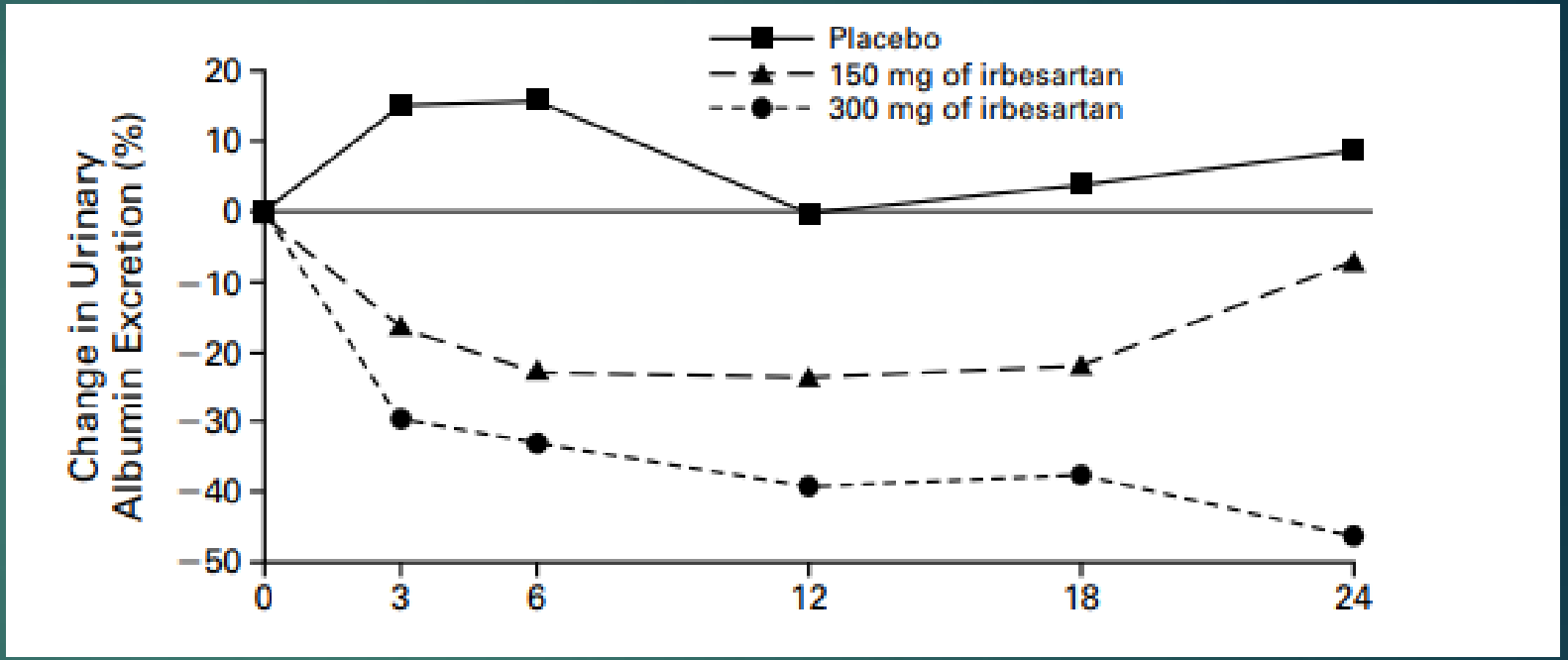


Incidence of Progression to Diabetic Nephropathy during Treatment with 150 mg of Irbesartan Daily, 300 mg of Irbesartan Daily, or Placebo in Hypertensive Patients with Type 2 Diabetes and Persistent Microalbuminuria

Difference between the placebo group and the 300-mg group was significant

Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870-878.

Parving et al.. conti

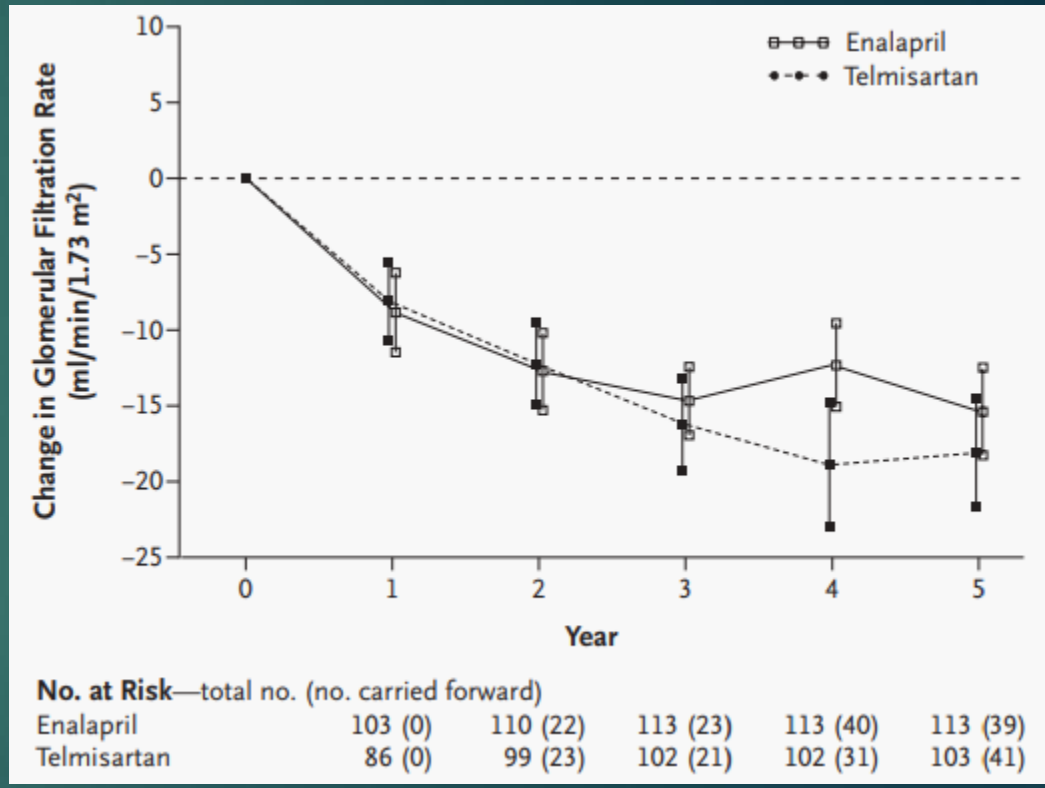


Irbesartan is renoprotective independently of its blood-pressure–lowering effect in hypertensive patients with type 2 diabetes and microalbuminuria.

Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870-878.

DETAIL trial

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have similar efficacy in type 2 diabetic patients with moderately increased albuminuria.
- DETAIL trial compared enalapril with telmisartan in 250 type 2 diabetic patients with early nephropathy



No. at Risk—total no. (no. carried forward)

Enalapril	103 (0)	110 (22)	113 (23)	113 (40)	113 (39)
Telmisartan	86 (0)	99 (23)	102 (21)	102 (31)	103 (41)

Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy [published correction appears in N Engl J Med. 2005 Apr 21;352(16)1731]. N Engl J Med. 2004;351(19):1952-1961.

DETAIL trial

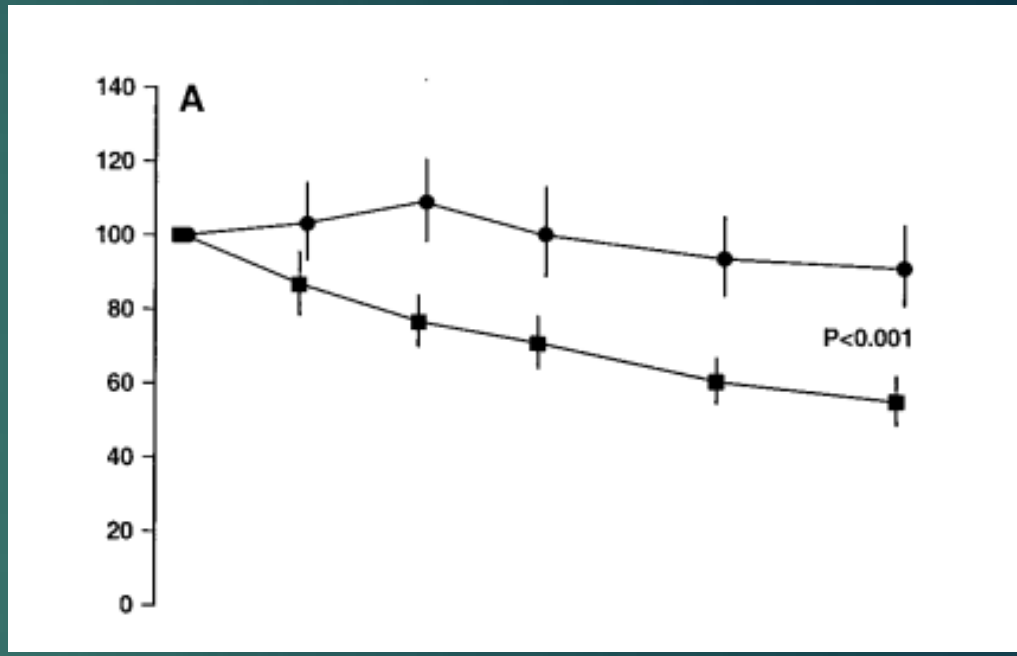
- At five years, both groups had similar findings which included annual changes in the GFR, blood pressure, serum creatinine concentration, urinary albumin excretion, and rates of end-stage kidney disease, cardiovascular events, and mortality.
- The results are consistent with the conclusion that ACE inhibitors are at least as effective as ARBs in type 2 diabetics with moderately increased albuminuria

Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004; 351:1952.

ARB vs Calcium channel blocker

MARVAL study

- MARVAL trial in which 332 such patients were randomly assigned to valsartan or amlodipine [46].
- Albumin excretion was reduced by 44 percent with valsartan compared to 8 percent with amlodipine, a difference that was highly significant.
- There was no difference in blood pressure between the two groups during the course of the study.



Percentage of baseline UAER in type 2 diabetic patients with microalbuminuria allocated to valsartan () or amlodipine (o) between-group differences in baseline to 24-week change.

Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 2002;106(6):672-678.

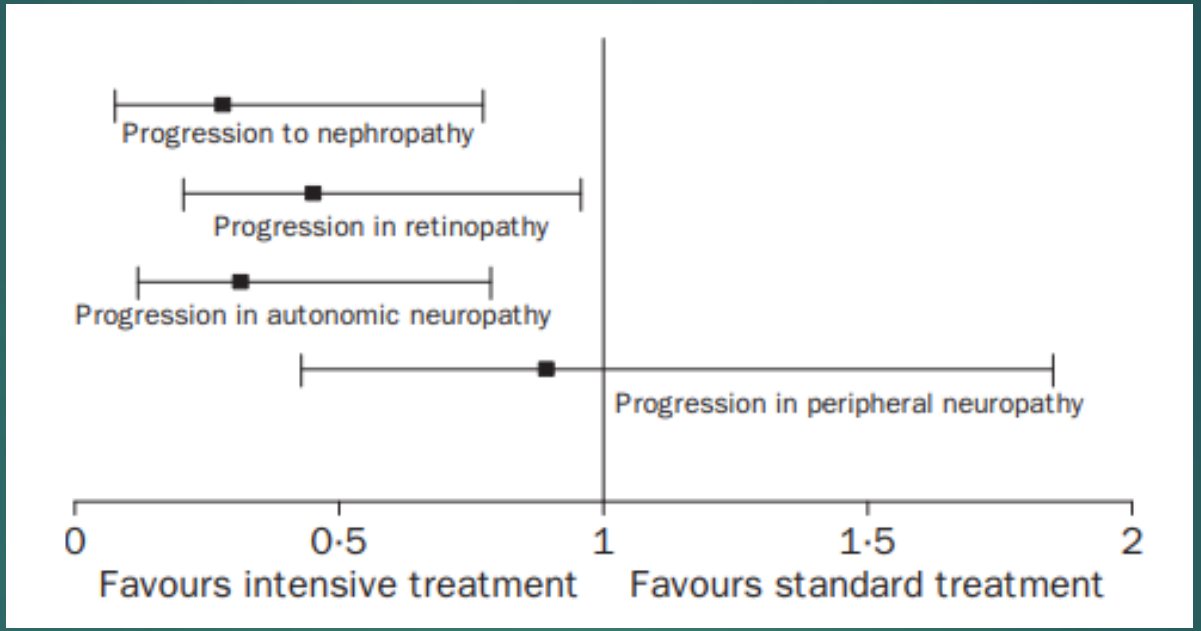
Glycemic control on albuminuria

Intensive combined risk factor modification therapy (Steno type 2 trial)

- Open, parallel trial patients were allocated standard treatment (n=80) or intensive treatment (n=80).
- **Standard treatment** followed Danish guidelines.
- **Intensive treatment** was a stepwise implementation of
  - Behaviour modification,
  - Pharmacological therapy targeting hyperglycaemia,
  - Hypertension,
  - Dyslipidaemia, and
  - Microalbuminuria.
- The primary endpoint was the development of nephropathy

Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999; 353:617

Intensive combined risk factor modification therapy (Steno type 2 trial) Conti…



Development and/or progression of microvascular complications during follow-up

Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria slows progression to nephropathy, and progression of retinopathy and autonomic neuropathy.

Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999; 353:617

Microalbuminuria in type 2 diabetes

- Microalbuminuria in a patient with type 2 diabetes should be attributed to diabetes if diabetic retinopathy is present or the patient progresses to macroalbuminuria.
- However, lack of retinopathy does not preclude diabetic nephropathy;
- In one study, diabetic retinopathy was absent in 12 of 27 patients with biopsy-confirmed diabetic nephropathy.

Parving HH, Gall MA, Skøtt P, et al. Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. Kidney Int 1992; 41:758.

Microalbuminuria in type 2 diabetes

- Other causes of chronic kidney disease should be considered when there are findings that are not characteristic of diabetic nephropathy. These include:
  - A low or rapidly decreasing glomerular filtration rate
  - Rapidly increasing protein excretion or acute onset of nephrotic syndrome
  - Refractory hypertension

Microalbuminuria in type 2 diabetes

- Other causes of chronic kidney disease should be considered when there are findings that are not characteristic of diabetic nephropathy. These include:
  - Active urine sediment (eg, glomerular hematuria and red cell or other cellular casts)
  - Signs and/or symptoms of another systemic disease
  - More than a 30 percent reduction in glomerular filtration rate from baseline values after initiation of therapy with an ACE inhibitor or angiotensin II receptor blocker

PRIMARY PREVENTION

PRIMARY PREVENTION

For the primary prevention of moderately increased albuminuria and subsequent overt nephropathy in patients with type 2 diabetes.

- ACE inhibitors and ARBs
- Glycemic control

Glycemic control

Intensive Glycemic control

- Several randomized trials have demonstrated that strict glycemic control is effective for the primary prevention of moderately increased albuminuria.
- The UKPDS evaluated the importance of strict glycemic control in 3867 patients with newly diagnosed type 2 diabetes.
- The patients were randomly assigned to intensive or conventional therapy.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.

Intensive Glycemic control

- Over 10 years, the average hemoglobin A1C value was 7.0 percent in the intensive therapy group, compared to 7.9 percent in the conventional therapy group (an 11 percent reduction).
- At nine-year follow-up Intensive insulin therapy was associated with a significantly lower rate of Microalbuminuria and a nonsignificantly lower rate of severely increased albuminuria.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.

ADVANCE trial

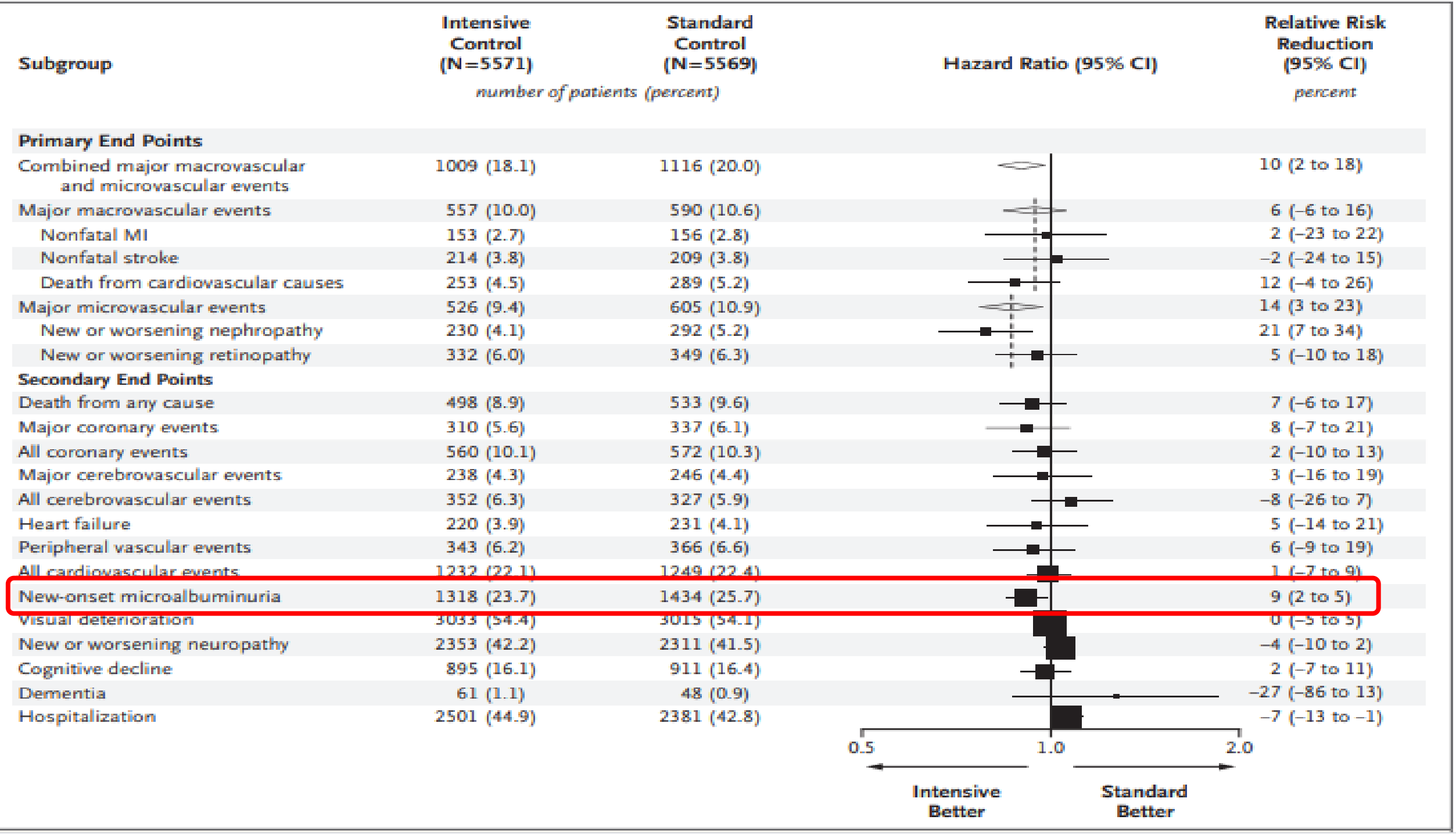
- Benefit from intensive therapy was also noted in the ADVANCE trial in which 11,140 patients with type 2 diabetes (mean duration eight years) were randomly assigned to intensive therapy to achieve a hemoglobin A1c below 6.5 percent or to standard therapy.
- At a median follow-up of five years, the intensive and standard groups achieved mean hemoglobin A1c values of 6.5 and 7.3 percent, respectively.
- Intensive therapy was associated with a small but significant reduction in the rate of new-onset moderately increased albuminuria (23.7 versus 25.7 %, relative risk reduction 9 %).

•The ADVANCE Collaborative Group. N Engl J Med 2008; 358:2560-2572

ADVANCE trial

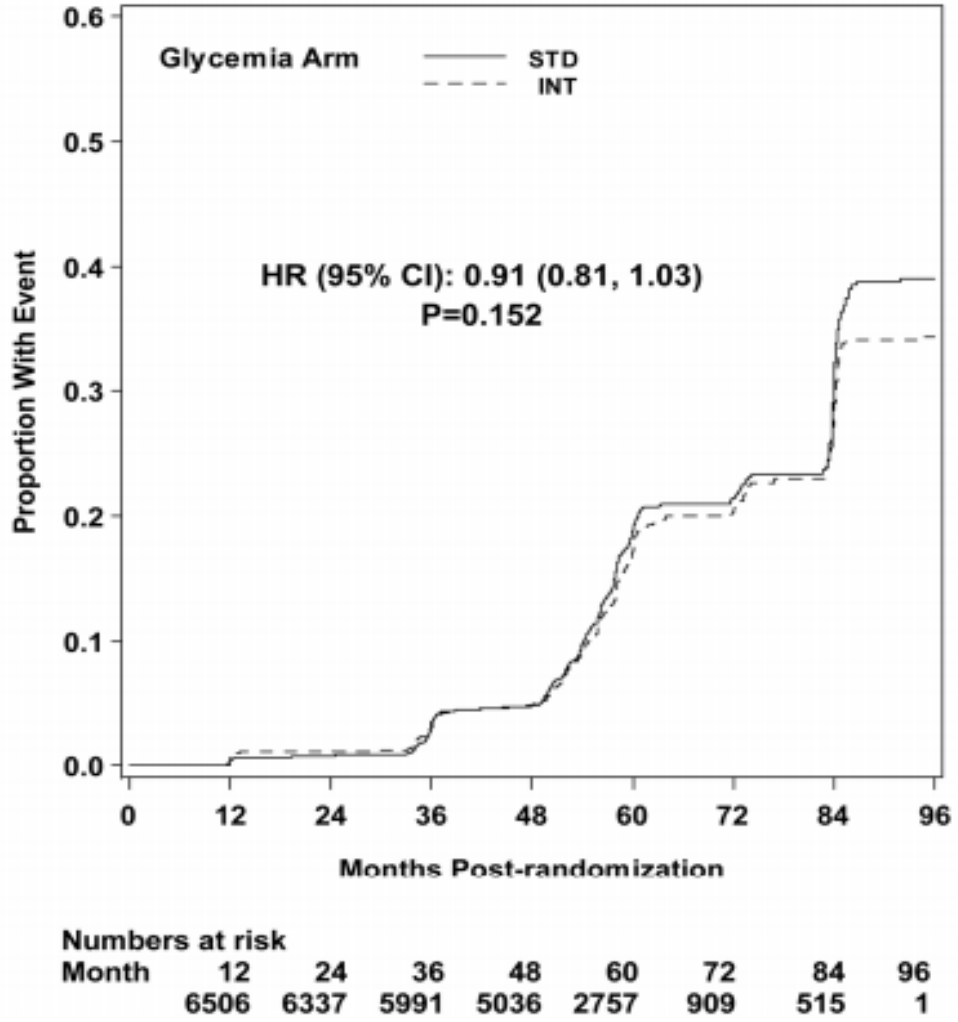
- 11,140 patients, a fixed combination regimen of perindopril-indapamide significantly reduced the rate of new-onset moderately increased albuminuria (19.6 versus 23.6 percent).
- New onset microalbuminuria was reduced by intensive therapy

Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370:829.


Subgroup
Intensive Control (N=5571)
Standard Control (N=5569)
number of patients (percent)
Hazard Ratio (95% CI)
Relative Risk Reduction (95% CI)
percent
Primary End Points
Combined major macrovascular and microvascular events 1009 (18.1) 1116 (20.0) 10 (2 to 18)
Major macrovascular events 557 (10.0) 590 (10.6) 6 (–6 to 16)
Nonfatal MI 153 (2.7) 156 (2.8) 2 (–23 to 22)
Nonfatal stroke 214 (3.8) 209 (3.8) –2 (–24 to 15)
Death from cardiovascular causes 253 (4.5) 289 (5.2) 12 (–4 to 26)
Major microvascular events 526 (9.4) 605 (10.9) 14 (3 to 23)
New or worsening nephropathy 230 (4.1) 292 (5.2) 21 (7 to 34)
New or worsening retinopathy 332 (6.0) 349 (6.3) 5 (–10 to 18)
Secondary End Points
Death from any cause 498 (8.9) 533 (9.6) 7 (–6 to 17)
Major coronary events 310 (5.6) 337 (6.1) 8 (–7 to 21)
All coronary events 560 (10.1) 572 (10.3) 2 (–10 to 13)
Major cerebrovascular events 238 (4.3) 246 (4.4) 3 (–16 to 19)
All cerebrovascular events 352 (6.3) 327 (5.9) –8 (–26 to 7)
Heart failure 220 (3.9) 231 (4.1) 5 (–14 to 21)
Peripheral vascular events 343 (6.2) 366 (6.6) 6 (–9 to 19)
All cardiovascular events 1232 (22.1) 1249 (22.4) 1 (–7 to 9)
New-onset microalbuminuria 1318 (23.7) 1434 (25.7) 9 (2 to 5)
Visual deterioration 3033 (54.4) 3015 (54.1) 0 (–5 to 5)
New or worsening neuropathy 2353 (42.2) 2311 (41.5) –4 (–10 to 2)
Cognitive decline 895 (16.1) 911 (16.4) 2 (–7 to 11)
Dementia 61 (1.1) 48 (0.9) –27 (–86 to 13)
Hospitalization 2501 (44.9) 2381 (42.8) –7 (–13 to –1)
0.5
1.0
2.0
Intensive Better
Standard Better

ACCORD trial

- Intensive treatment did reduce the development of macroalbuminuria, loss of three lines of visual acuity, and peripheral neuropathy.
- Intensive glycemic therapy with a target HbA1c of <6.0% versus standard therapy with a target of 7.0 to 7.9%



Kaplan-Meier curves for microvascular outcome Neph-1 (development of microalbuminuria)

Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial [published correction appears in Lancet. 2010 Oct 30;376(9751):1466]. Lancet. 2010;376(9739):419-430.

ACE inhibitors or ARBs

ACE inhibitors or ARBs

- There have been variable results related to the efficacy of ACE inhibitors or ARBs for the primary prevention of moderately increased albuminuria in clinical trials of patients with type 2 diabetes.
- This is due in part to variations in study design, specific antihypertensive agents administered, and type of individual enrolled, particularly normotensive and hypertensive patients.

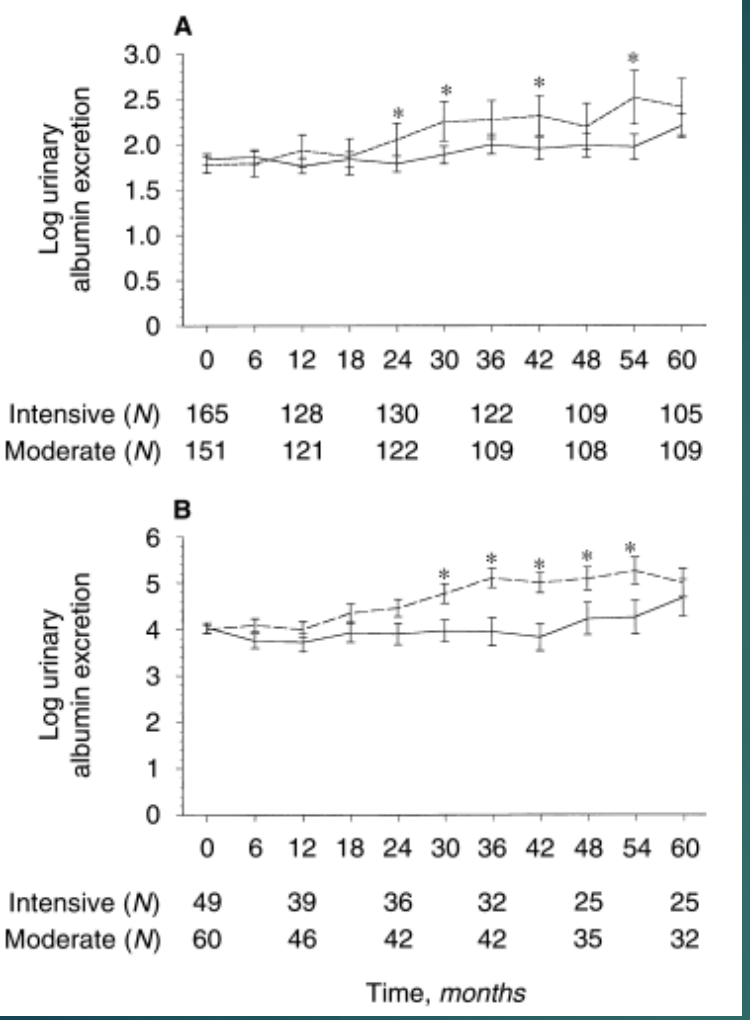
Bilous R, Chaturvedi N, Sjølie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med 2009; 151:11.
Parfrey PS. Angiotensin-receptor blockers in the prevention or treatment of microalbuminuria. Ann Intern Med 2009; 151:63.

In Normotensive patients

ABCD trial

- Appropriate Blood pressure Control in Diabetes (ABCD) trial of 480 patients, the rate of progression to moderately increased albuminuria was significantly lower with enalapril compared with placebo [56,57] and with nisoldipine compared with placebo, but after five years, there was no significant difference [57].
- The rate of progression to moderately increased albuminuria was equivalent with enalapril and nisoldipine [57].
- In addition, treating patients with normoalbuminuria with a renin-angiotensin system blocker does not change the natural history of diabetic nephropathy, but it may alter the progression of retinopathy [64,65].

Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int. 2002;61(3):1086-1097.

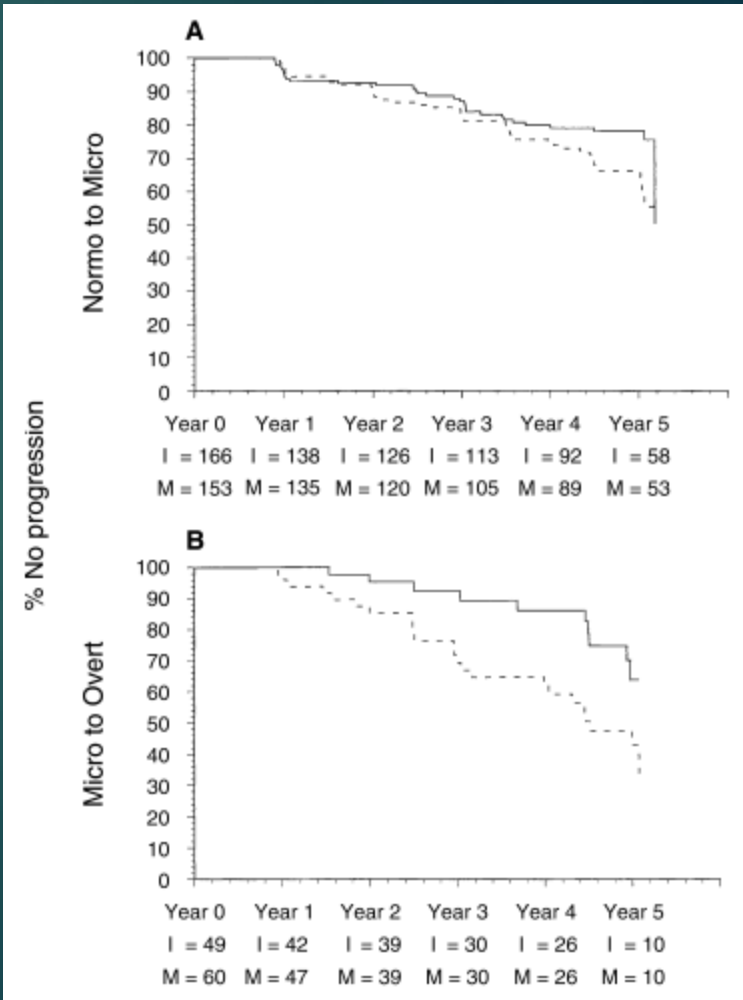


Log urinary albumin excretion (UAE) for intensive (solid line) and moderate (dashed line) blood pressure control groups:

(A) normoalbuminuria at baseline;

(B) microalbuminuria at baseline.

*T test performed at various time intervals revealed a P value <0.05.

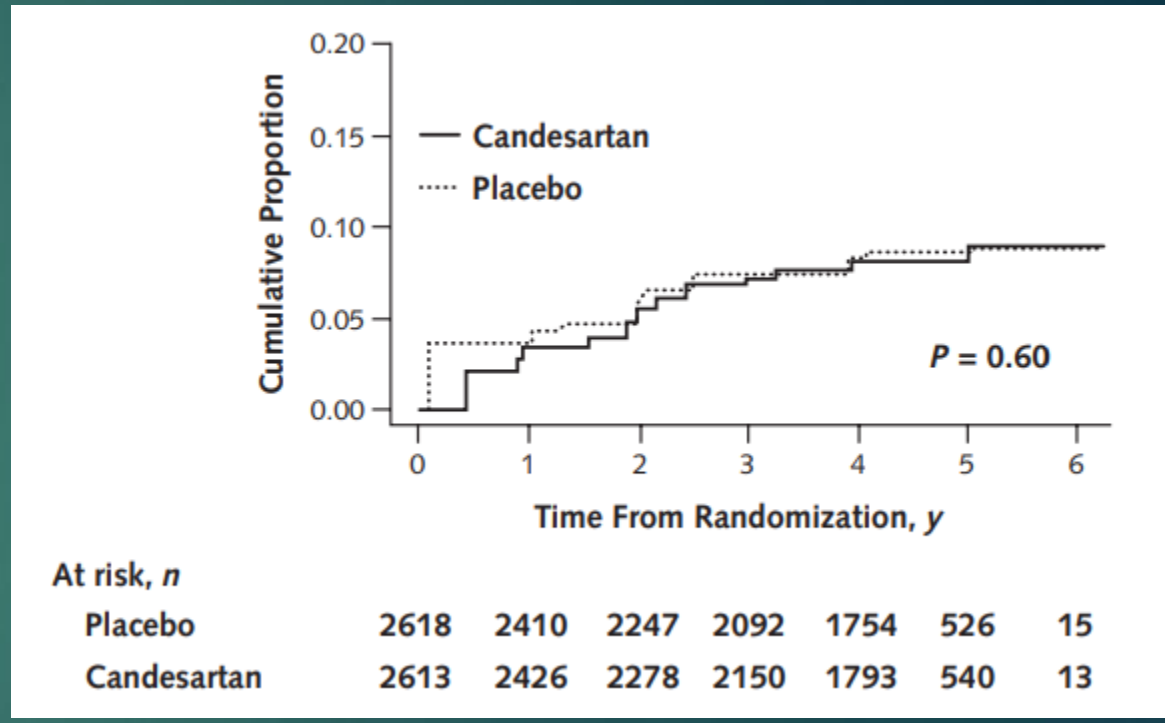


Kaplan-Meier curves demonstrating progression from normoalbuminuria to microalbuminuria (A; P 0.04) and from microalbuminuria to overt albuminuria (B; P 0.02) in patients on (solid line) intensive versus (dashed line) moderate therapy.

Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int. 2002;61(3):1086-1097.

DIRECT Protect-2

- 725 normotensive patients with normal albuminuria
- The rate of progression to moderately increased albuminuria was nonsignificantly lower with candesartan compared with placebo.



Cumulative proportion of patients with microalbuminuria

Bilous R, Chaturvedi N, Sjølie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Me
2009;151(1):11-W

ACEi in Albuminuria in normotensives

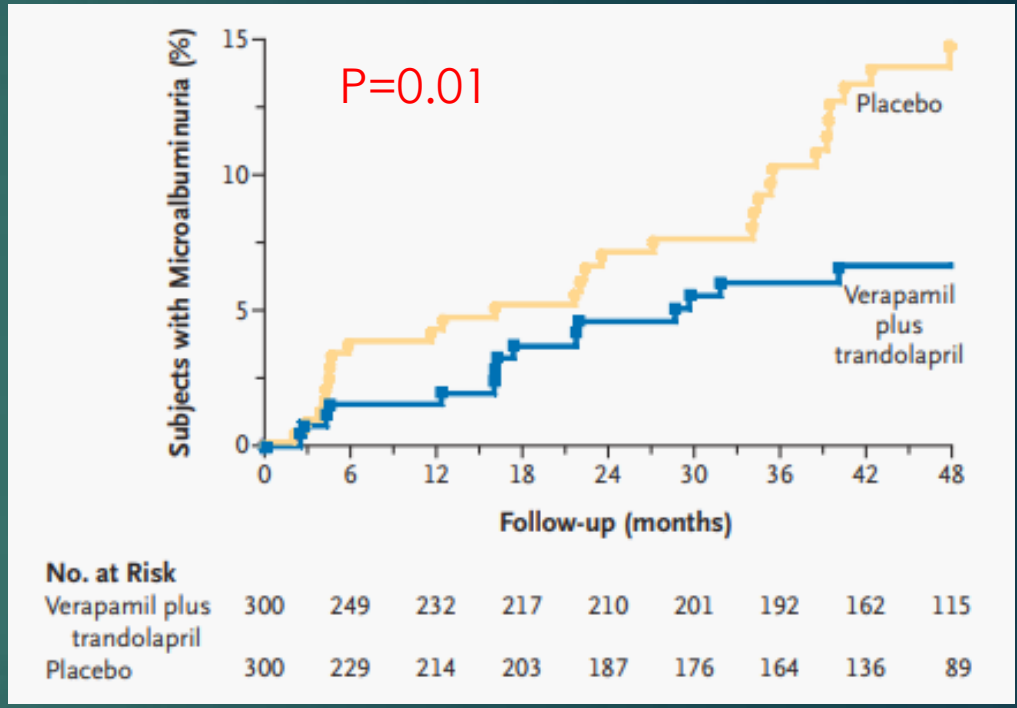
- These observations, coupled with information obtained from kidney biopsies in some studies, suggest that ACE inhibitors and ARBs do not change the natural history of kidney disease in such patients.
- It is suggested to not treat with an ACE inhibitor or ARB solely for the prevention of moderately increased albuminuria in such patients.
- These patients should be screened yearly for moderately increased albuminuria and an ACE inhibitor or ARB initiated if persistent moderately increased albuminuria is documented.

Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009; 361:40.
Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. Diabetes 2013; 62:3224.

Hypertensive patients

BENEDICT trial

- 1204 patients with a mean baseline blood pressure of 150/87 mmHg were randomly assigned to
  - Trandolapril,
  - Verapamil,
  - The combination of these medications, or
  - Placebo.
- The rate of new-onset moderately increased albuminuria at three years or more was significantly lower with trandolapril alone or with verapamil (6.0 and 5.7 percent, respectively) than with verapamil alone or placebo (11.9 and 10.0 percent respectively).

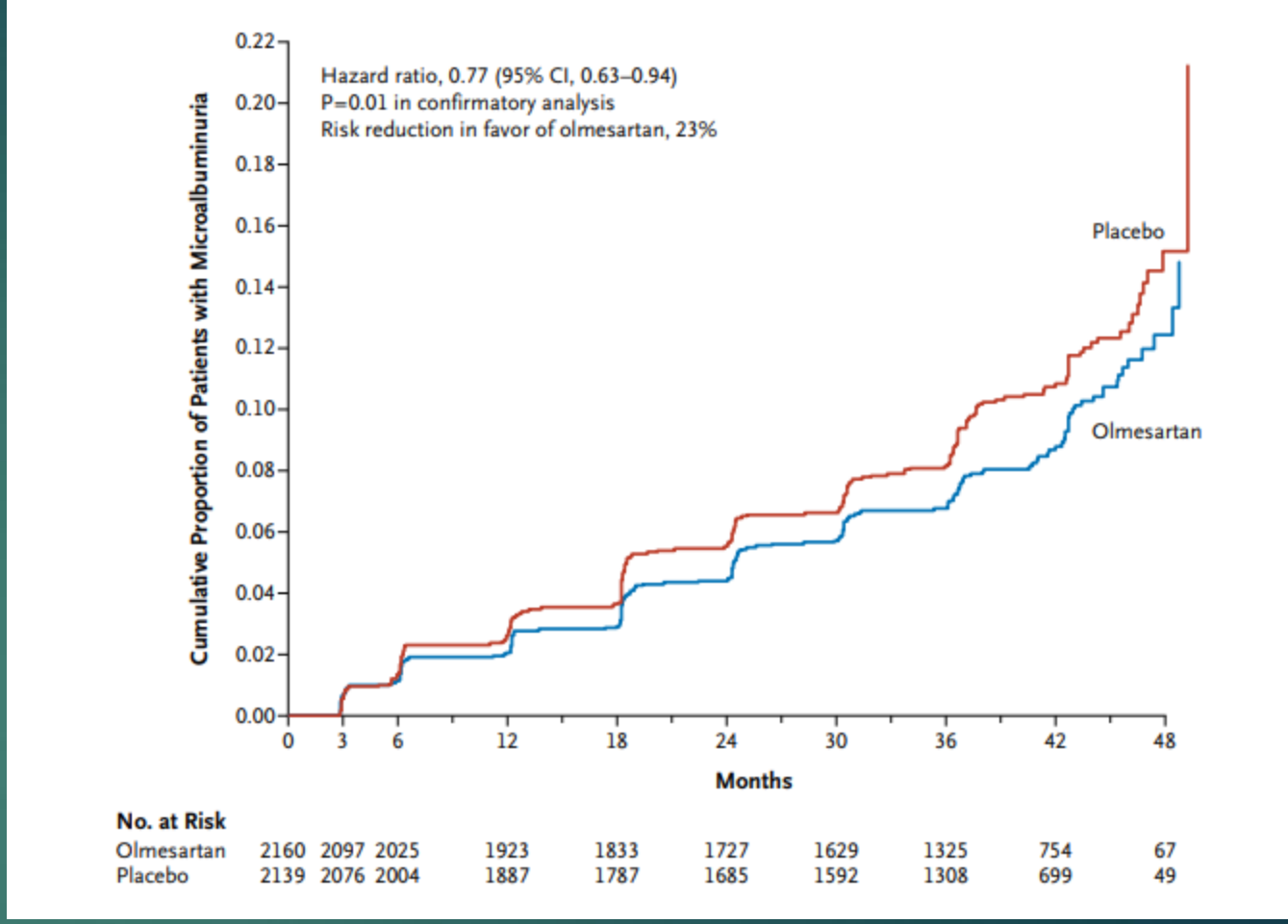


Kaplan–Meier Curves for the Percentages of Subjects with Microalbuminuria during Treatment with Trandolapril plus Verapamil or Placebo.

Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004; 351:1941.

ROADMAP trial

- 4,447 patients with type 2 diabetes to receive olmesartan (at a dose of 40 mg once daily) or placebo for a median of 3.2 years
- Olmesartan was associated with a delayed onset of microalbuminuria



Occurrence of Microalbuminuria during the 48-Month Follow-up Period in the Two Study Groups

Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011;364(10):907-917.

ACEi in Albuminuria in Hypertensives

- In the aggregate, these trials suggest that **ACE inhibitors and ARBs are effective in preventing the new onset of moderately increased albuminuria in hypertensive patients** with type 2 diabetes
- BENEDICT trial provides support for these drugs being more effective than at least verapamil.
- None were designed to analyze effects on kidney function decline, and, in ROADMAP, mortality was increased despite reductions in albuminuria.

SUMMARY AND RECOMMENDATIONS

- Moderately increased albuminuria (the new term for what was formerly called "microalbuminuria") is defined as persistent urinary albumin excretion between 30 and 300 mg/day (20 to 200 mcg/min).
- Severely increased albuminuria (the new term for what was formerly called "macroalbuminuria") refers to albumin excretion above 300 mg/day (200 mcg/min).
- Among patients with type 2 diabetes, the reported prevalence of moderately increased albuminuria at 10 years is between 25 to 40 percent.

SUMMARY AND RECOMMENDATIONS

- Some patients have moderately increased albuminuria at the time of diagnosis, which may be due to previously undiagnosed diabetes or some other disease that is responsible for the moderately increased albuminuria.
- With type 2 diabetes, moderately increased albuminuria is associated with higher cardiovascular risk, possible progression to severely increased albuminuria, and increased long-term mortality.
- However, remission to normal albuminuria may occur.

SUMMARY AND RECOMMENDATIONS

- Factors associated with remission include short duration of moderately increased albuminuria, better glycemic control, better blood pressure control, and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).
- The preferred screening strategy for moderately increased albuminuria is measurement of the urine albumin-to-creatinine ratio in an untimed urinary sample.
- A value of 30 to 300 mg/g of creatinine (or, using standard [SI] units, 3.4 to 34 mg/mmol of creatinine) suggests that albumin excretion is between 30 and 300 mg/day.

SUMMARY AND RECOMMENDATIONS

- Urine albumin-to-creatinine ratio be measured yearly in patients with type 2 diabetes, although it is uncertain whether yearly testing should be continued in patients already treated with an ACE inhibitor or ARB.
- An elevated ratio should be confirmed with at least two additional tests performed over the subsequent three to six months, with confirmation of the diagnosis requiring at least two of three positive samples.
- Among patients with persistent moderately increased albuminuria and blood pressures above goal, we recommend therapy with an ACE inhibitor or ARB rather than other antihypertensive agents (Grade 1B). Other drugs are added as necessary.

SUMMARY AND RECOMMENDATIONS

- Issues related to goal blood pressure in patients with diabetes are discussed separately.
- Data are limited on the value of treating moderately increased albuminuria with an ACE inhibitor or ARB in patients with type 2 diabetes who are normotensive, since no trials have been limited to patients who have a baseline blood pressure below 135/85 mmHg.
- In such patients, aggressive glycemic and lipid control are recommended, but angiotensin inhibition is not warranted solely to reduce albuminuria.

SUMMARY AND RECOMMENDATIONS

- There is sufficient evidence to not recommend ACE inhibitor or ARB therapy for primary prevention in patients with type 2 diabetes who have normal albumin excretion and who are normotensive. In addition, there is evidence that such therapy is not helpful.
- These patients should be screened yearly for moderately increased albuminuria and an angiotensin inhibition initiated if persistent moderately increased albuminuria is documented.
- Patients with type 2 diabetes who have normal albumin excretion and who are hypertensive should be treated to attain goal blood pressure.


Thank
you