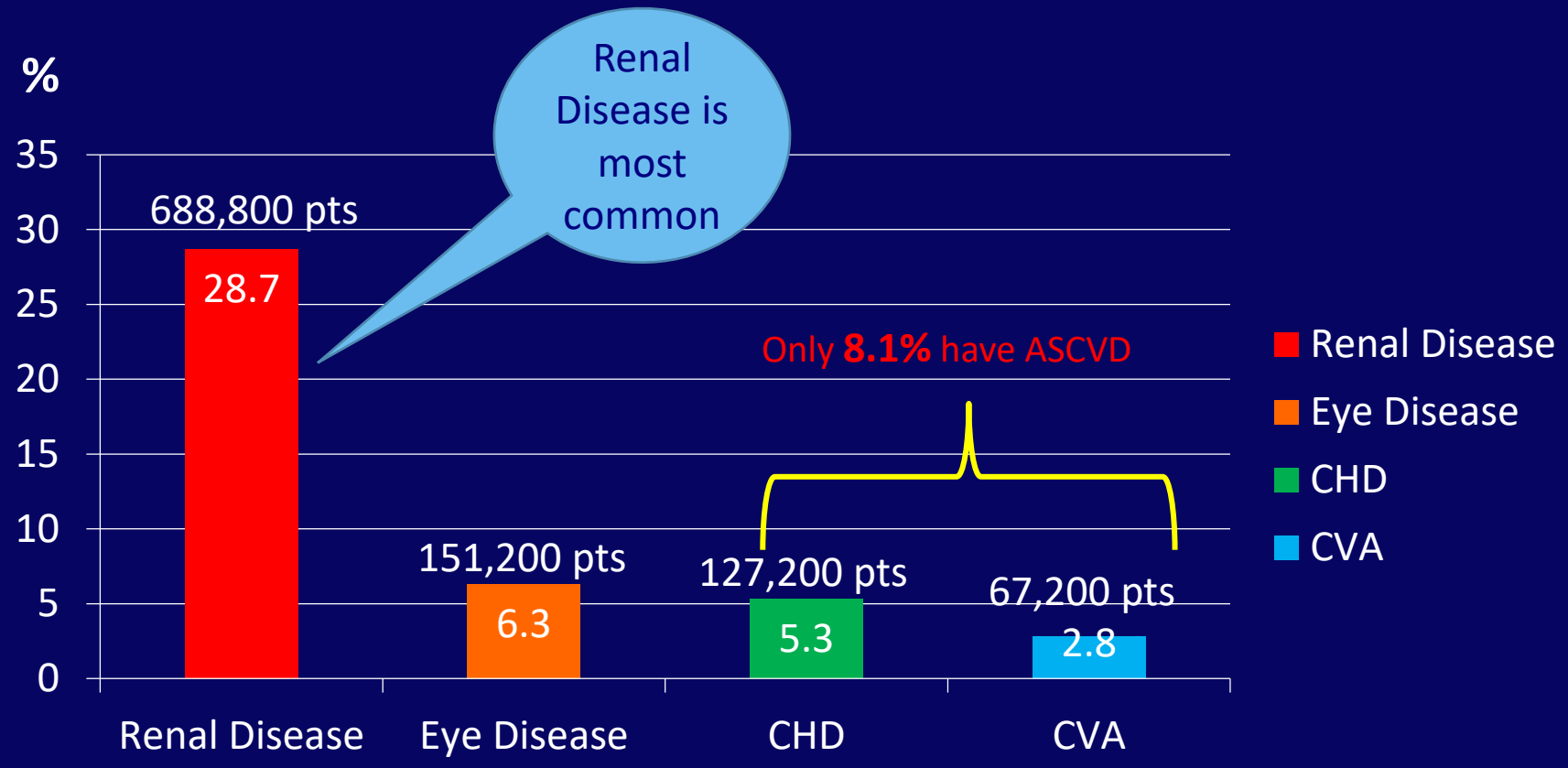
Diabetic nephropathy

Outline

- Epidemiology
- Definition
- Natural history
- Renal pathology
- Pathophysiology
- Risk factors
- Treatment

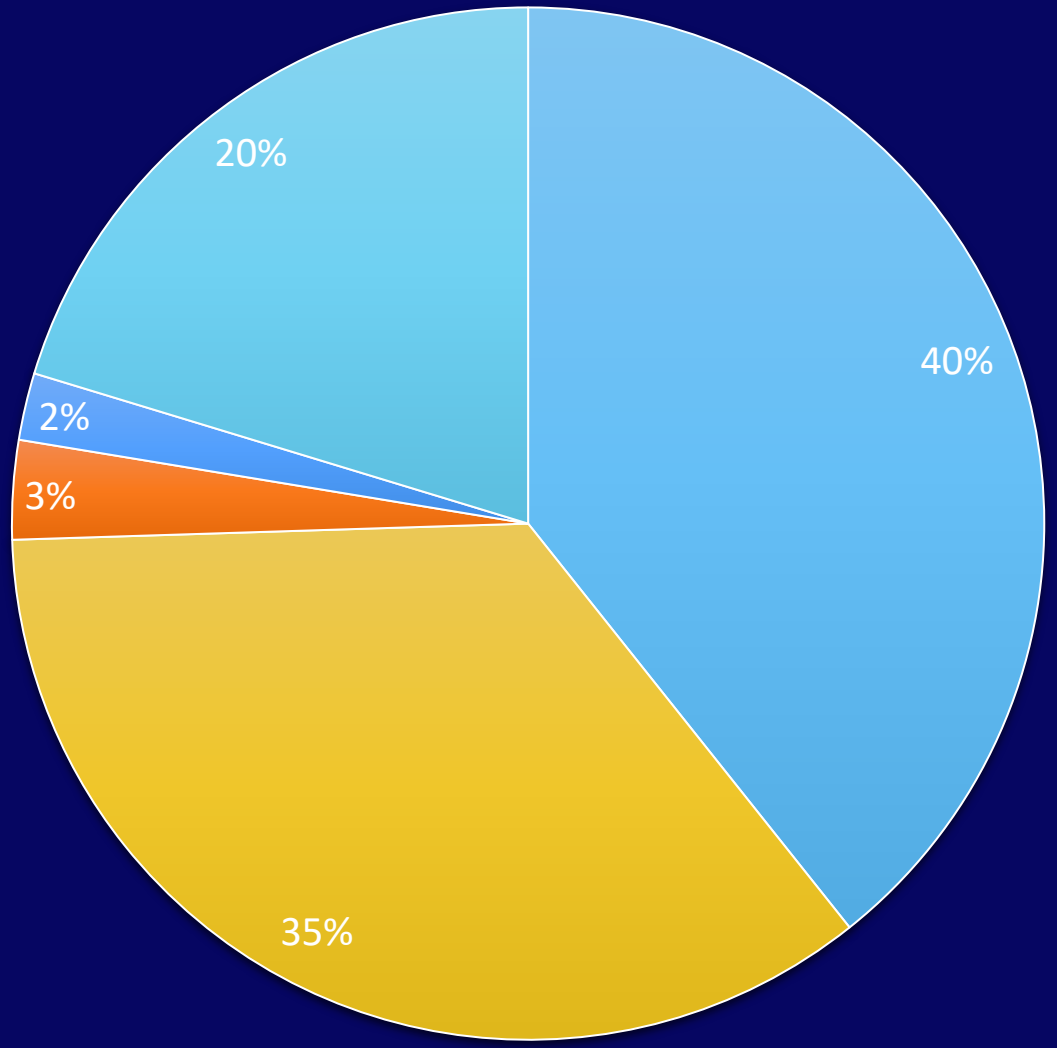
Prevalence of Diabetes Complications in Thailand

2.4 million Thai Diabetes Patients treated



2554 An **A**ssessment on **Q**uality of **C**are among Patients Diagnosed with type 2 **D**iabetes and **H**ypertension visiting Hospitals in care of Ministry of Public Health and Bangkok Metropolitan Administration in Thailand, 2011

Dialysis incidence cases in Thailand 2012



total N = 7860

- DN
- HTN
- Obstruction
- CGN
- others

DEFINITION “DKD”

- **Most patients with diabetes, CKD should be attributable to diabetes if:**
  - Macroalbuminuria is present

  or
  - Microalbuminuria is present
    - in the presence of diabetic retinopathy
    - in type 1 diabetes of at least 10 years' duration

NKF KDOQI GUIDELINES for Diabetes and Chronic Kidney Disease 2007

Relation of Diabetes nephropathy and diabetes retinopathy

- Type 1 DM : DR 90-95% (PDR 60%)
  - Early DR in early stage of overt nephropathy
  - Advanced DR relate to kidney pathology and have at least microalbuminuria

- Type 2 DM
  - Study in 35 pts with proteinuria (>300mg/day)
    - 27 (77%) found DN
    - 15/27 (56%) found DR

Parving HH, et al. Kidney Int 1992 Apr;41(4):758-62

When to considered for Other causes of CKD

- Absence of diabetic retinopathy
- Low or rapidly decreasing GFR
- Rapidly increasing proteinuria or nephrotic syndrome
- Refractory hypertension
- Presence of active urinary sediment
- Signs or symptoms of other systemic disease
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

NKF KDOQI GUIDELINES for Diabetes and Chronic Kidney Disease 2007

Parameter to distinguish non-DN from DN (meta-analysis)

- 26 relevant studies with 2,322 patients
- Distinguish NDRD from DN in patients with diabetes
  - Absence of DR
  - Shorter duration of DM
  - Lower HbA1C
  - Lower BP

Liang S, et al. PLoS One. 2013 14;8(5):e64184.

When to screening

- Initial screening :
  - 5 years after the diagnosis of type 1 diabetes
  - From diagnosis of type 2 diabetes
- Patients with diabetes should be screened annually for DKD.

- Screening should include:
  - Urine dipstick/microalbuminuria
  - Measurements of UACR in a spot urine sample
  - Measurement of serum creatinine and estimation of GFR

NKF KDOQI GUIDELINES for Diabetes and Chronic Kidney Disease 2007

Screening

Recommendations

- *At least once a year, assess UACR and eGFR in patients with type 1 DM ≥5 years and all patients with type 2 DM regardless of treatment.*
- *Patients with UACR >30 mg/g creatinine and/or an eGFR <60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy.* **C**

American Diabetes Association Diabetes Care 2020 Jan; 43(Supplement 1): S135-S151.

Definition of Abnormal Albuminuria in Diabetes Mellitus

	Microalbuminuria	Macroalbuminuria (Nephropathy)
Renal Risk	Marker of future nephropathy in some	Marker progressive renal disease
Cardiovascular Risk	Increased	Increased

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	(mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

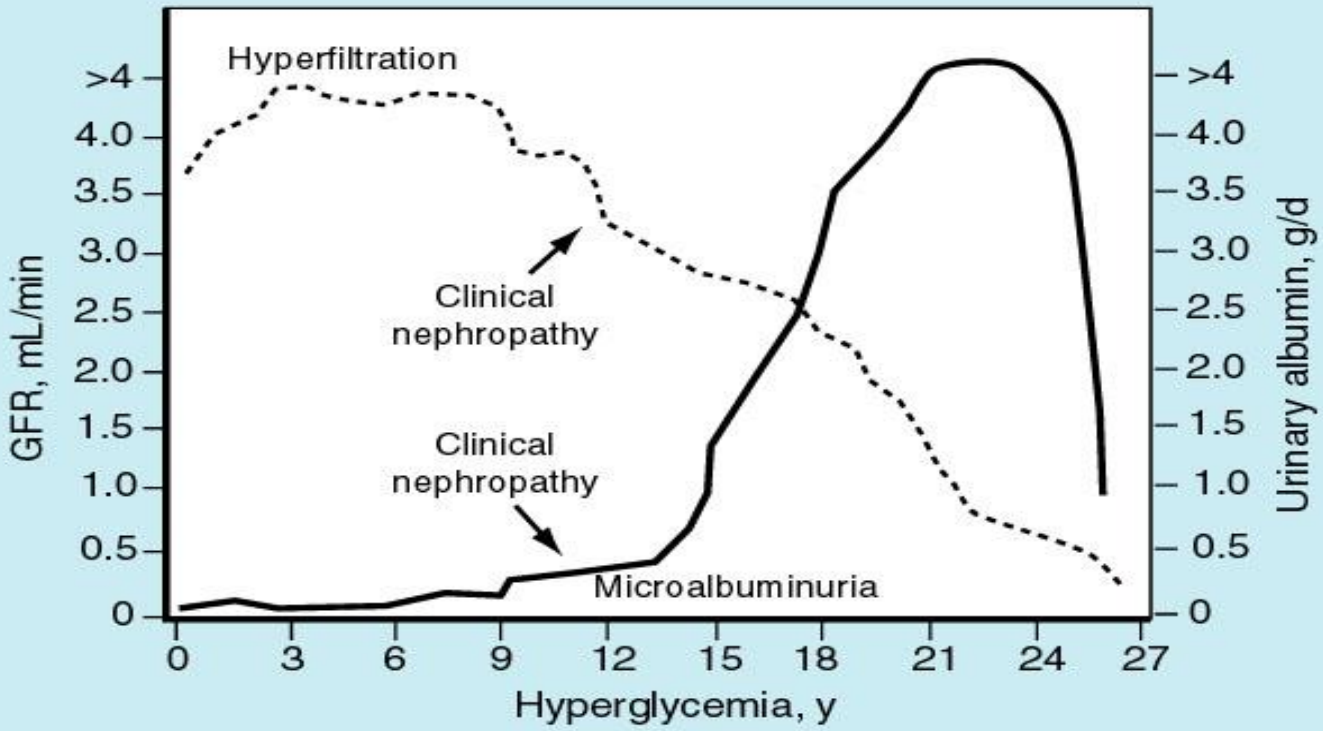
* Random (Spot) urine preferably A.M. recommended

Diabetic nephropathy staging

	Designation	Characteristics	GFR (ml/min)	Albumin excretion	Blood pressure
Stage1	Hyperfunction and Hypertrophy	Glomerular hyperfiltration	Increase	May be increase	Normal
Stage2	Silent stage	Thickened BM Expanded mesangium	Normal	<30 mg/24hr	Normal
Stage3	Incipient	Microalbuminuria	GFR begins to fall	30-300mg/24hr	High
Stage4	Overt diabetic nephropathy	Macroalbuminuria	GFR fall	>300mg/24hr	High
Stage5	Uremia	ESRD	0-10	Decreasing	High

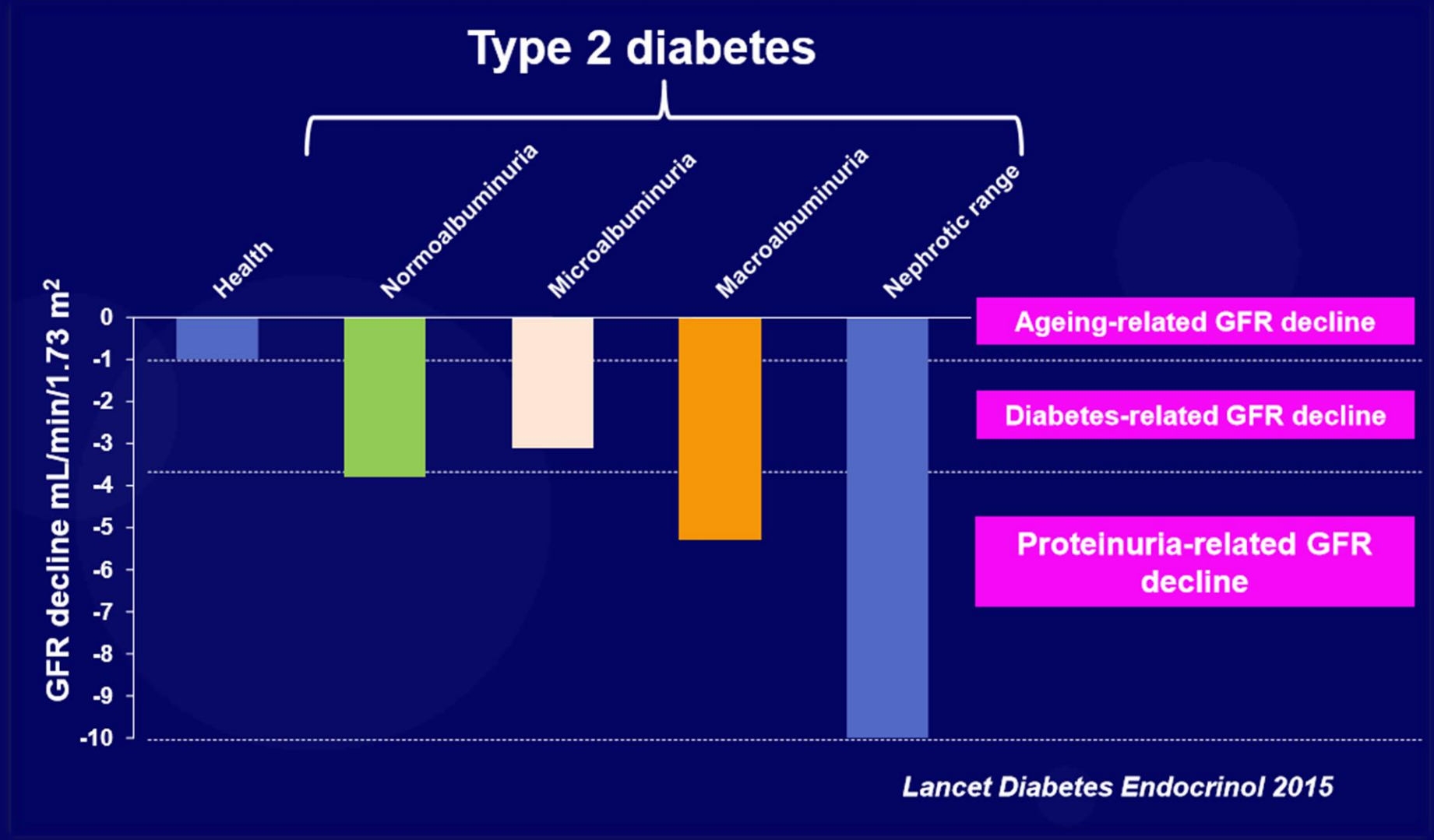
Mogensen CE, et al. Diabetes. 1983 ;32 Suppl 2:64-78.

Natural History of DKD

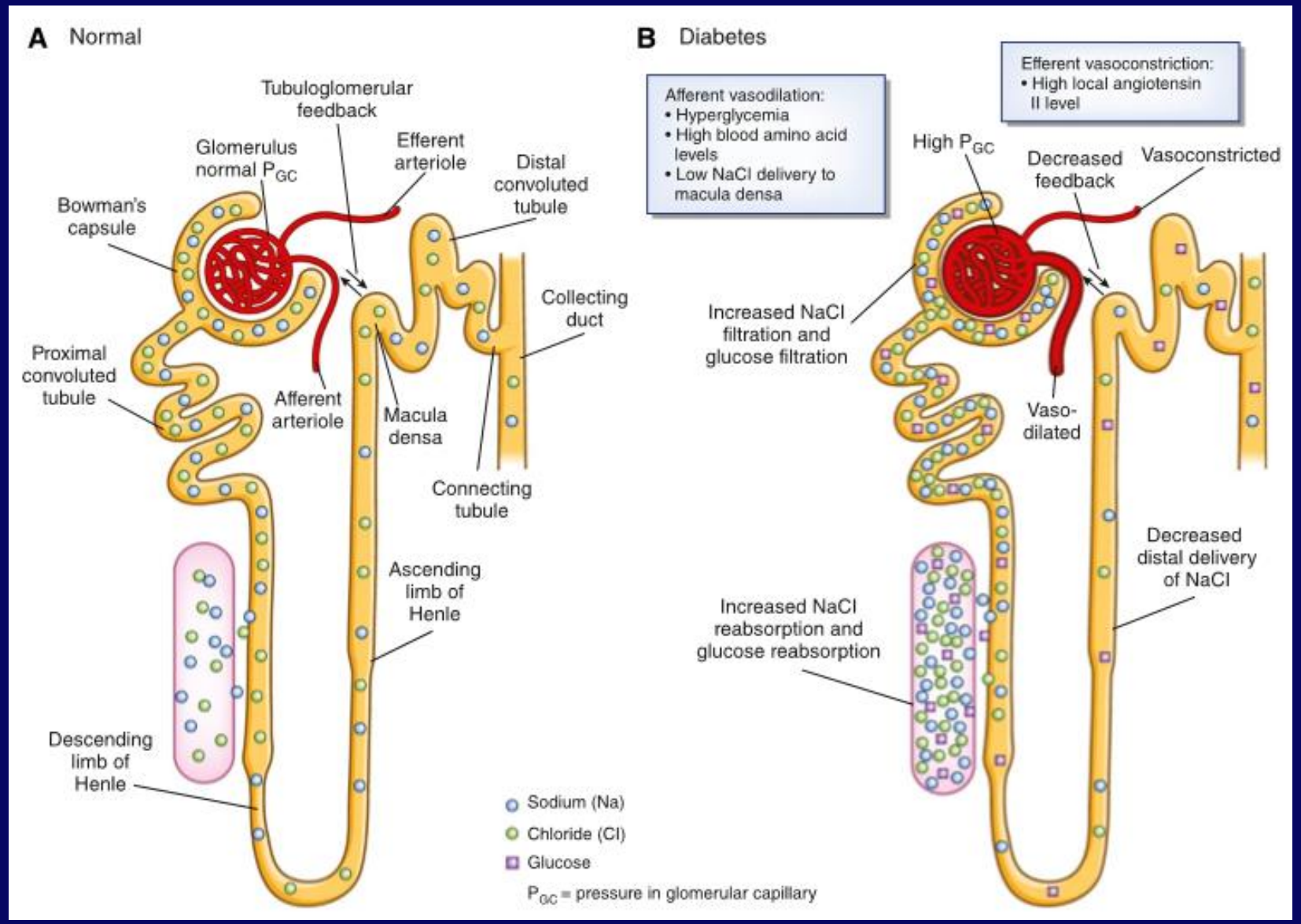


Overt nephropathy is typically between 10 and 15 years after the onset of the disease.

Loss of renal function in T2DM patients

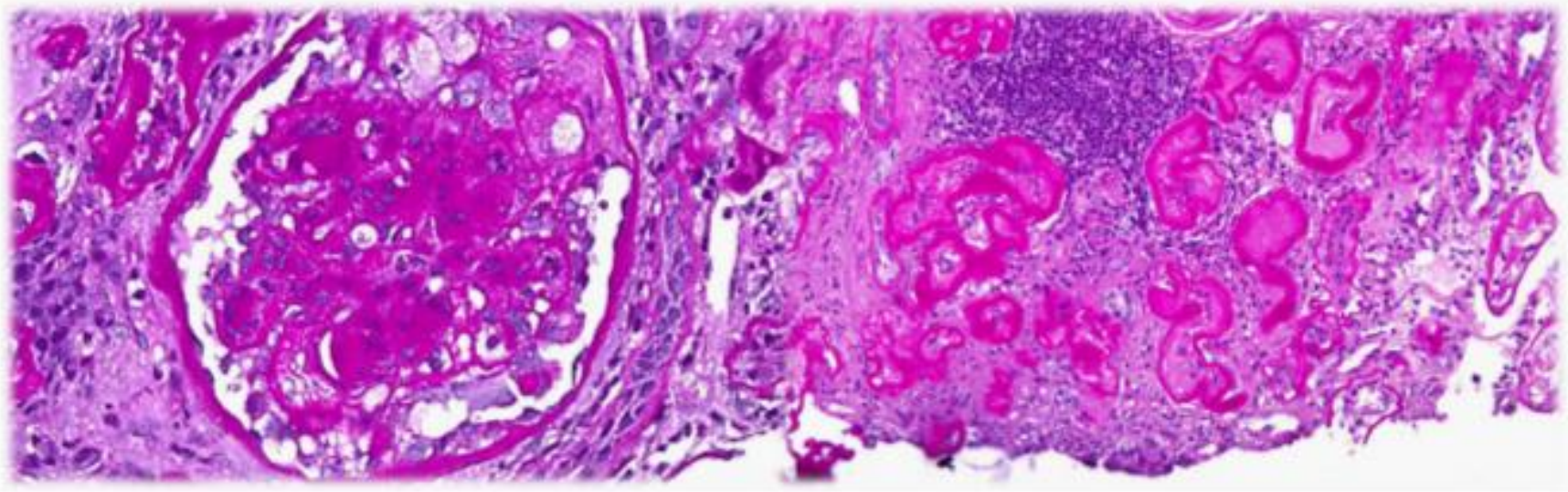


Nephron with altered renal hemodynamics in diabetic kidney



Clin J Am Soc Nephrol 12: 2032–2045, December, 2017

Pathology



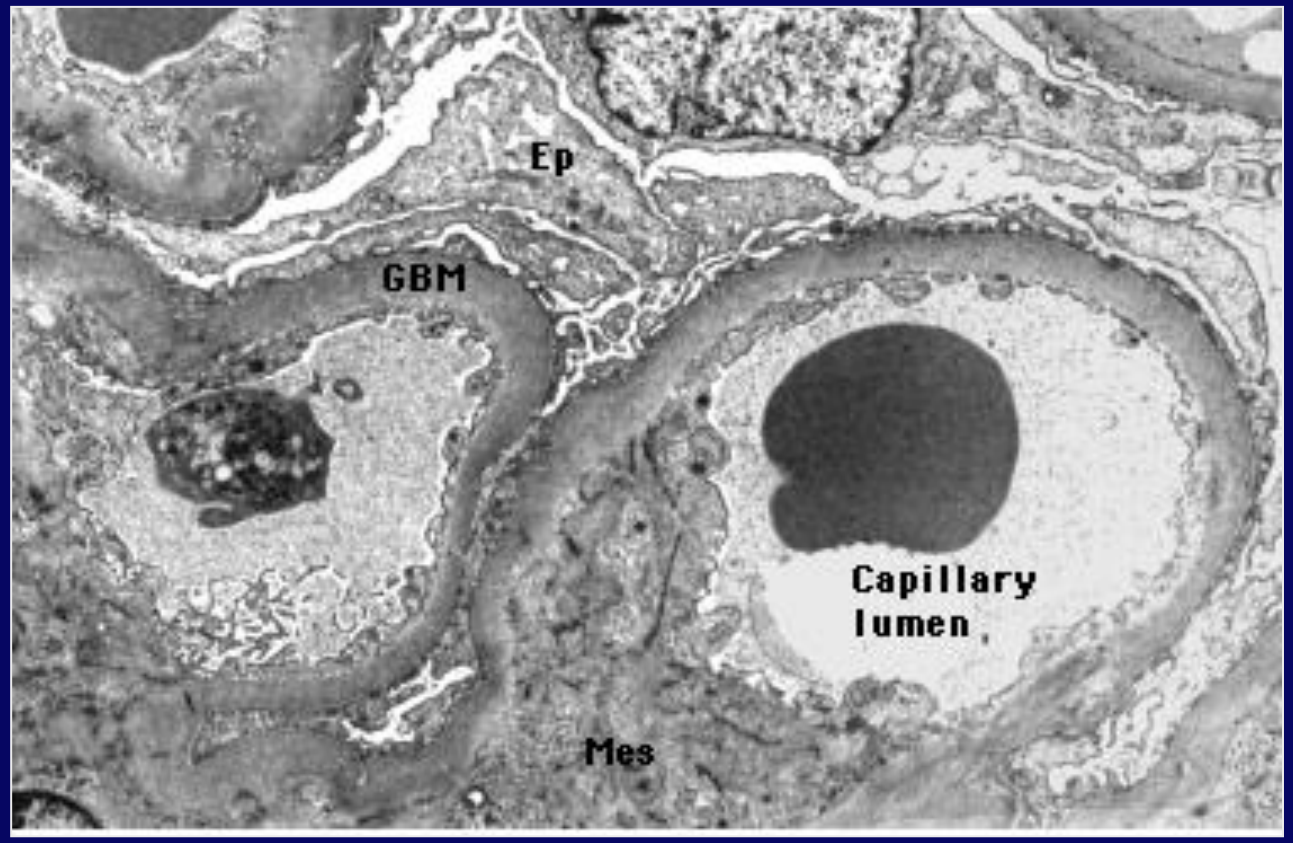
Typical diabetic nephropathy

- Nodular mesangial expansion
- Thickened GBM
- Arteriolar hyalinosis

Atypical patterns of renal injury

- Tubular atrophy
- Thickened tubular BM
- Interstitial fibrosis/inflammation
- Advanced arteriolar hyalinosis

Early lesion

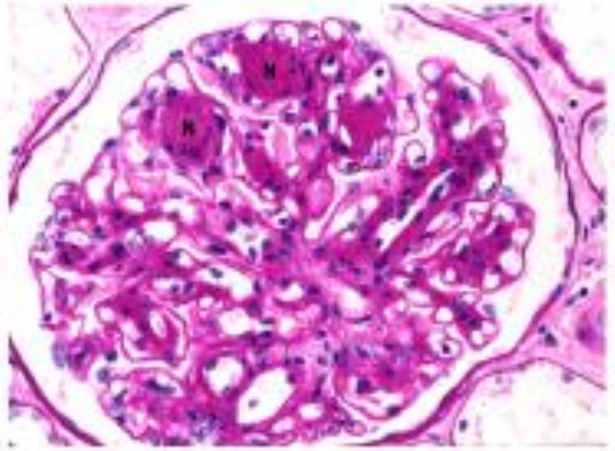


GBM Thickening is a characteristic early change in type 1 and type 2 DN

Perrin NE, et al. Kidney Int 69: 699-705: 2006

Kimmelstiel-Wilson lesion

"Kimmelstiel–Wilson syndrome" **nodular glomerulosclerosis** ,a hallmark of diabetic nephropathy



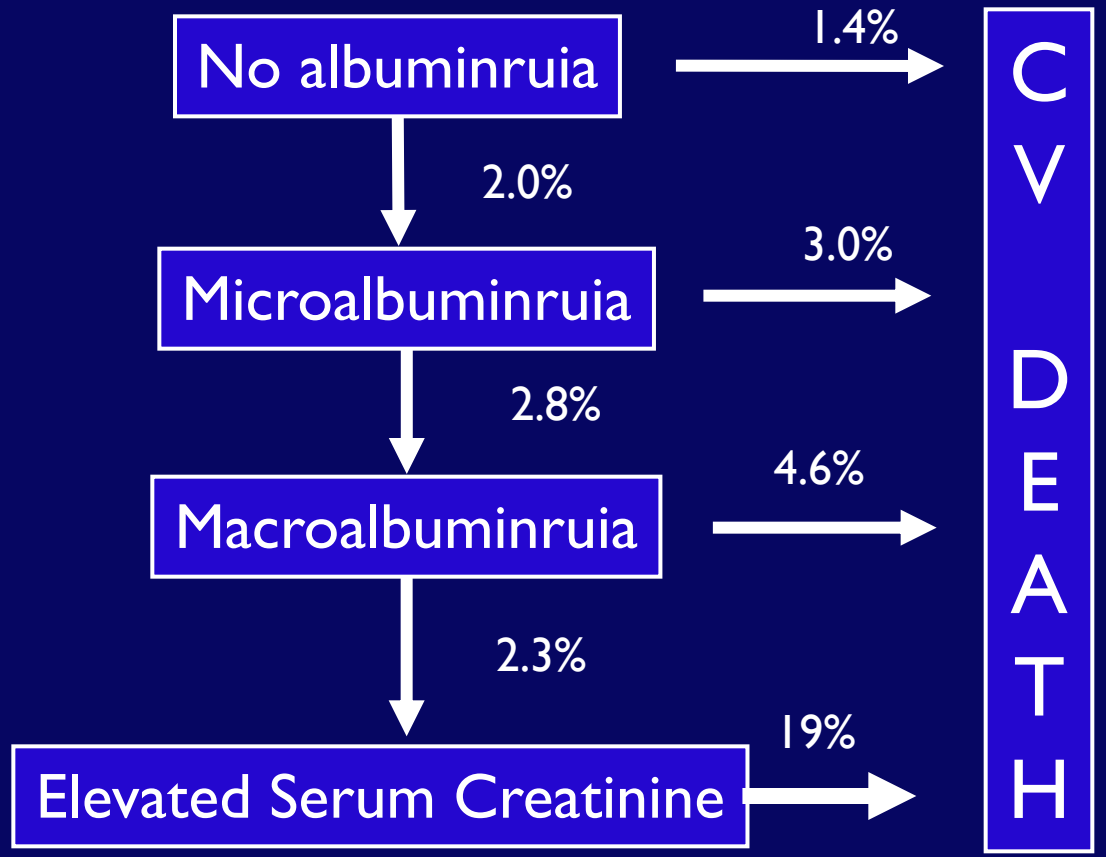
-Longer duration of diabetes
-Severity of retinopathy
-Higher serum creatinine
-Poor prognosis

Not specific for DN

-Dysproteinemias
-MIDD
-Idopathic nodular glomerulosclerosis
-Fibrillary and immunotactoid GN
-Chronic MPGN

Diabetics with Macroalbuminuria are More Likely to Die than Develop ESRD

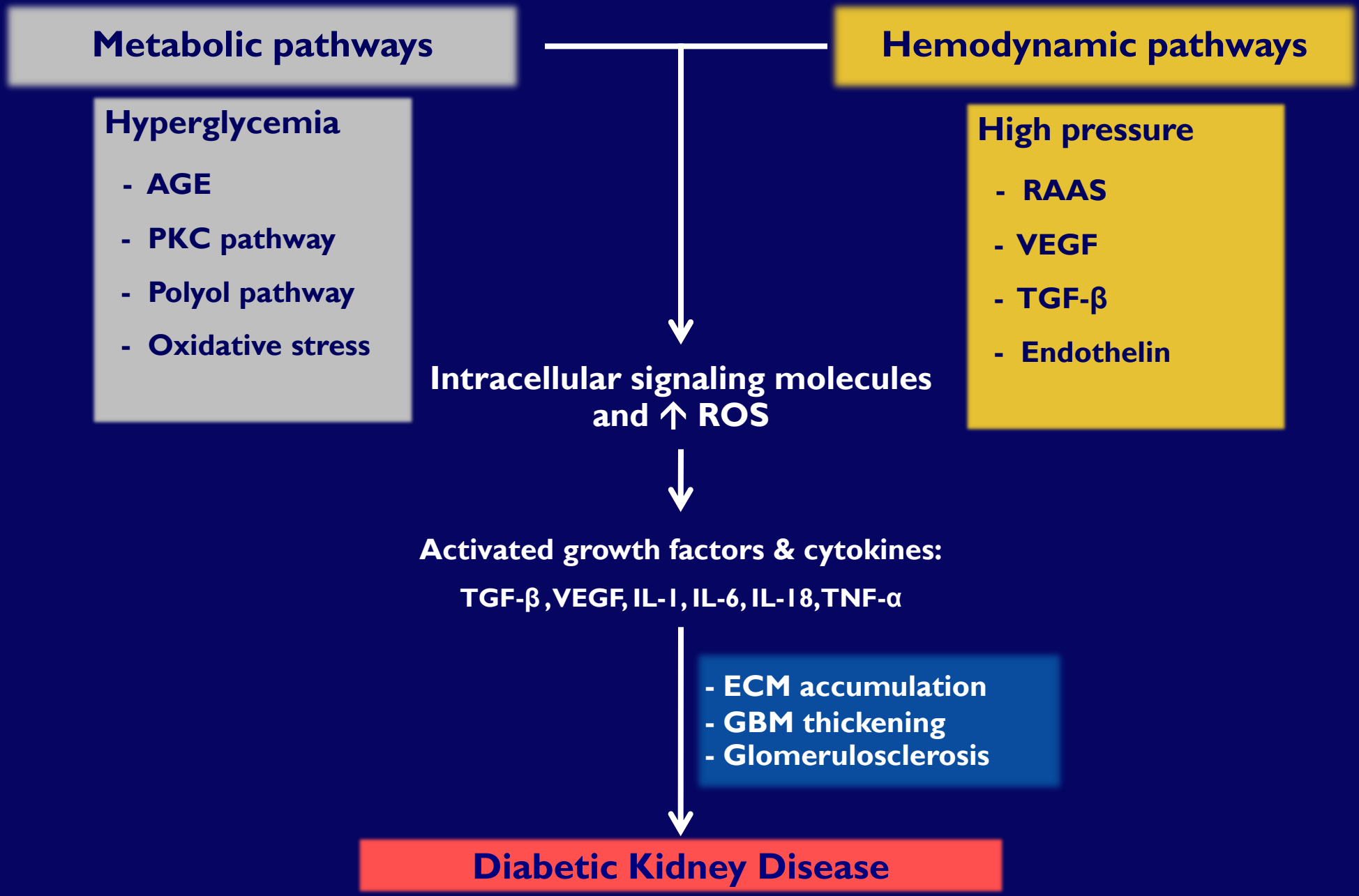
The United Kingdom Prospective Diabetes Study (approx. 5000 Type 2 Diabetics)
Newly diagnosed, predominantly white, medically treated



Adler et al. *Kid Int, 2003*

PATHOPHYSIOLOGY

1. Metabolic Effects
    - -Glucotoxicity
    - -Polyol Pathway
    - -AGEs
    - -Oxidative Stress
2. Hemodynamic Effects
    - -Systemic BP
    - -Intraglomerular pressure
3. Signaling Pathways
    - -Kinase Pathways
    - -Nuclear Factors
4. Cytokines, Chemokines and Growth Factors
    - TGF-β, IGF-I, VEGF, MCP-1, Angiotensin, Aldosterone
5. Genetic Factors

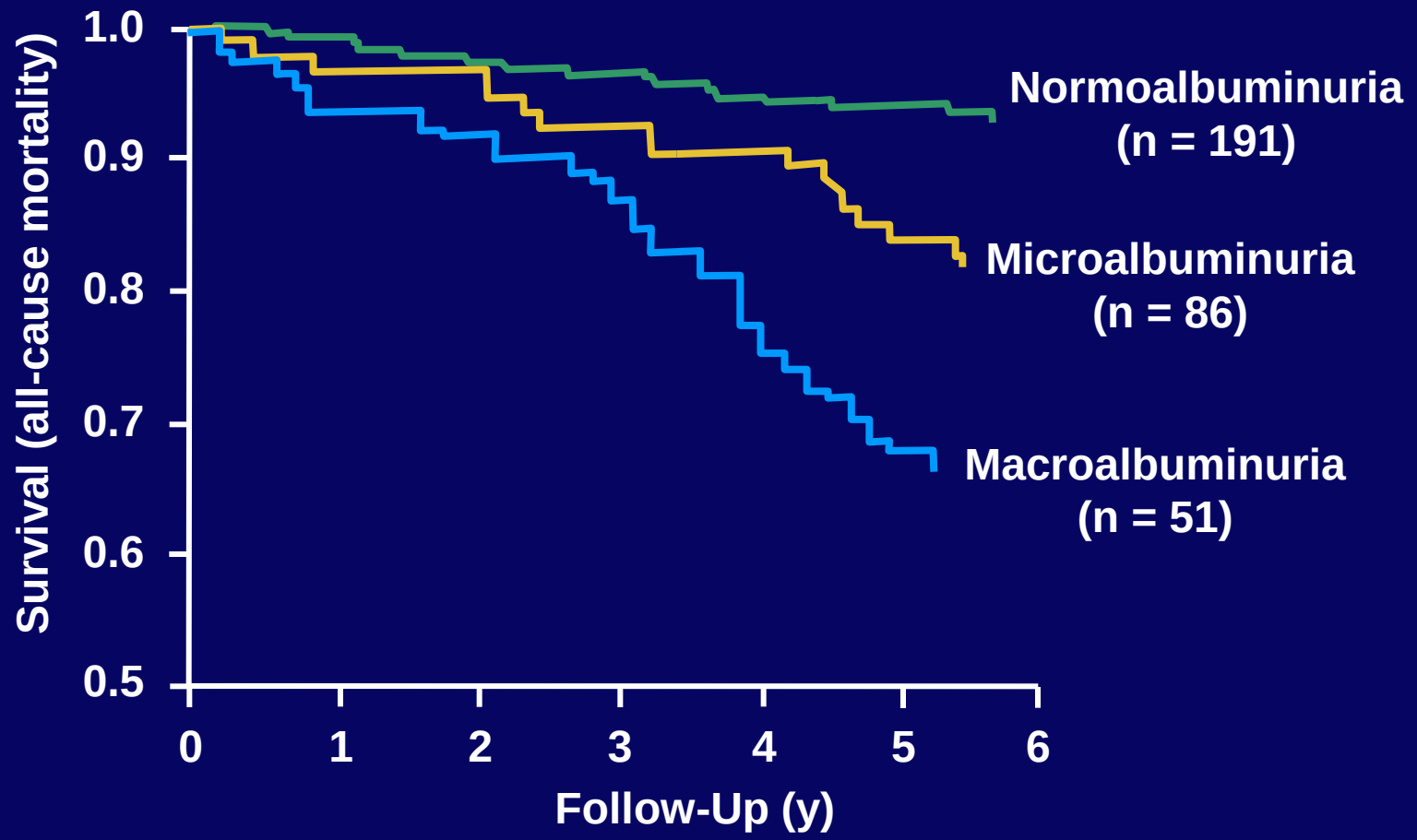

Metabolic pathways
Hemodynamic pathways
Hyperglycemia
- AGE
- PKC pathway
- Polyol pathway
- Oxidative stress
High pressure
- RAAS
- VEGF
- TGF-β
- Endothelin
Intracellular signaling molecules and ↑ ROS
Activated growth factors & cytokines:
TGF-β, VEGF, IL-1, IL-6, IL-18, TNF-α
- ECM accumulation
- GBM thickening
- Glomerulosclerosis
Diabetic Kidney Disease

Genetic factors

Table 1 Some of the genes implicated in the susceptibility and/or progression of diabetic nephropathy (modified after 12)

Gene	Gene variant
Promoter of RAGE	63-bp deletion (decreased risk)
Histocompatibility antigen	DR3/4
Angiotensin-converting enzyme	D/I
Angiotensinogen	M235T
Aldose reductase	Z + 2 alleles
Transforming growth factor β1	Leu10Pro, Arg25Pro
Apolipoprotein E	e2 allele
Paraoxonase 1	T107C, Leu54Met
Interleukin 1β	T105C
Atrial natriuretic peptide	C708T
Glucose transporter 1	Xba1/HacIII
Mannose-binding lectin	YA/YA, XA/YA

Proteinuria Is a Risk Factor for Mortality



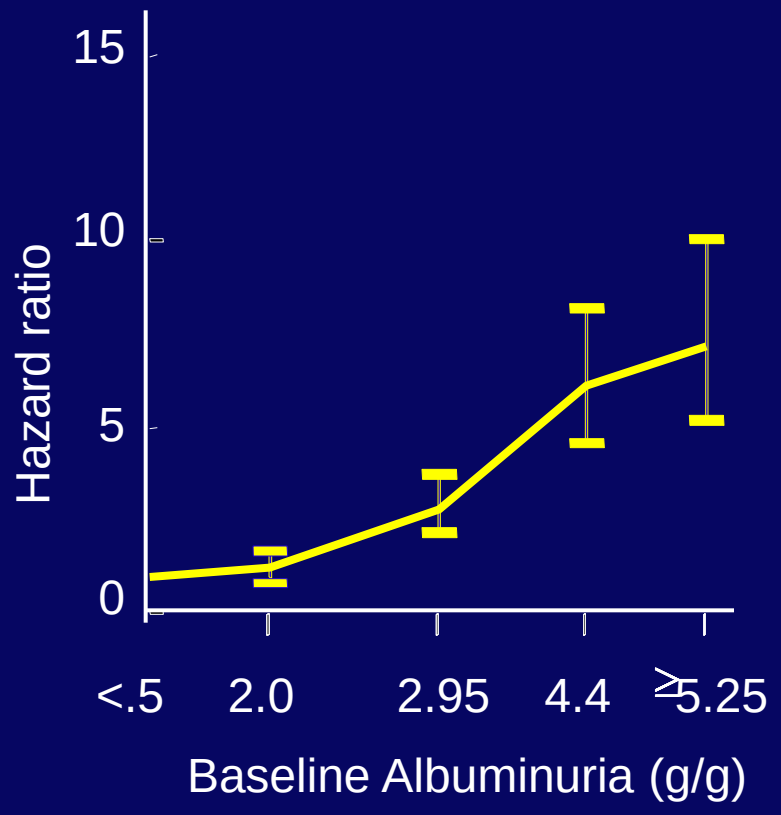
P<0.01 normo- vs microalbuminuria; *P*<0.001 normo- vs macroalbuminuria; *P*<0.05 micro- vs macroalbuminuria.

Gall et al. Diabetes. 1995;44:1303-1309.

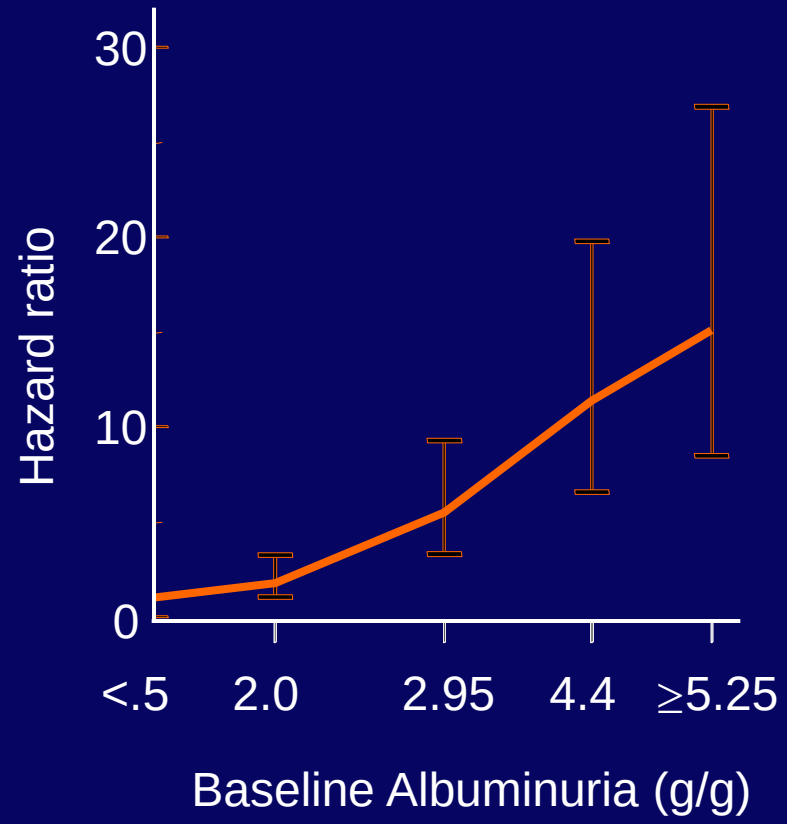
Proteinuria as a Determinant for RENAL Events

(adjusted for all conventional risk factors)

Primary composite Endpoint

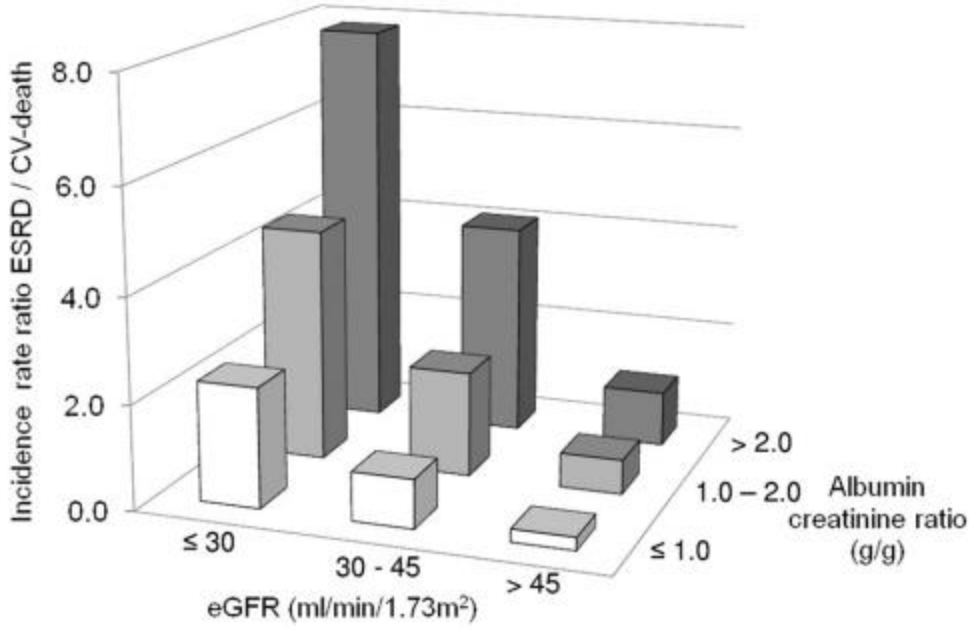


ESRD



De Zeeuw et al; Kidney Int 2004

Proteinuria “Important marker”



ACR (g/g)	eGFR (ml/min/1.73m²) ≤30	30 - 45	>45
> 2.0	12.87 (5.97-27.74)	7.46 (3.63-15.33)	7.40 (3.32-16.47)
1.0 – 2.0	7.12 (3.16-16.04)	3.47 (1.63-7.40)	2.80 (1.18-6.64)
≤1.0	3.61 (1.49-8.73)	1.49 (0.64-3.48)	1.00 (reference)

- Predictor of kidney function deterioration, DN progression and CV death
- Risk for ESRD increases as proteinuria increases and eGFR decreases.

Treatment of diabetic nephropathy

Specific treatment

4 major arenas

- Blood pressure control
- Inhibition of the renin-angiotensin system (RAS)
- Glycemic control
- Cardiovascular risk reduction

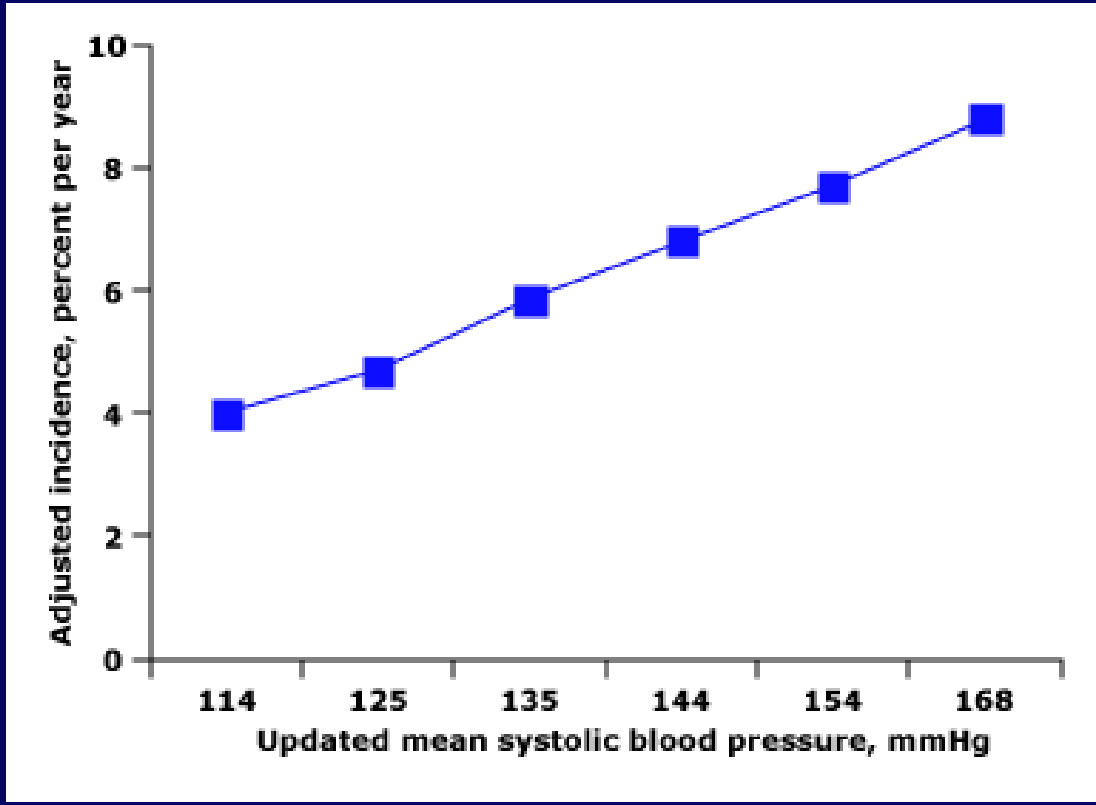
Reno-cardioprotection in DKD

Intervention	Therapeutic goal
Renoprotective therapy	
Antihypertensive agents	BP ≤130/80 mmHg for albuminuria≥ 30 mg/day BP ≤140/90 mmHg for albuminuria< 30 mg/day
ACEi or ARB (Avoid combining ACEi+ARB)	Urine protein <0.5-1.0 g/day GFR decline <2 mL/min/year
Glycemic control	HbA1c~7%
Dietary protein restriction	0.8 g/kg/day in GFR < 30 mL/min/1.73 m^2
Adjunctive cardiorenal protective therapy	
Dietary salt restriction	<5 g/day
Lipid-lowering agents (statin)	LDL-C <70-100 mg/dL
Anti-platelets therapy	Thrombosis prophylaxis
Physical activity	Aiming for at least 30 minutes 5 times per wk)
Weight control	Ideal body weight
Smoking cessation	Abstinence

Satirapoj B, Adler SG. Kidney Res Clin Pract. 2014; 121–131.

Hypertensive control

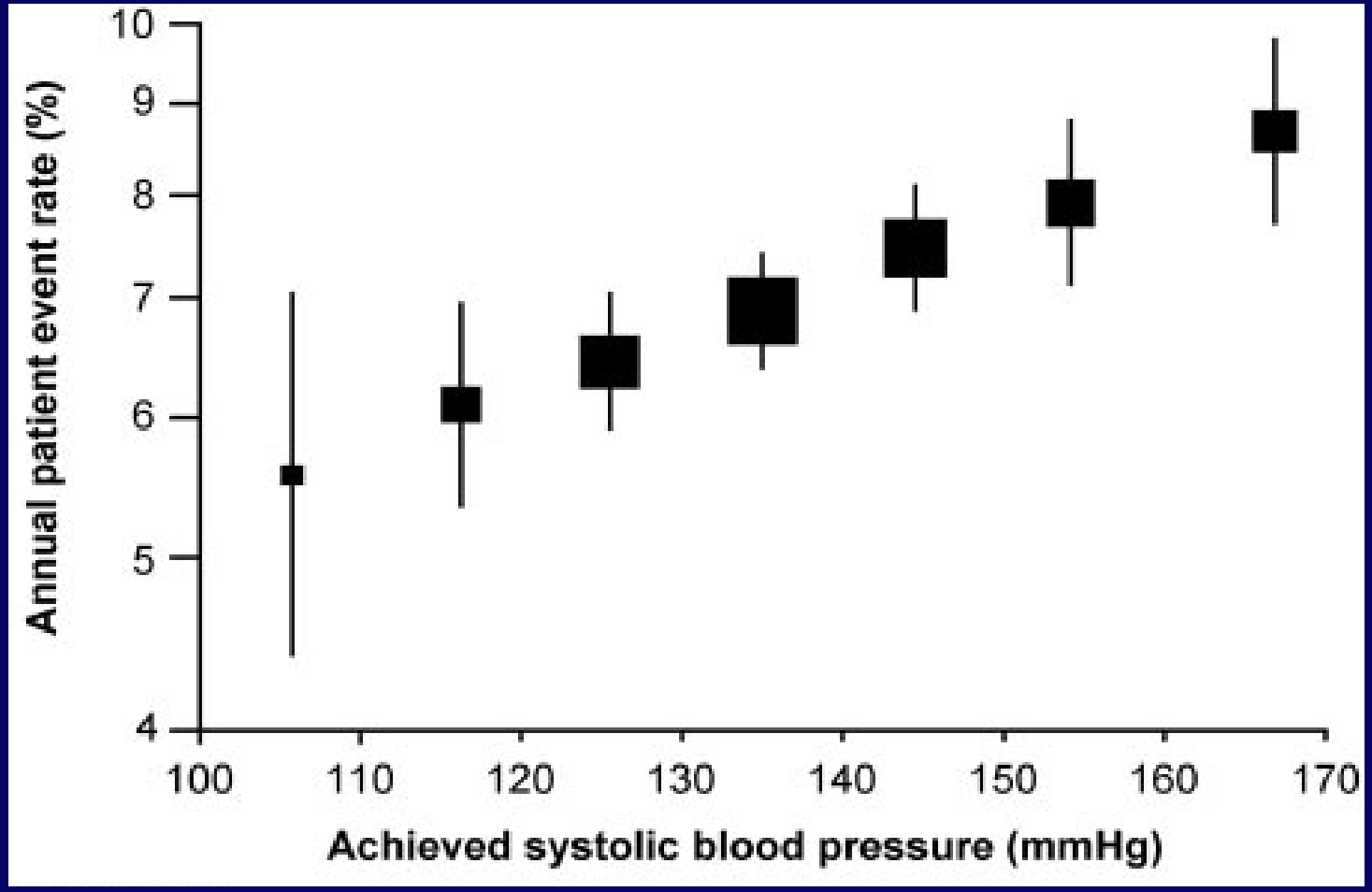
UKPDS study: Lower systolic pressure reduces complications in type 2 diabetes (3,642 pts)



Each 10 mmHg reduction in systolic BP → 12% risk reduction in diabetic complications (P<0.001)
The lowest risk occurred at a systolic BP < 120 mmHg

Adler, AI,, et al, BMJ 2000; 321:412.

ADVANCE Study: Lowering SBP reduces renal events in type 2 diabetes



Harrap S, et al. J Am Soc Nephrol. 2009 Apr;20(4):883-92

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

- 4733 participants with type 2 DM
- Intensive therapy : targeting a SBP <120 mmHg (119.3mmHg)
- Standard therapy : targeting a SBP <140 mmHg (133.5mmHg)
- Conclusions : In patients with type 2DM at high risk for cardiovascular events, targeting a SBP <120 mm Hg, as compared with <140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.

n engl j med 362;17 nejm.org april 29, 2010

Table 3. Primary and Secondary Outcomes.

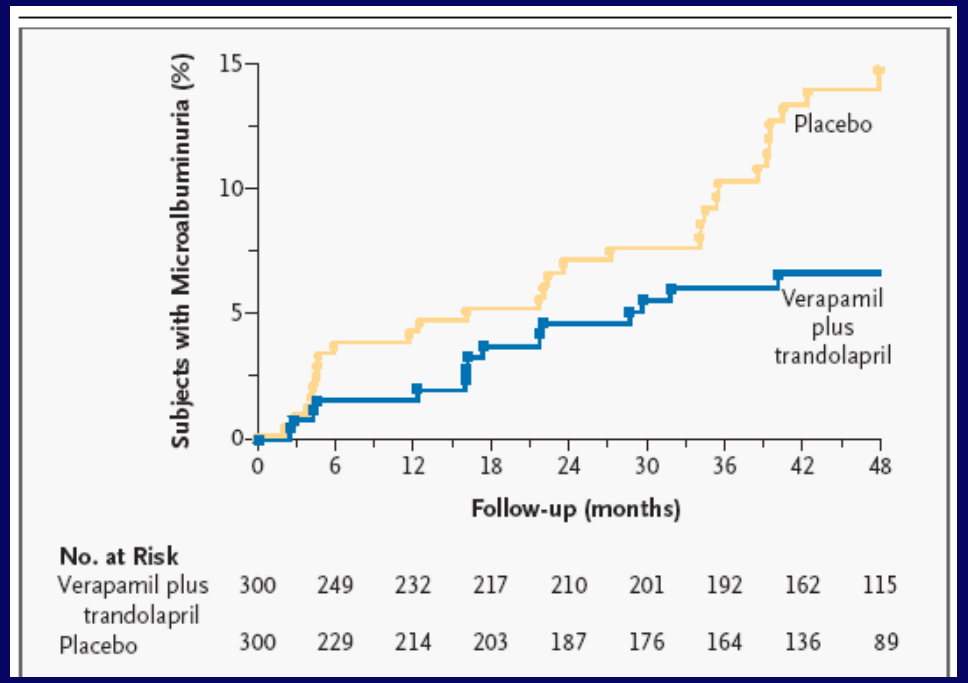
Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

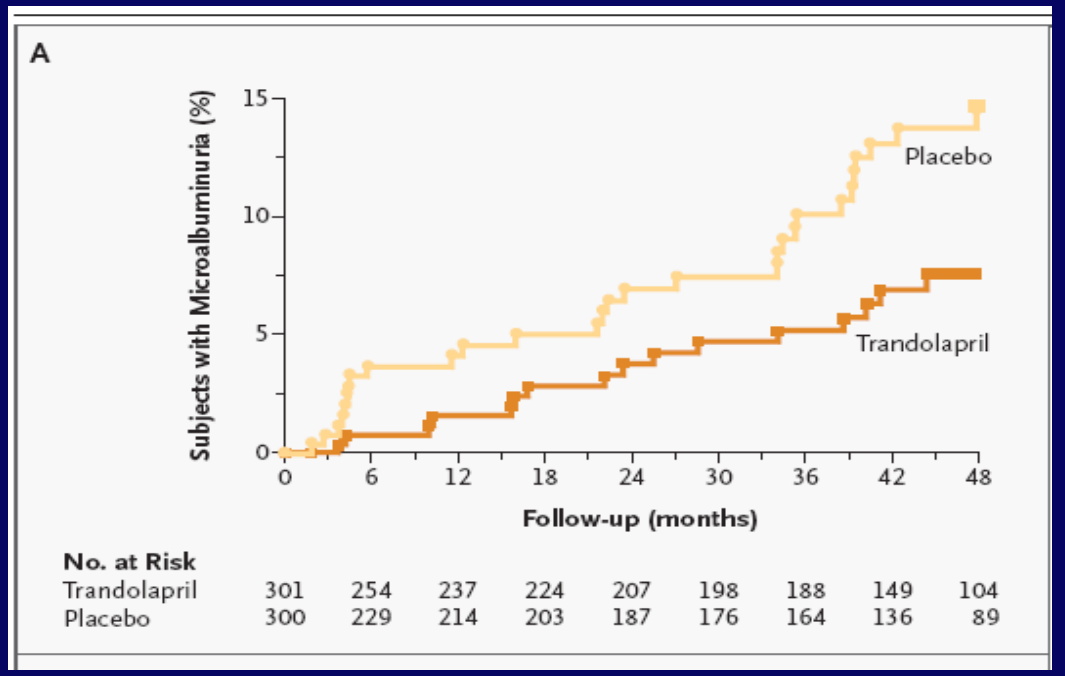
- Intensive BP management did reduce the rate of total stroke and nonfatal stroke.
- NNT to prevent one stroke over the course of 5 years was 89

n engl j med 362;17 nejm.org april 29, 2010

Inhibition of the renin-angiotensin system

BENEDICT: ACEI: Preventing Microalbuminuria in Type 2 Diabetes with HT/normoalbuminuria



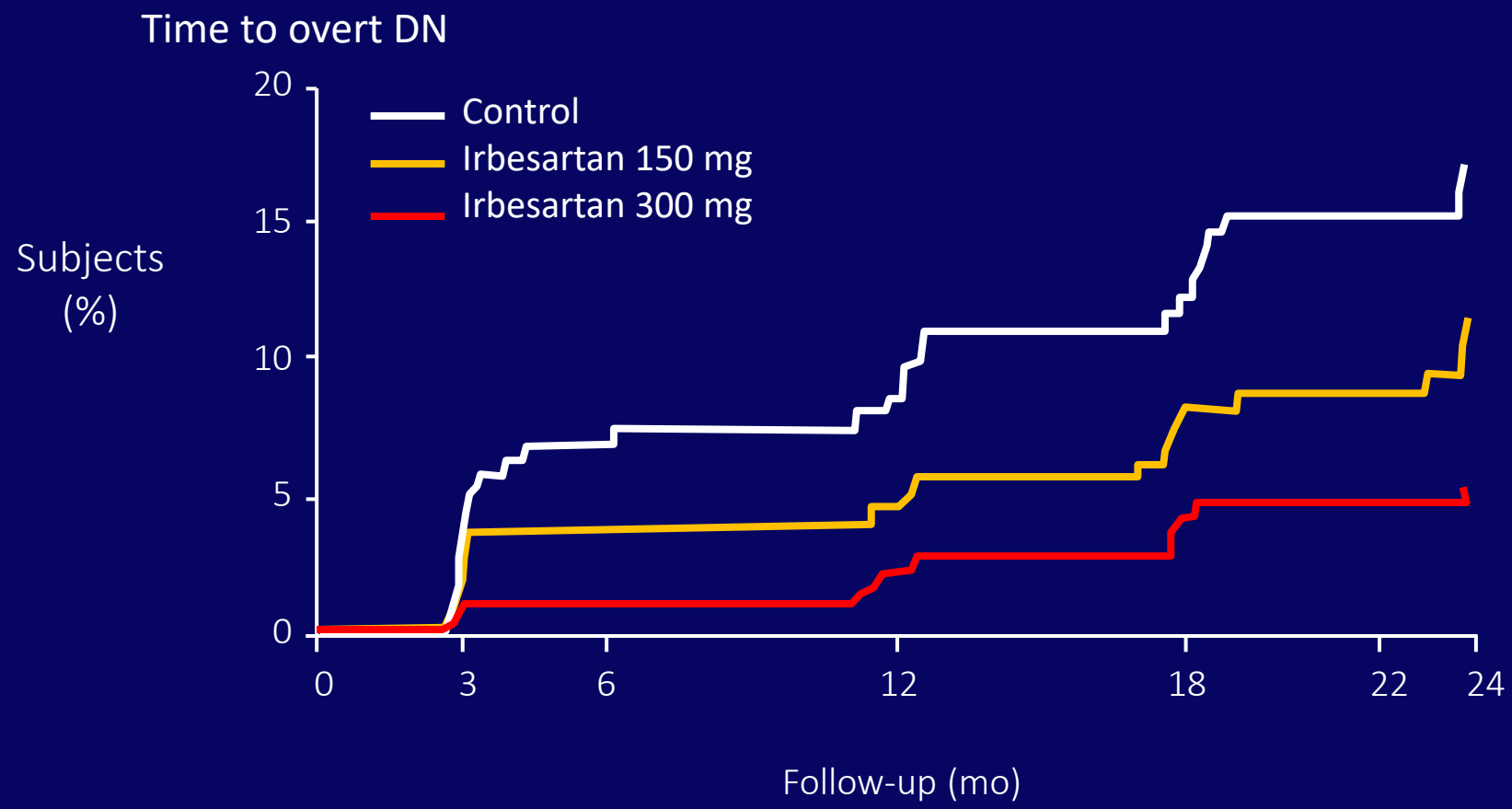


T2DM and HTN, normoalbuminuria and normal GFR

Trandolapril plus verapamil or trandolapril alone prevented the onset of microalbuminuria

Ruggenenti P, et al. New Eng J Med 2004; 351:

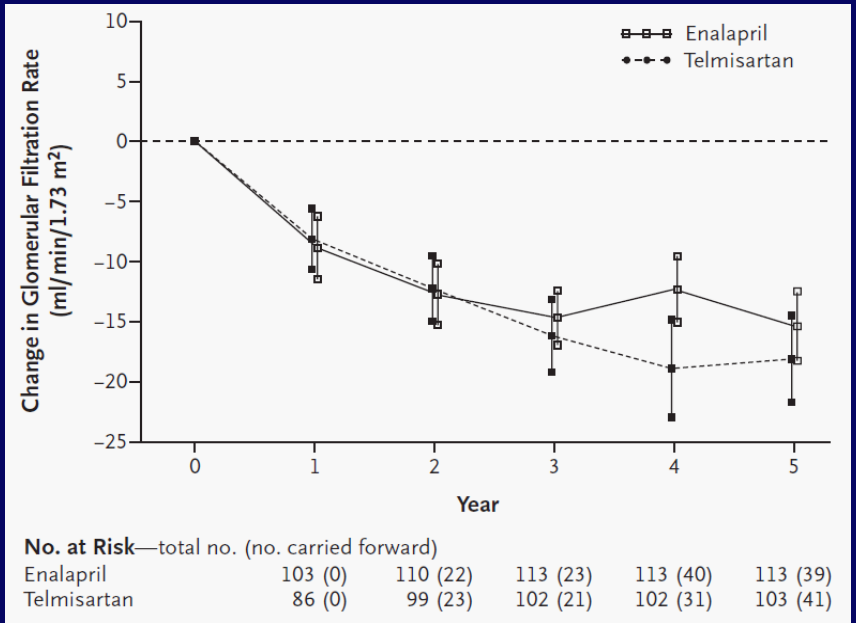
IRMA 2 : ARB : slow progression from microalbuminuria to Overt Proteinuria



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

ARB vs ACEI in type 2 diabetes and nephropathy

250 patients with early nephropathy as defined by albuminuria (82% microalbuminuria and 18% macroalbuminuria)



End point	Change from baseline		Difference (95% CI)
	Telmisartan	Enalapril	
Serum creatinine (mg/dL)	0.10	0.10	0 (-0.66 to 0.65)
Urinary albumin excretion (ratio)	1.03	0.99	1.04 (0.71to 1.51)

ACEI are at least as effective as ARBs in diabetic patients with microalbuminuria.

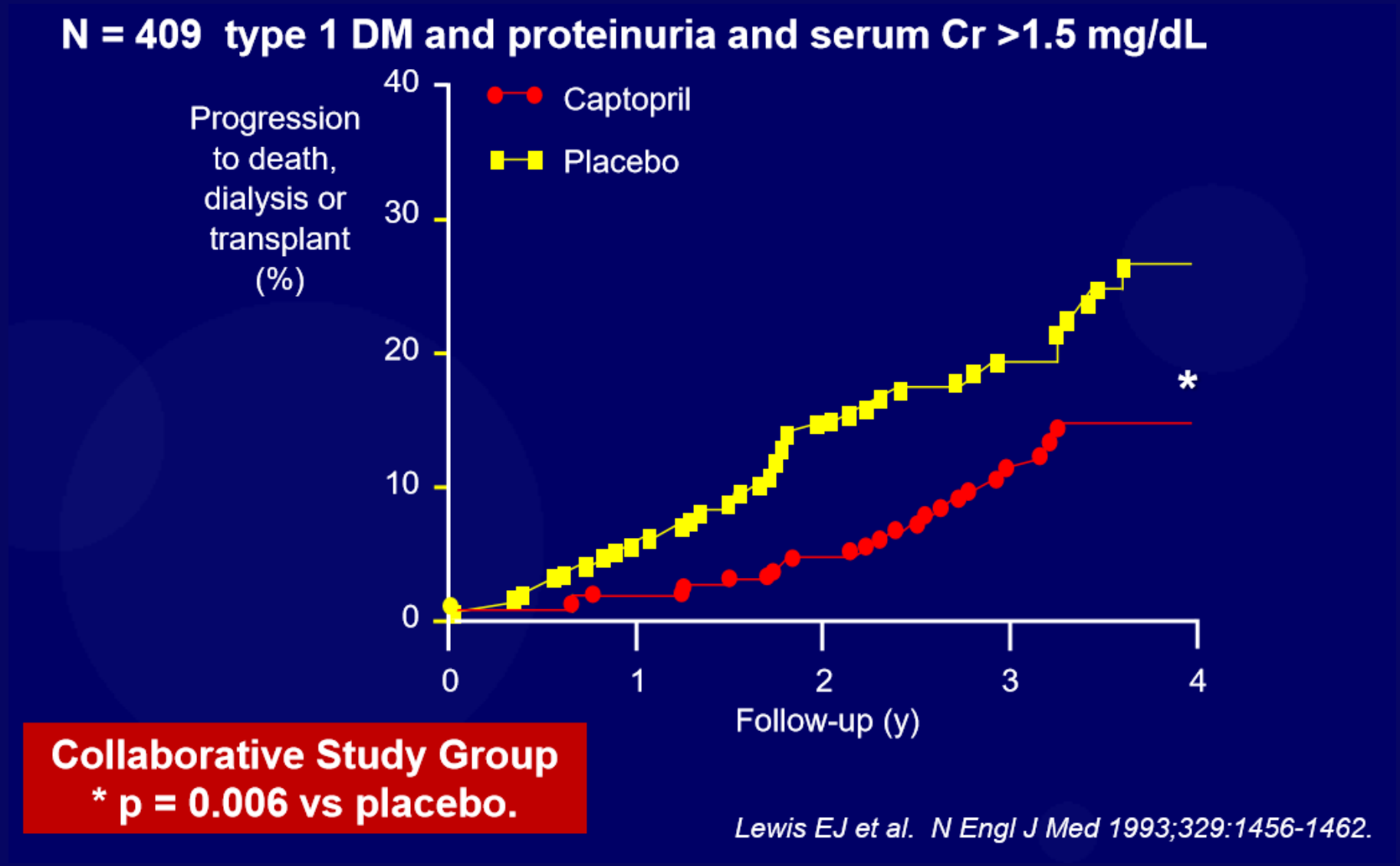
Barnett AH, et al. N Engl J Med 2004 Nov 4;351(19):1952-61.

ACE Inhibitors vs. Other Antihypertensives in Patients with Type 2 Diabetes and Proteinuria

Investigator	Treatment	Follow-up (y)	Proteinuria		Decline in GFR (ml/min/yr)	
			ACE inhibitor	Non-ACE inhibitor	ACE inhibitor	Non-ACE inhibitor
Walker et al (n=86)	ACE inhibitor vs conventional therapy	3	↓↓	↓	3.0	4.1
Lebovitz et al (n=46)	ACE inhibitor vs conventional therapy	3	↓	→	6.4	9.6
Bakris et al (n=52)	ACE inhibitor vs CCB vs beta blocker	5	↓↓	↓↓ (CCB) ↓ (BB)	1.0	1.4 (CCB) 3.3 (BB)
Nielsen et al (n=36)	ACE inhibitor vs beta blocker	3	↓↓	→	7.0	6.5
Estacio et al (n=83)	ACE inhibitor vs CCB	5	↓	↓	5.5	5.5
Fogari et al (n=51)	ACE inhibitor vs CCB	2	↓↓	↓	2.0	1.2

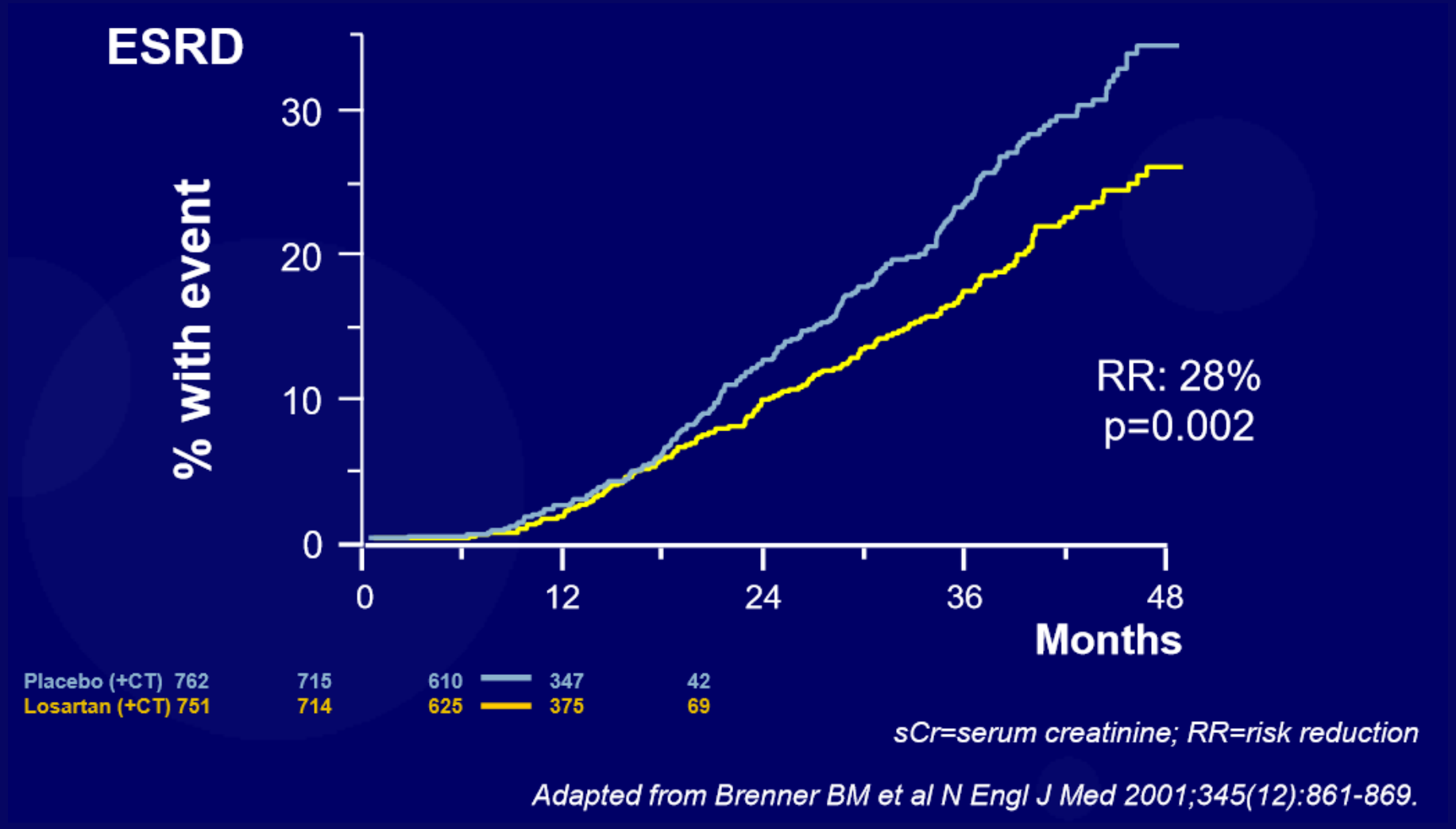
Parving H-H et al. Curr Opin Nephrol Hypertens 2001;10:515-522.

ACEI on nephropathy in T1DM patients



Lewis EJ et al. N Engl J Med 1993;329:1456-1462.

RENAAL study : ARBs on ESRD in T2DM



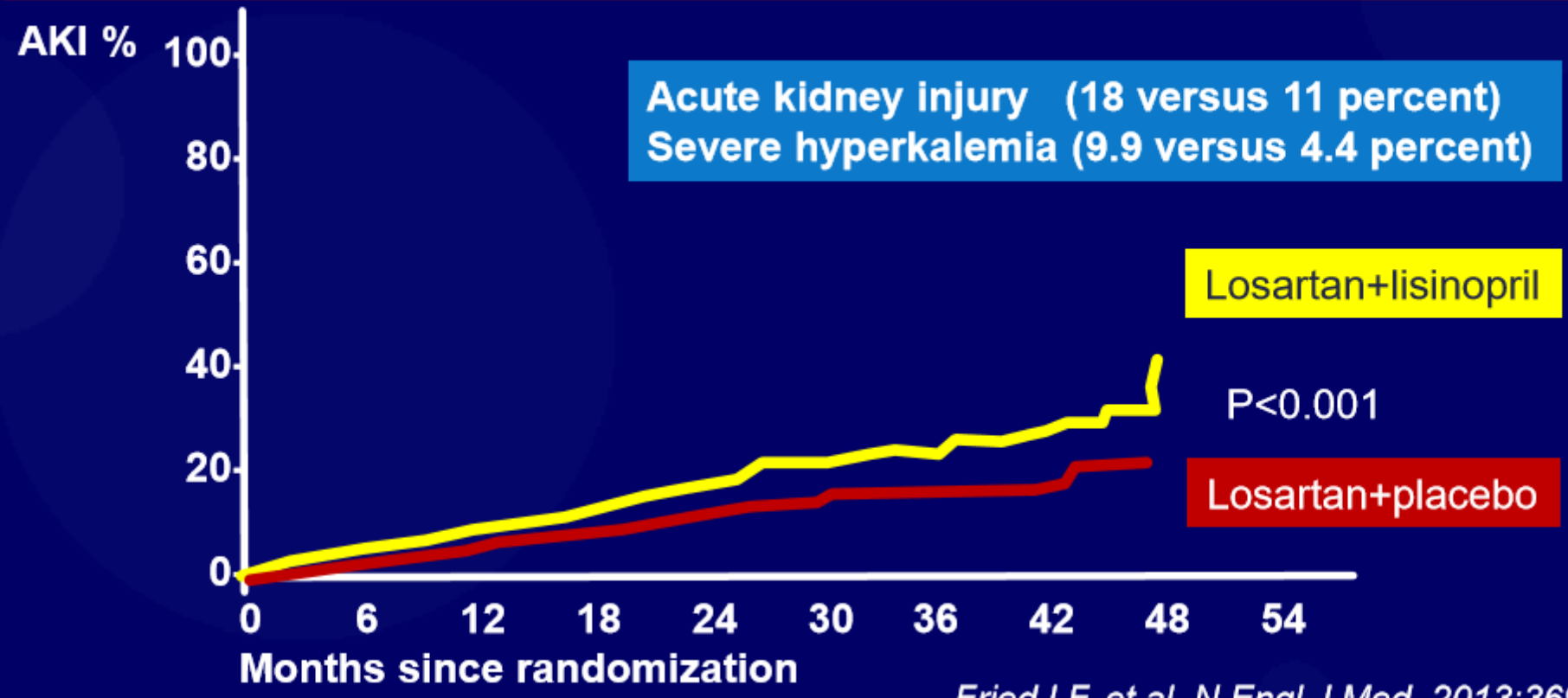
sCr=serum creatinine; RR=risk reduction

Adapted from Brenner BM et al N Engl J Med 2001;345(12):861-869.

Combined ACEI and ARBs (VA NEPHRON-D)

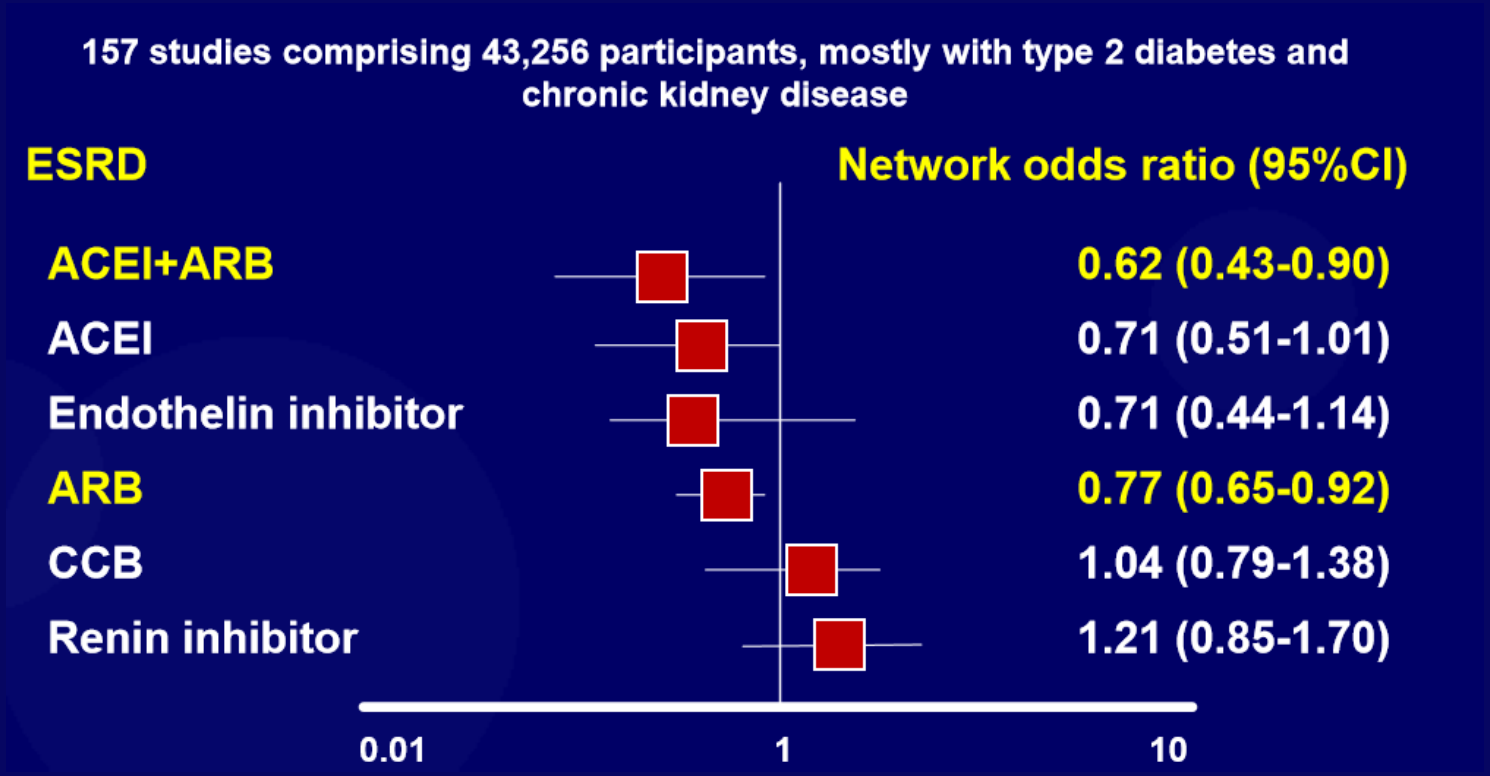
1448 patients with DN (GFR 54ml/min/1.73m2, albuminuria 852mg/g)

The trial was discontinued early after a median of 2.2 years because of safety concerns



Fried LF, et al. N Engl J Med. 2013;369(20):1892.

BP lowering agents in diabetic and kidney disease patients : A network meta-analysis



Borderline increases in estimated risk

OR 2.69, 95%CI 0.97-7.47 for hyperkalemia
OR 2.69, 95% CI 0.98-7.38 for AKI

Palmer SC, et al. Lancet 2015; 385(9982):2047-56.

Dual RAAS blockade for kidney failure: hope for the future

- Treating 1,000 patients with diabetes and CKD with dual ACEI and ARB treatment vs monotherapy for 1 year

- Prevent 3 cases of ESRD
- Regress albuminuria in 90 people

Jafer TH and Assam PN, Lancet 2015

ADA 2020

- *In nonpregnant patients with diabetes and hypertension, either an ACEi or ARB is recommended for those with UACR ≥300 mg/g creatinine and/or estimated GFR <60 mL/min/1.73 m^2.*
- *Periodically monitor serum creatinine and potassium levels when ACEi, ARB, or diuretics are used.*
- *An ACEi or ARB is not recommended for the primary prevention of CKD in patients with diabetes who have normal BP, normal UACR (<30 mg/g creatinine), and normal GFR.*

American Diabetes Association Diabetes Care 2020 Jan; 43(Supplement 1): S135-S151.

ACEI and ARBs warnings

- Angioedema
- Hyperkalemia
- Acute kidney injury
  - Severe bilateral renal artery stenosis
  - Volume depletion
- Pregnancy category C in 1st trimester
  - Adverse effect on the fetus in animal with CVS (ASD/VSD) and CNS (spina bifina, microcephaly) malformations
- Pregnancy category D in 2nd & 3rd trimester
  - Positive evidence of human renal dysgenesis, oligohydramnios and death

KDIGO : management of BP in CKD

Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy and tolerance of treatment

	Albuminuria (ACR <30 mg/g)	Albuminuria (ACR 30-300 mg/g)	Albuminuria (ACR >300mg/g)
Diabetes	<140/90 (1B)	<130/80 (2D)	<130/80 (2D)
Non diabetes	<140/90 (1B)	<130/80 (2D)	<130/80 (2C)

Kidney International Supplements (2012) 2, 338

ADA 2017

- The hypertension treatment recommendation for diabetes now suggests that for patients without albuminuria, any of the
  - ACE inhibitors,
  - angiotensin receptor blockers,
  - thiazide-like diuretics,
  - dihydropyridine calcium channel blockers

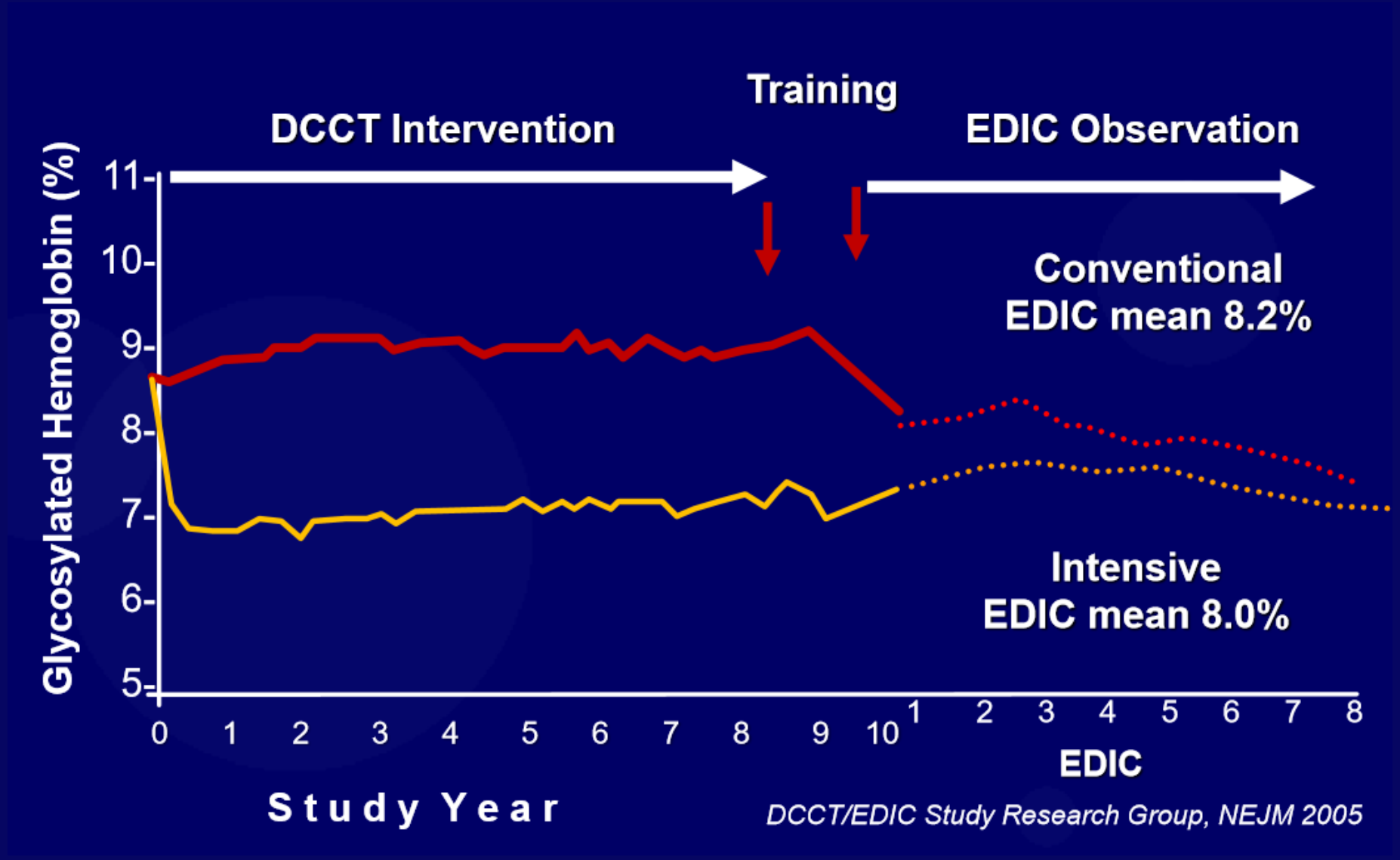
  that have shown beneficial cardiovascular outcomes may be used.

Glycemic control

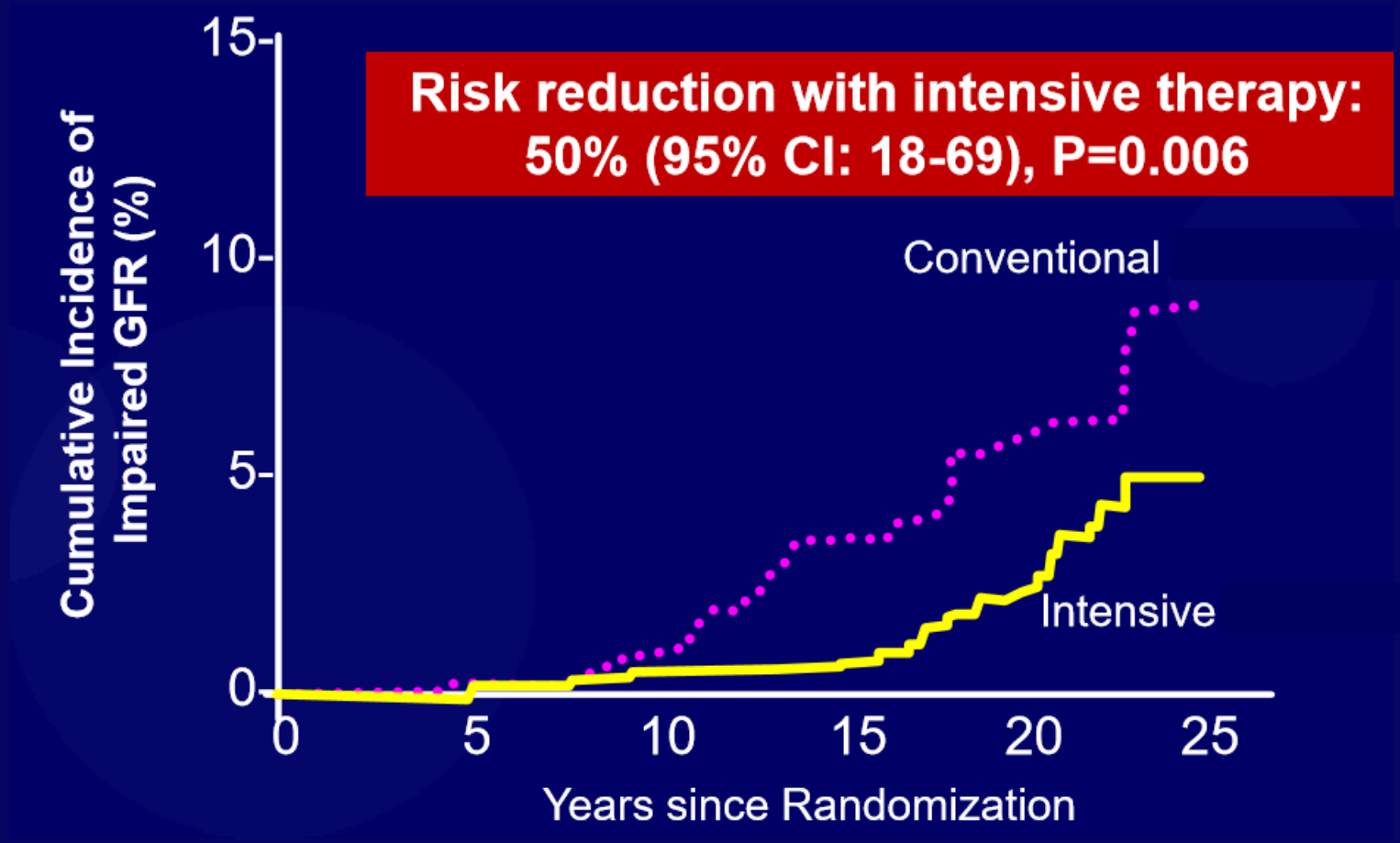
Intensive glycemic control reduce in incidence of microvascular complications

HbA1c	Type 1 DCCT 9 → 7%	Type 2 Kumamoto 9 → 7%	Type 2 UKPDS 8 → 7%
Retinopathy	76%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	-	-

EDIC (long term observation from DCCT)

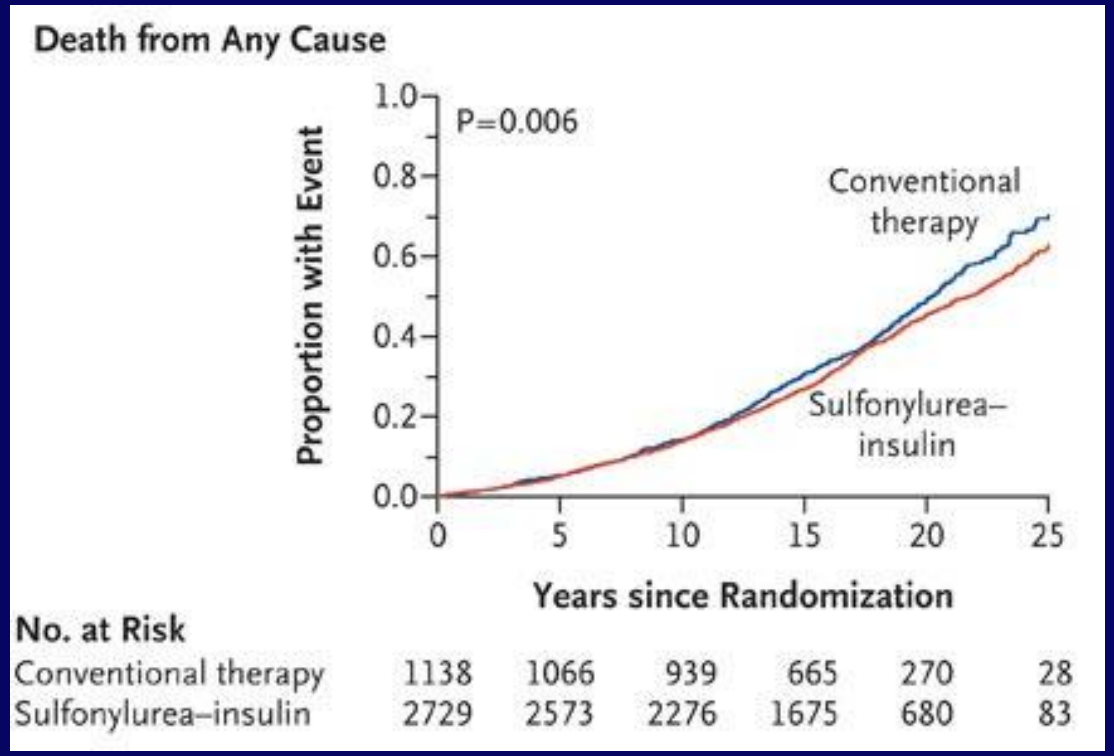


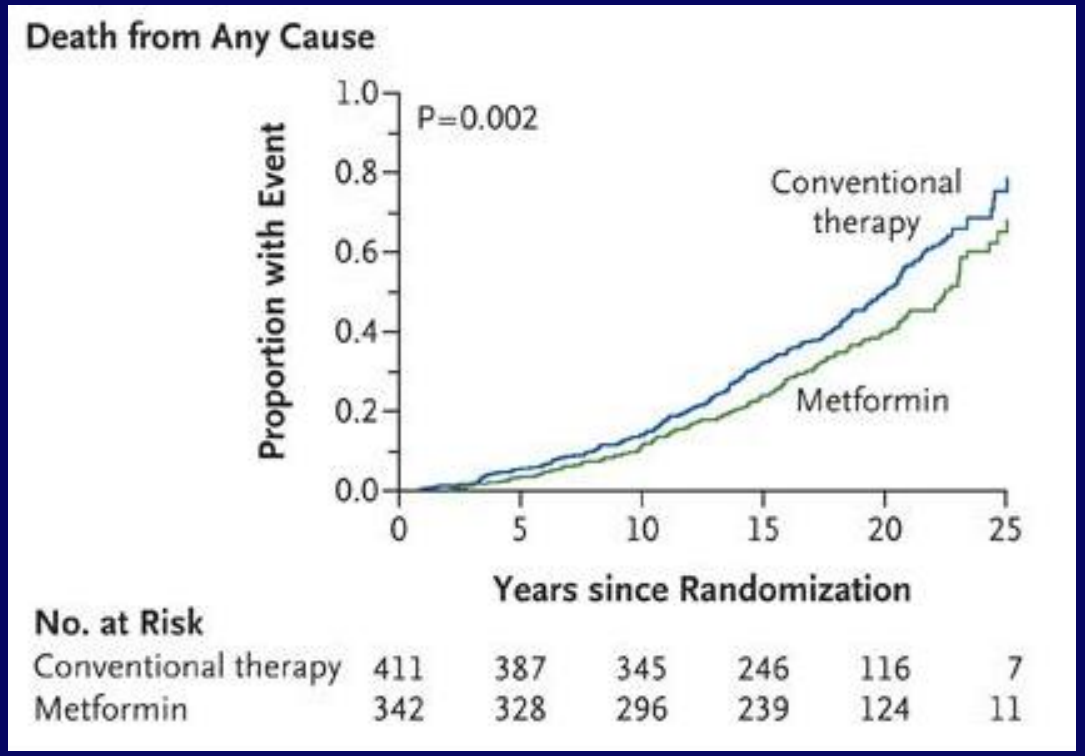
Long-term risk of an impaired GFR was significantly lower in intensive therapy



The DCCT/EDIC Research Group. N Engl J Med 2011;365:2366-76.

Metabolic Memory Effect in UKPDS study





Conclusion: Early glycemic control may be critically important for long term outcome

Holman R, et al. N Engl J Med; 2008: 359: 1577.

Intensive glucose lowering studies

	ACCORD[1]	ADVANCE[3]	VADT[4]
Number of patients	10,251	11,140	1791
HbA1c with intensive vs standard treatment	6.4% vs 7.5%	6.4% vs 7.0%	6.9% vs 8.4%
Diabetes duration	10 yrs	8 yrs	11.5 yrs
Effect on cardiovascular risk	Decreased risk of nonfatal MI; increased risk of death from CVD	No benefit	No benefit
Effect on mortality	Increased*	No difference	No difference
Adverse effects	More hypoglycemia, weight gain, fluid retention	More hypoglycemia, weight gain	More hypoglycemia, weight gain

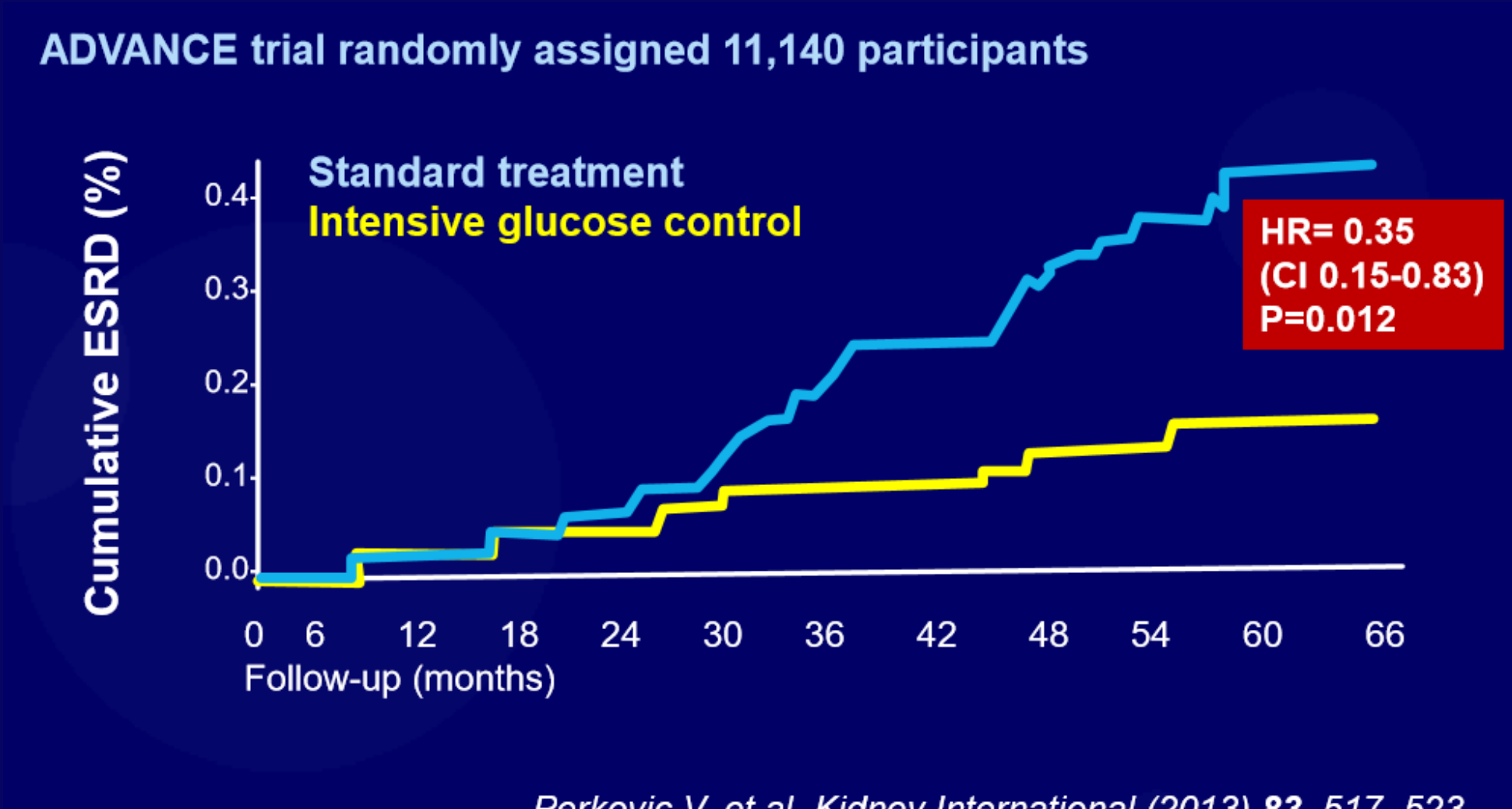
1. *ACCORD Study Group. N Engl J Med. 2008;358:2545-2559.*
2. *Ismail-Beigi F, et al. Lancet. 2010;376:419-430.*
3. *ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572.*
4. *Duckworth W, et al. N Engl J Med. 2008;360:129-139.*

Intensive therapy and albuminuria outcome

Study	Intensified treatment versus normal treatment HbA1C goals	Albuminuria outcome
ADVANCE	6.5% vs 7.3%	9% ↓ in new ACR 3-30 mg/mmol 30% ↓ in ACR progression to >30 mg/mmol
ACCORD	6.3% vs 7.6%	21% ↓ in new ACR 3-30 mg/mmol 32% ↓ in ACR progression to >30 mg/mmol
VADT	6.9% vs 8.4%	32% ↓ in new ACR 3-30 mg/mmol 37% ↓ in ACR progression to >30 mg/mmol

KDIGO CLINICAL PRACTICE GUIDELINE FOR EVALUATION AND MANAGEMENT OF CKD 2012

Intensive glycemic control reduces ESRD in T2DM



Perkovic V, et al. Kidney International (2013) ***83,*** *517–523*

HbA1C target?

- Individual tailored strategy : risk and benefit?
- Goals should be individualized based on*
  - Duration of diabetes
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemia unawareness
  - Individual patient considerations

HbA_{1c} target

- A reasonable A1C goal for many nonpregnant adults is <7%. **A**

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

More or less stringent glycemic goals may be appropriate for individual patients

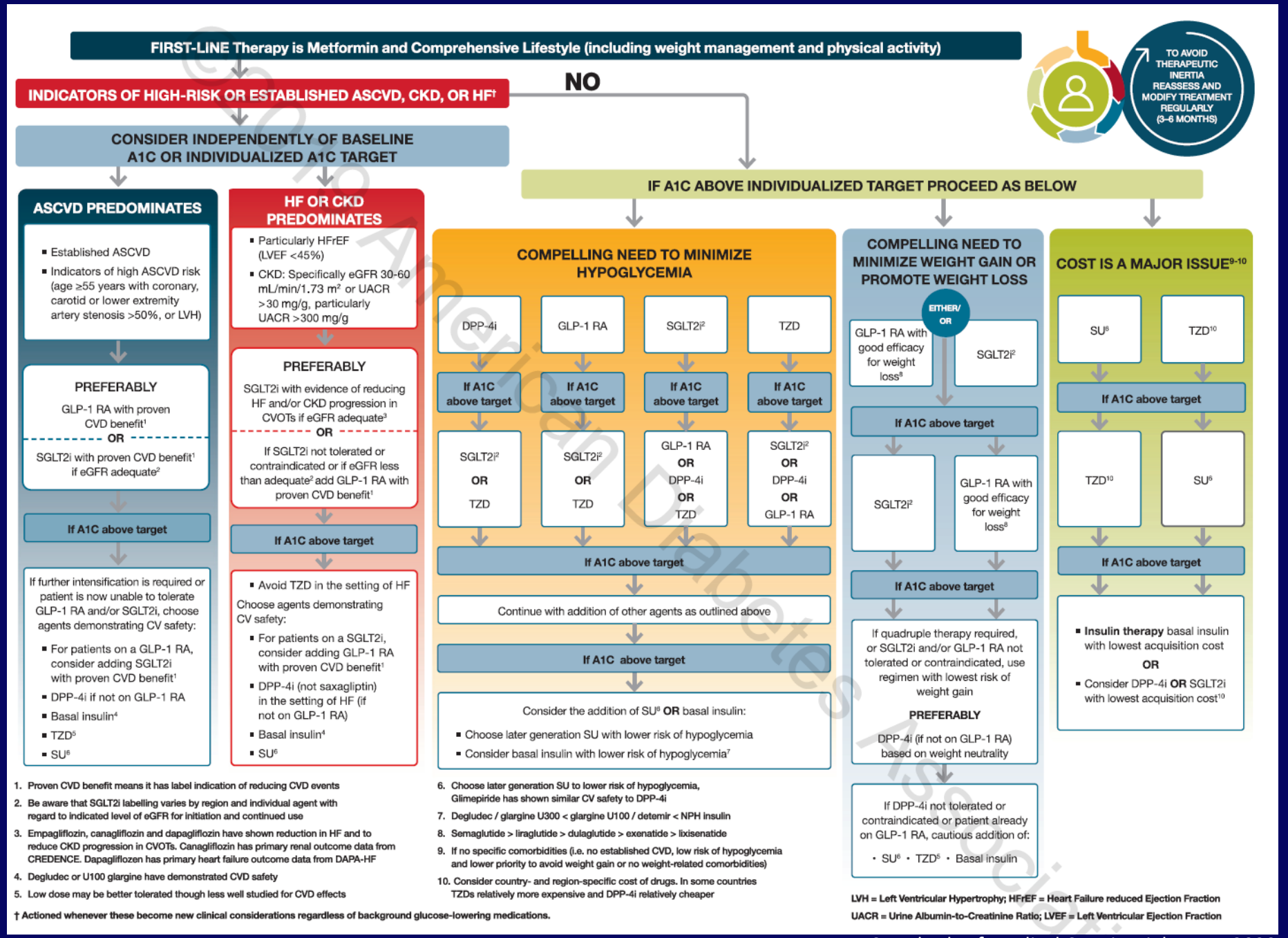
Standards of Medical Care in Diabetes—2020 January 2020 Volume 43,

Assessing risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease
- Hypoglycemia risk

A1C goals = 8% in

- History of severe hypoglycemia
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbid conditions
- Long-standing diabetes in whom the general goal is difficult to attain



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

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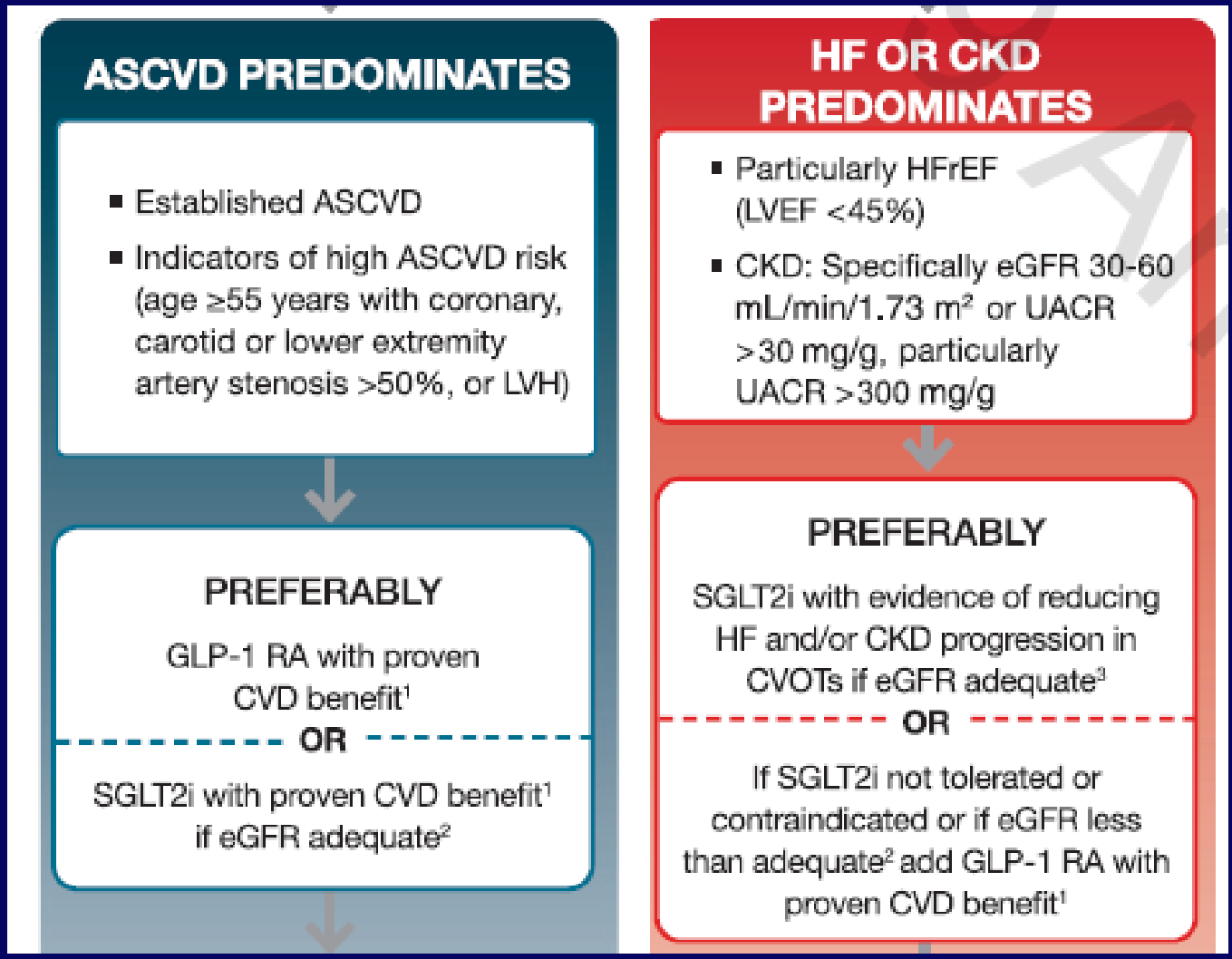
Standards of Medical Care in Diabetes—2020 January 2020 Volume 43,

High risk or established ASCVD/CKD/HF



Standards of Medical Care in Diabetes—2020 January 2020 Volume 43,

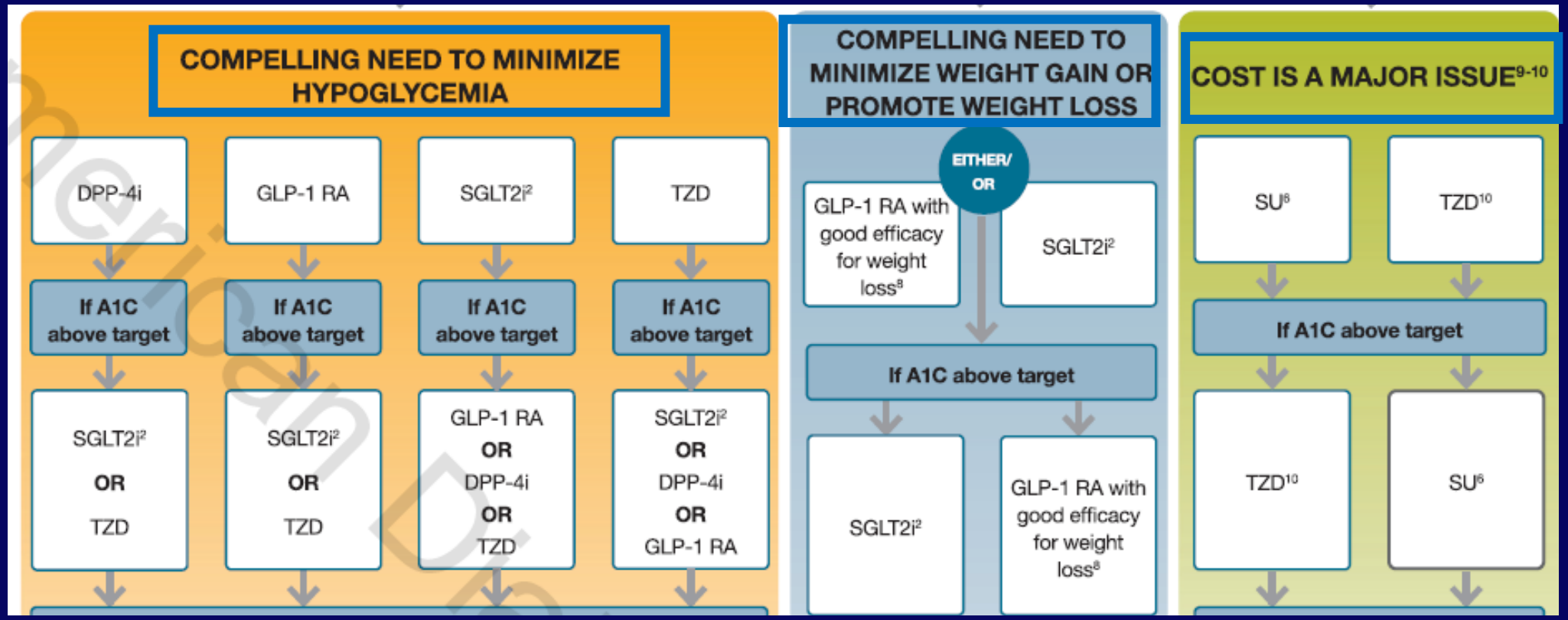
Selection of Glucose-Lowering Medications for Patients With Chronic Kidney Disease

- Optimize glucose control to reduce the risk or slow CKD progression. A
- Consider use of SGLT2 inhibitors in patients with GFR ≥ 30 mL/min/1.73 m2 and UACR >30 mg/g, particularly in those with UACR >300 mg/g, to reduce risk of CKD progression, cardiovascular events, or both. A
- In patients with CKD who are at increased risk for cardiovascular events, use of GLP-1 RAs may reduce risk of progression of albuminuria, cardiovascular events, or both. C

Special considerations : limitations of medications, mitigation of CKD progression, CVD, and hypoglycemia

Standards of Medical Care in Diabetes—2020 January 2020 Volume 43,

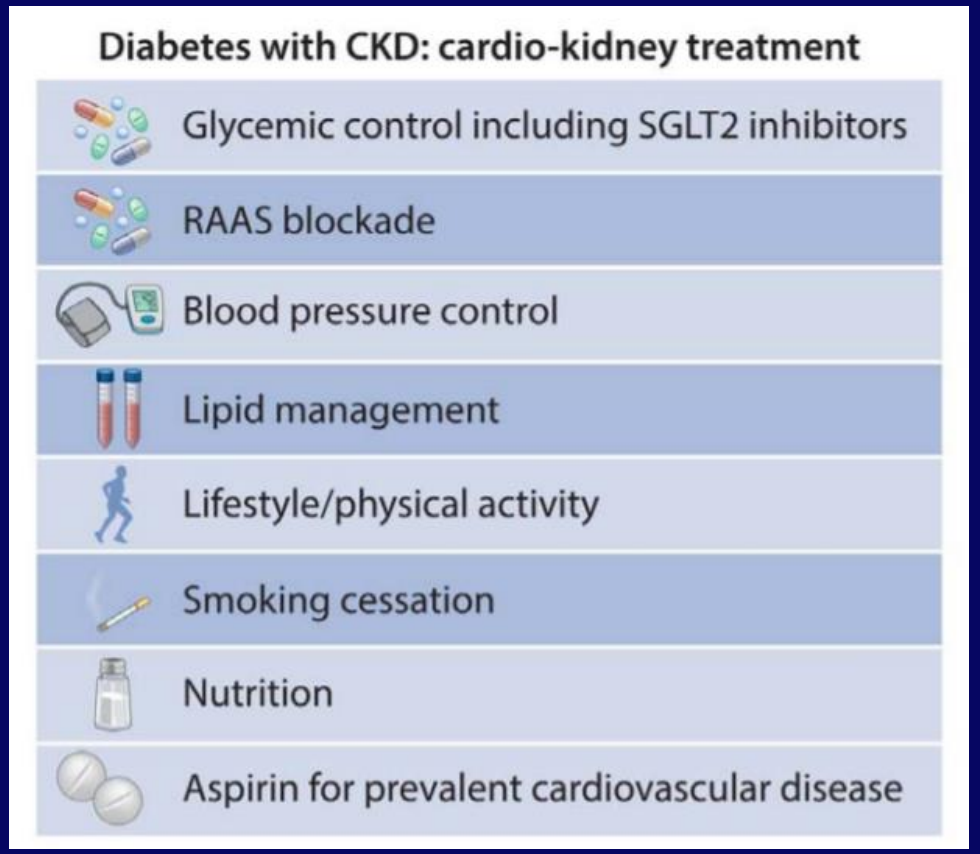
Not high risk or established ASCVD/CKD/HF



- Minimize hypoglycemia
- Minimize weight gain or promote weight loss
- cost

Standards of Medical Care in Diabetes—2020 January 2020 Volume 43,

KDIGO 2019 :Comprehensive management to reduce risks of kidney disease progression and cardiovascular disease in DM+ CKD.

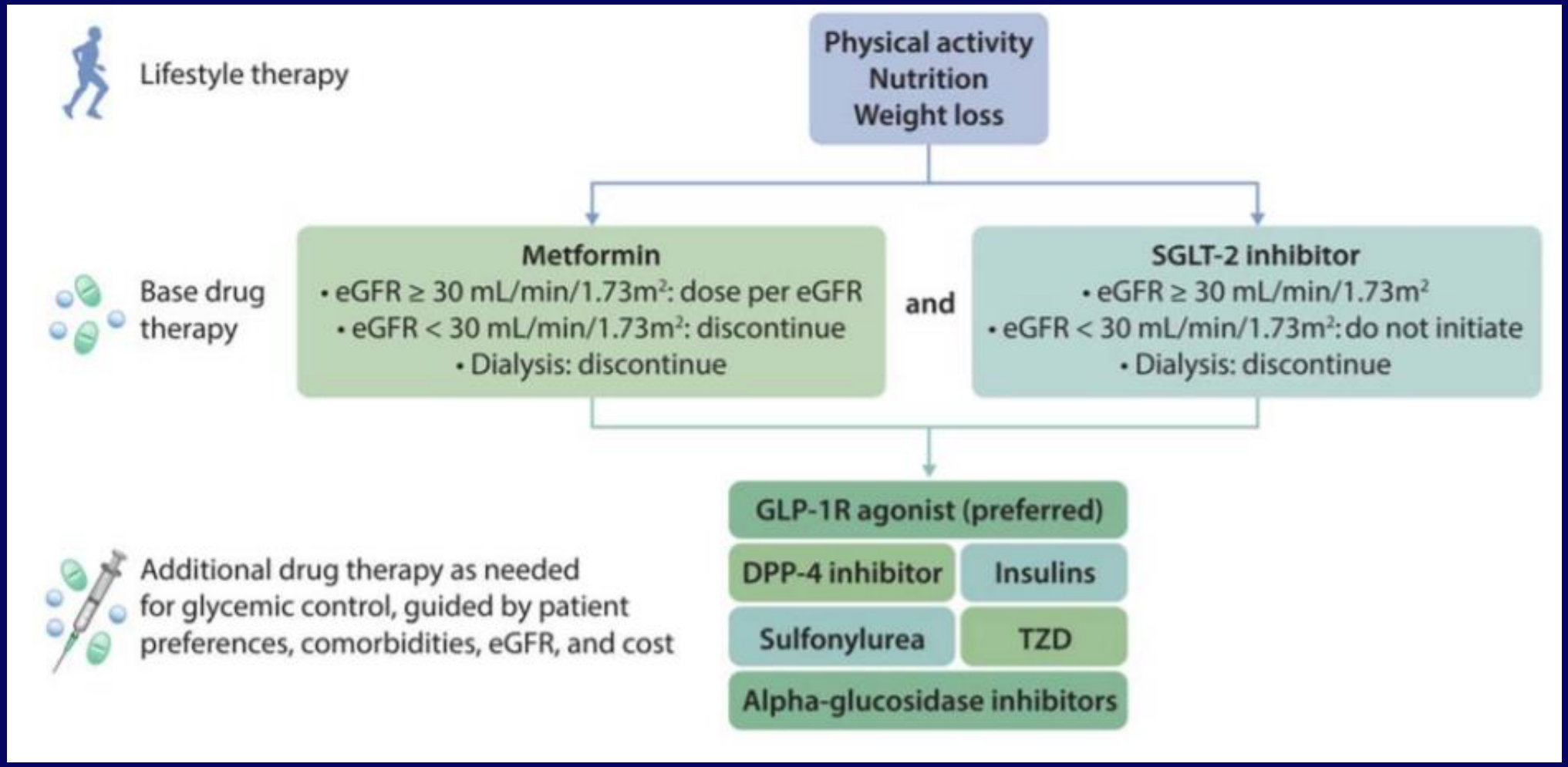


KDIGO CLINICAL PRACTICE GUIDELINE
ON DIABETES MANGEMENT
IN CHRONIC KIDNEY DISEASE

Glucose-Lowering Medications

- In patients with T2DM + CKD, and eGFR ≥30 ml/min/1.73 m2 → metformin be used as the first-line (1B).
- In patients with T2DM + CKD, and eGFR ≥30 ml/min/1.73 m2, we recommend including an SGLT2i in the treatment regimen (1A).
- In patients with T2DM + CKD who have not achieved glycemic targets despite use of metformin+SGLT2i, or who are unable to use those medications, we recommend GLP-1 RA (1B).

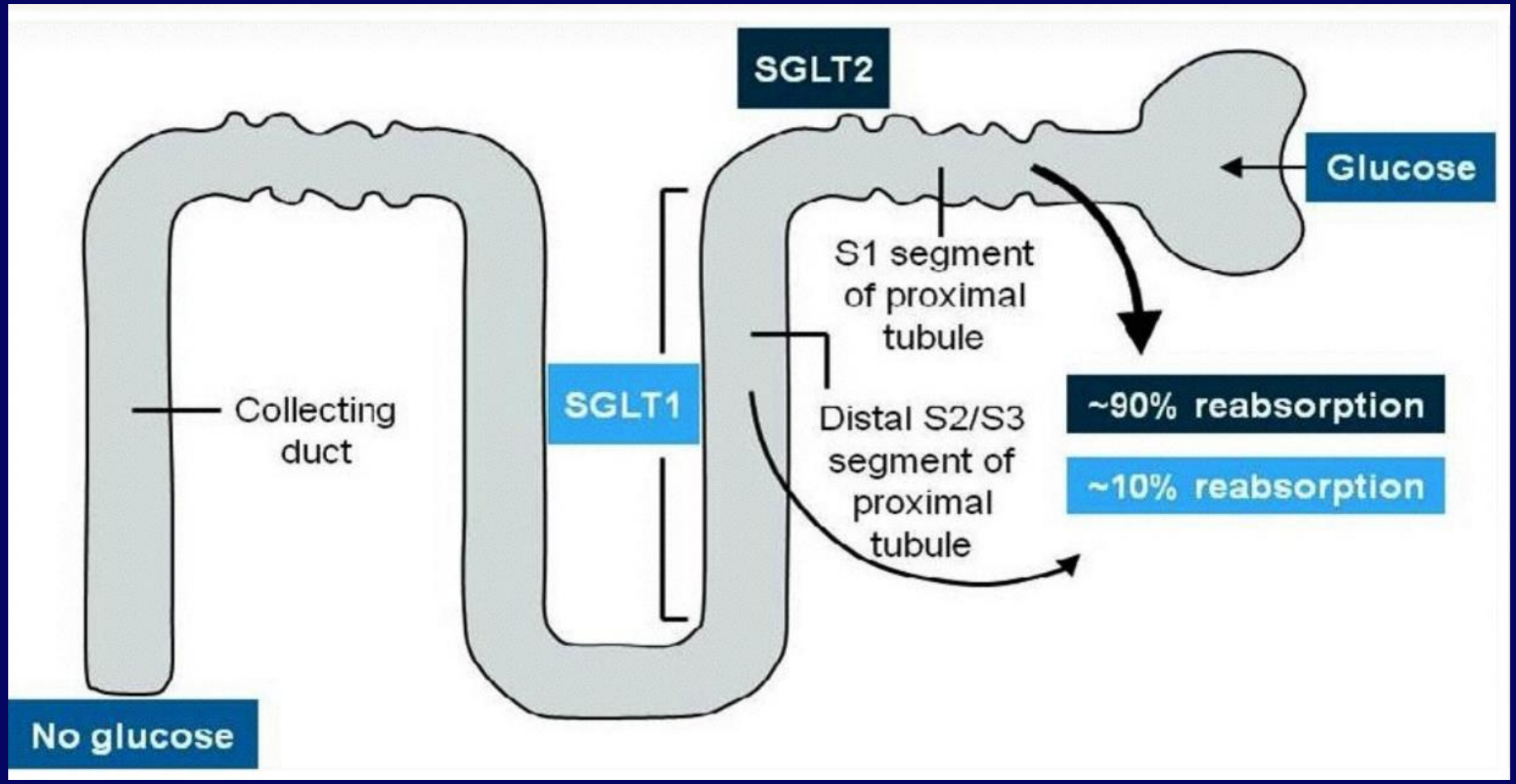
We recommend an individualized HbA1c from <6.5% to <8% in patients with diabetes and non-dialysis CKD (1C)

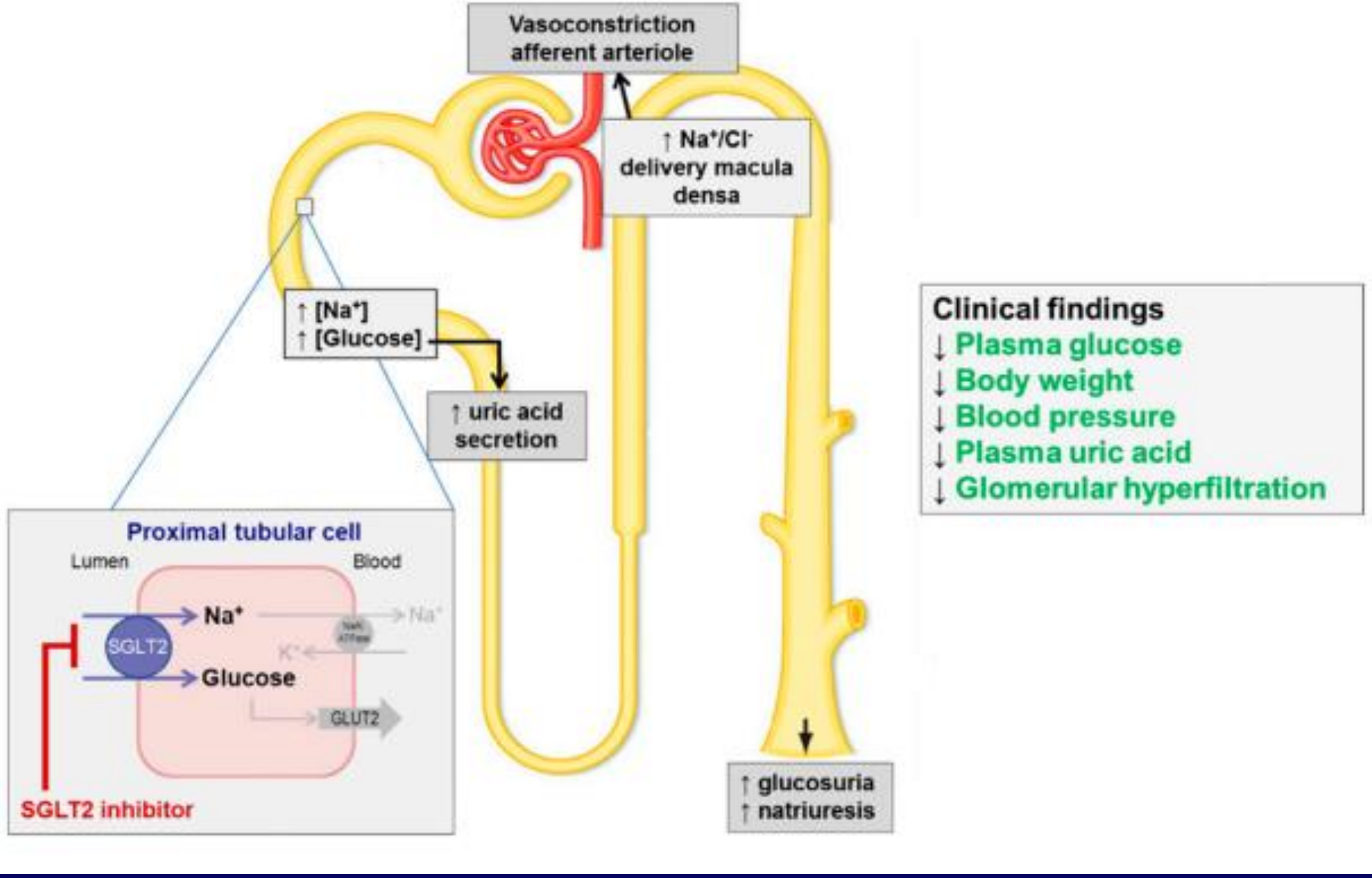


KDIGO CLINICAL PRACTICE GUIDELINE ON DIABETES MANGEMENT IN CHRONIC KIDNEY DISEASE

Class	Drugs	CKD stage 3 and 4	CKD stage 5 and dialysis	Major Complication
Sulfonylureas	Glipizide	No dose adjustment	No dose adjustment	Hypoglycemia
	Glyburide	Avoid	Avoid	
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid	
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with serum Cr >2 mg/dL	Avoid	Ileus, hepatic toxicity
Biguanides	Metformin	Avoid when GFR <30 Probably safe when GFR≥ 45 ml/min/1.73 m2	Avoid	Lactic acidosis
Meglitinides	Repaglinide	CCr 20-40 ml/min: 0.5 mg before meals: titrate with caution	HD: not defined	Hypoglycemia
	Nateglinide	Initiate at low dose, 60 mg before each meal	HD: not defined	
Thiazolidinediones	Pioglitazone	No dose adjustment	No dose adjustment	Black box warning: CHF
Incretin mimetic	Exenatide	CCr 30-50: caution with advised CCr <30 : avoid	Avoid	Pancreatitis
DPP-4 inhibitors	Linagliptin	No dose adjustment	No dose adjustment	
	Saxagliptin	CCr<50: 2.5 mg po OD	HD: give dose after dialysis	
	Alogliptin	CCr 30-59: 12.5 mg po OD CCr <30: 6.25 mg po OD	6.25 mg po OD	
	Sitagliptin	CCr 30-49: 50 mg po OD CCr <30: 25 mg po OD	25 mg po OD	
	Vildaglitin	CCr <50: 50 mg po OD	50 mg PO OD	
SGLT2 inhibitors	Canagliflozin	GFR 49-59: 100 mg po OD GFR 30-44: avoid GFR<30: contraindication	Avoid	UTI, vulvovaginitis, hypotension
	Dapaglitflozin	GFR 30-59: avoid GFR<30: contraindication	Avoid	
	Empagliflozin	GFR 30-44: avoid GFR<30: contraindication	Avoid	

SGLT 2 INH


SGLT2
Glucose
S1 segment of proximal tubule
Collecting duct
SGLT1
Distal S2/S3 segment of proximal tubule
~90% reabsorption
~10% reabsorption
No glucose


Vasoconstriction afferent arteriole
↑ Na⁺/Cl⁻ delivery macula densa
↑ [Na⁺]
↑ [Glucose]
↑ uric acid secretion
Proximal tubular cell
Lumen
Blood
Na⁺
SGLT2
Glucose
GLUT2
SGLT2 inhibitor
↑ glucosuria
↑ natriuresis
Clinical findings
↓ Plasma glucose
↓ Body weight
↓ Blood pressure
↓ Plasma uric acid
↓ Glomerular hyperfiltration

EMPA-REG OUTCOME Trial

- 7,020 adult patients with type 2DM at high cardiovascular risk
- A randomized, double-blind, placebo-controlled trial to assess the effect of once-daily empagliflozin (either 10 mg or 25 mg) versus placebo

CONCLUSIONS : Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.

N Engl J Med Volume 373(22):2117-2128 November 26, 2015

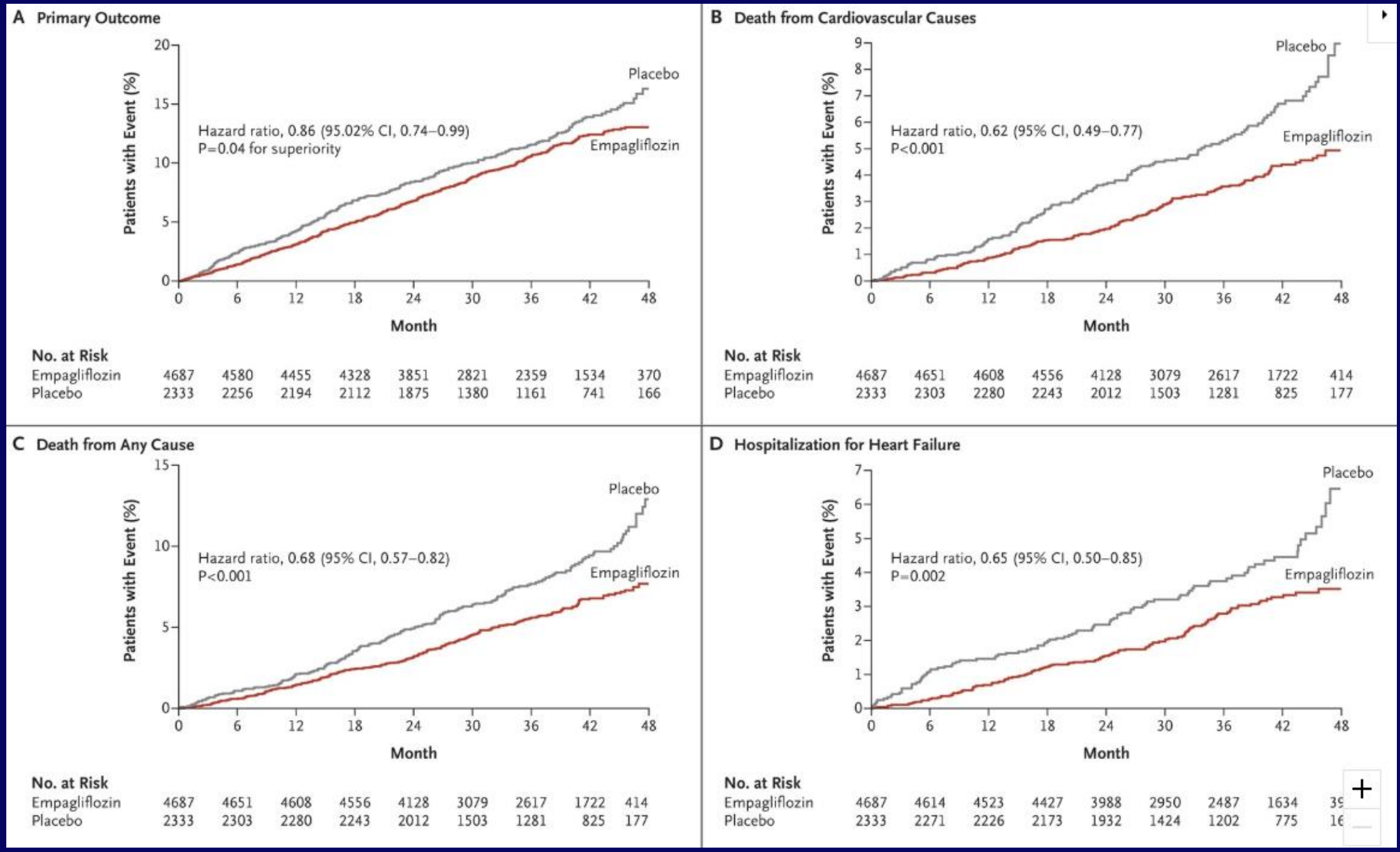

A Primary Outcome
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority
Month
No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166
B Death from Cardiovascular Causes
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001
Month
No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
C Death from Any Cause
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001
Month
No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
D Hospitalization for Heart Failure
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002
Month
No. at Risk
Empagliflozin 4687 4614 4523 4427 3988 2950 2487 1634
Placebo 2333 2271 2226 2173 1932 1424 1202 775

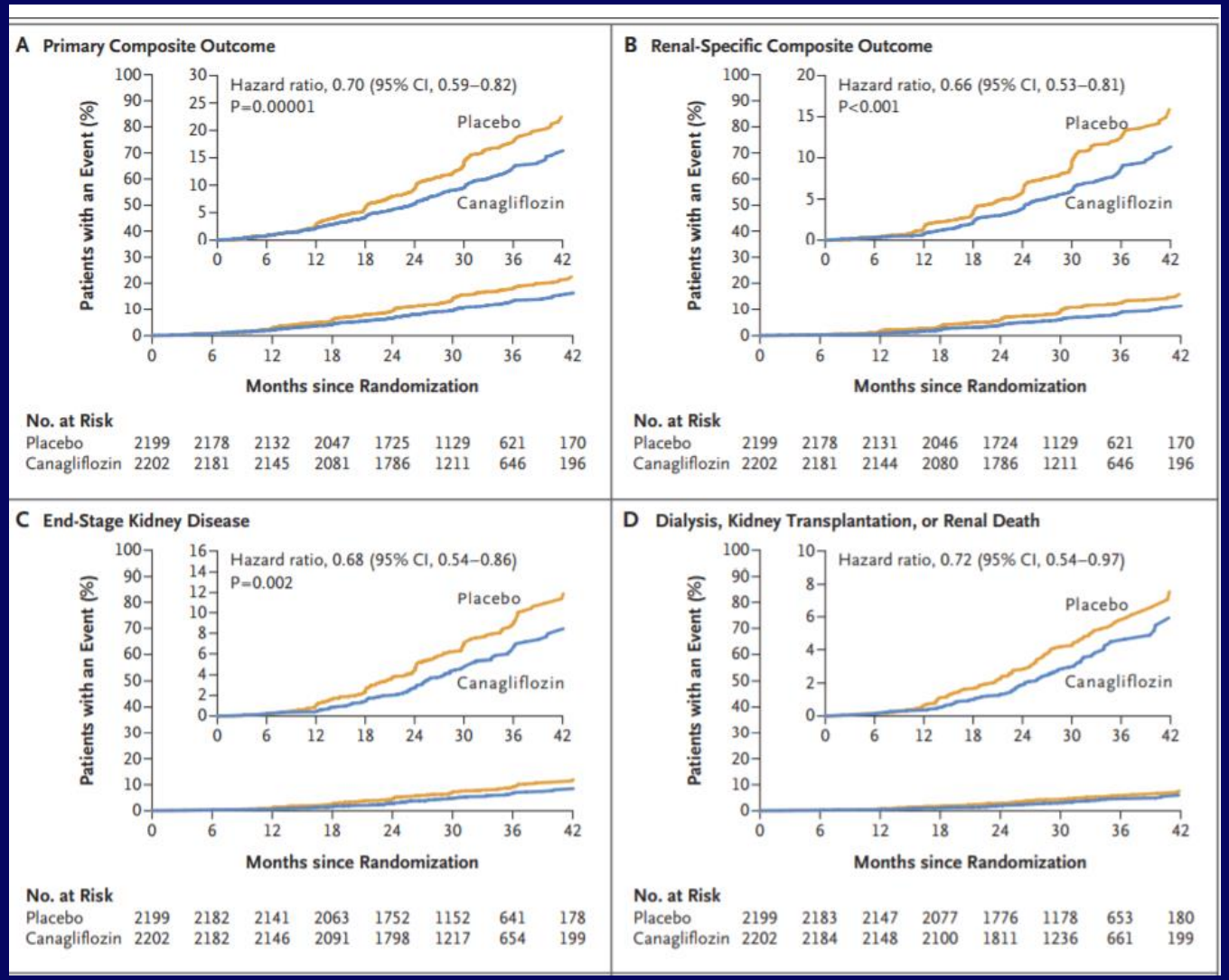
Table 3. End points of the EMPA-REG OUTCOME Trial

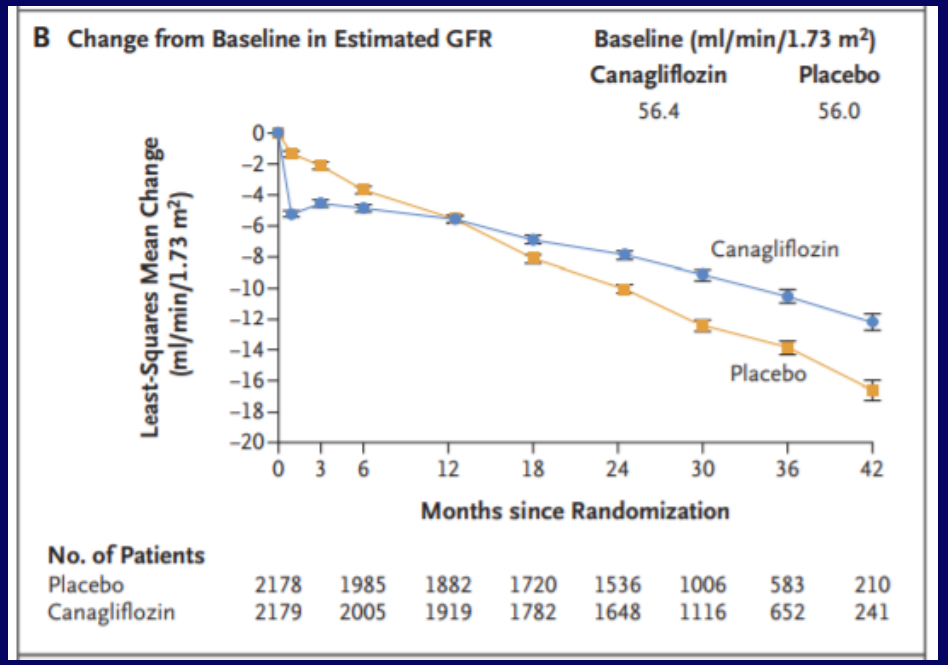
Outcome	Hazard Ratio Compared with Placebo (95% CI)
Prespecified	
Primary MACE (CV death, nonfatal MI, or nonfatal stroke)	0.86 (0.74 to 0.99)
CV death	0.62 (0.49 to 0.77)
All-cause mortality	0.68 (0.57 to 0.82)
Hospitalization for heart failure	0.65 (0.50 to 0.85)
Exploratory	
New onset of macroalbuminuria	0.62 (0.54 to 0.72)
New onset or worsening of DKD	0.61 (0.53 to 0.70)
Doubling of serum creatinine[a]	0.56 (0.39 to 0.79)
Initiation of RRT	0.45 (0.21 to 0.97)

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

- 4,401 adult patients with type 2DM and albuminuric CKD
  - GFR 30-89ml/min/1.73m2
  - UACR >300 to 5000 mg/g Cr
- A randomized, double-blind, placebo-controlled trial to assess the effect of Canaglifozin versus placebo
- The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR <15ml/min/1.73m2, a doubling of serum Cr, or death from renal or cardiovascular causes.

N Engl J Med 2019;380:2295-306

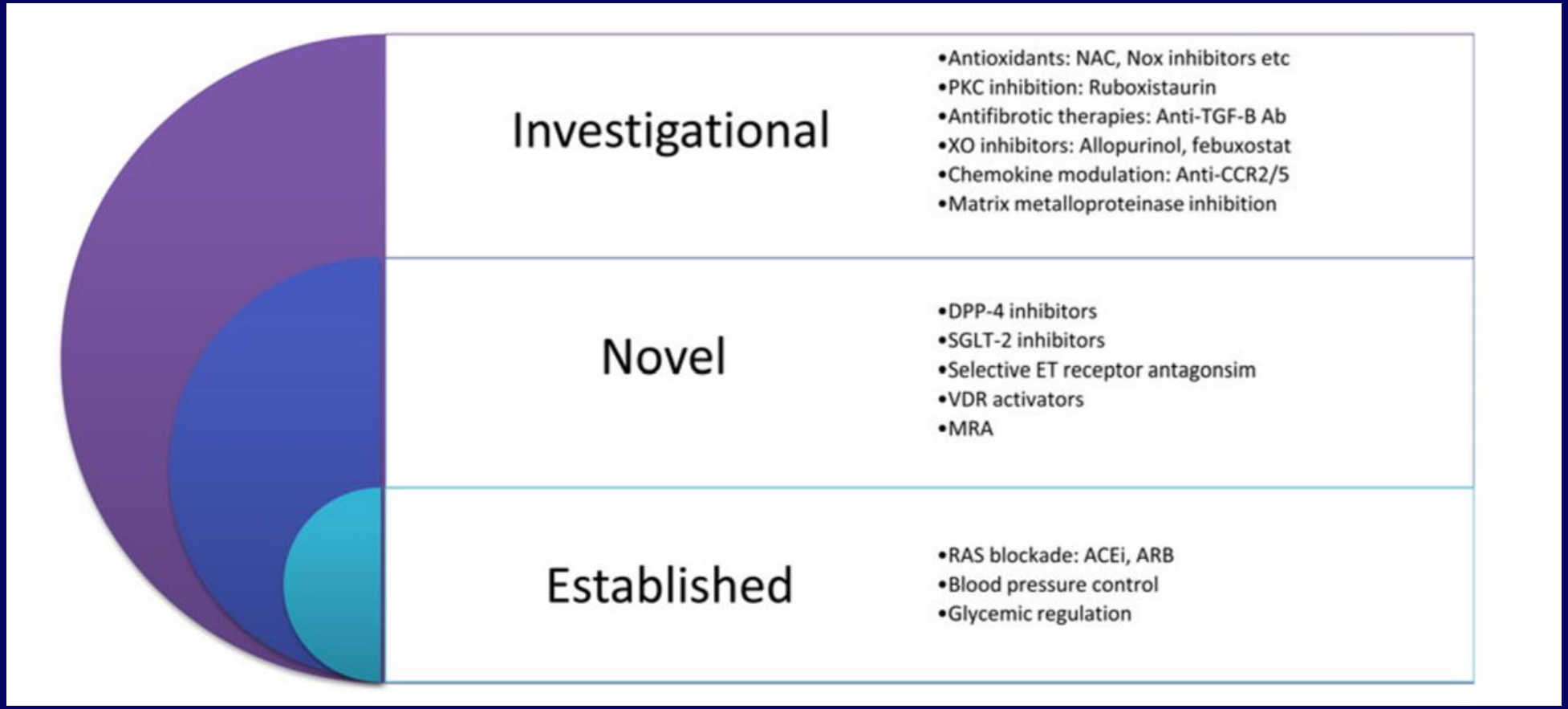




N Engl J Med 2019;380:2295-306


Thank You

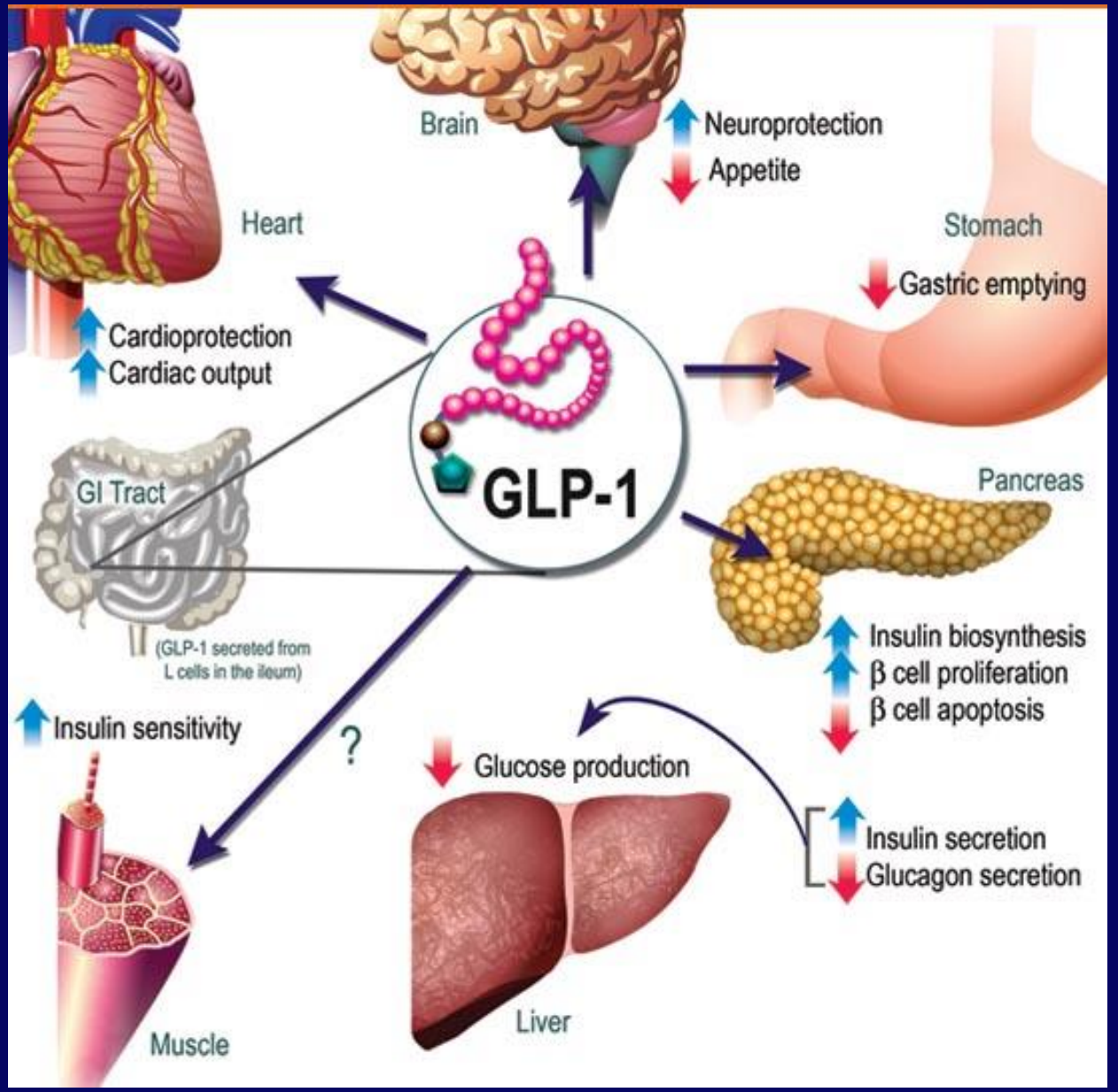
Current status of diabetic nephropathy treatment

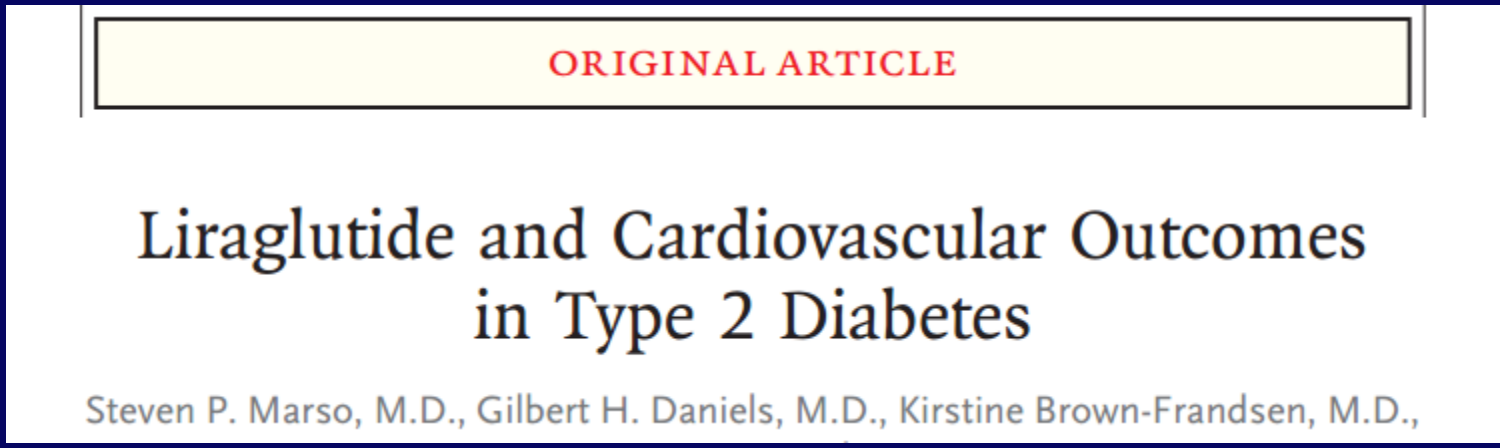


Nephrol Dial Transplant (2015) 0: 1–10

Liraglutide

- long-acting glucagon like peptide 1 receptor agonist (GLP-1)
- Adverse effect : pancreatitis, thyroid cancer




ORIGINAL ARTICLE

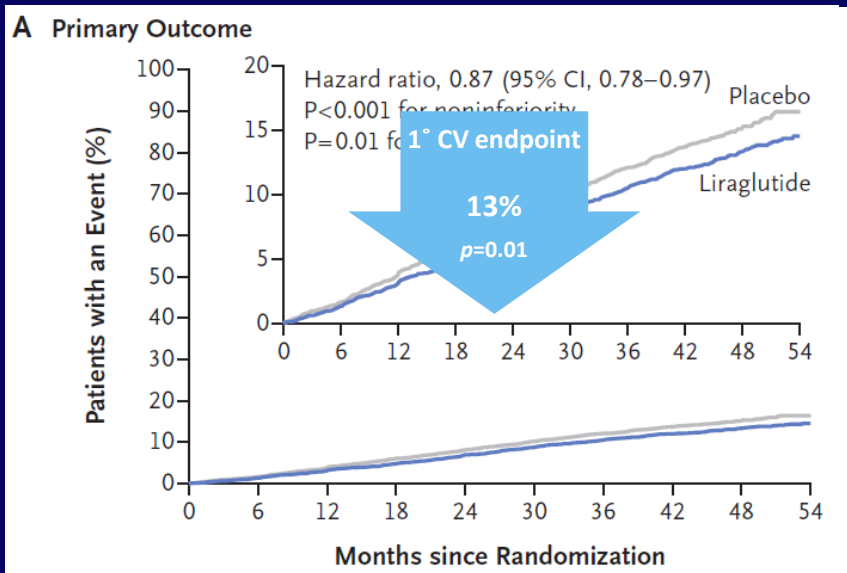
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

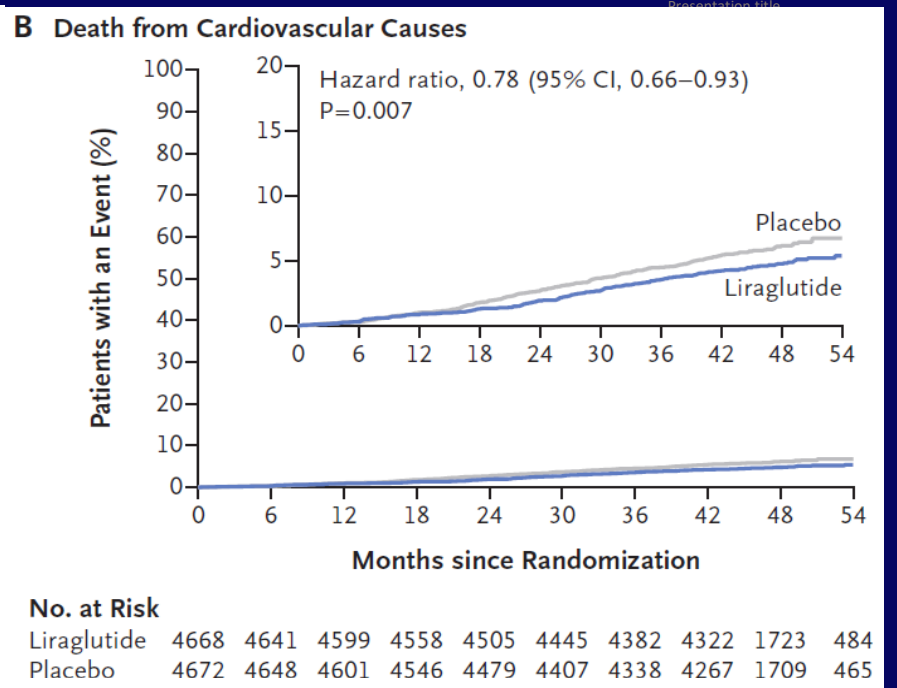
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D.,

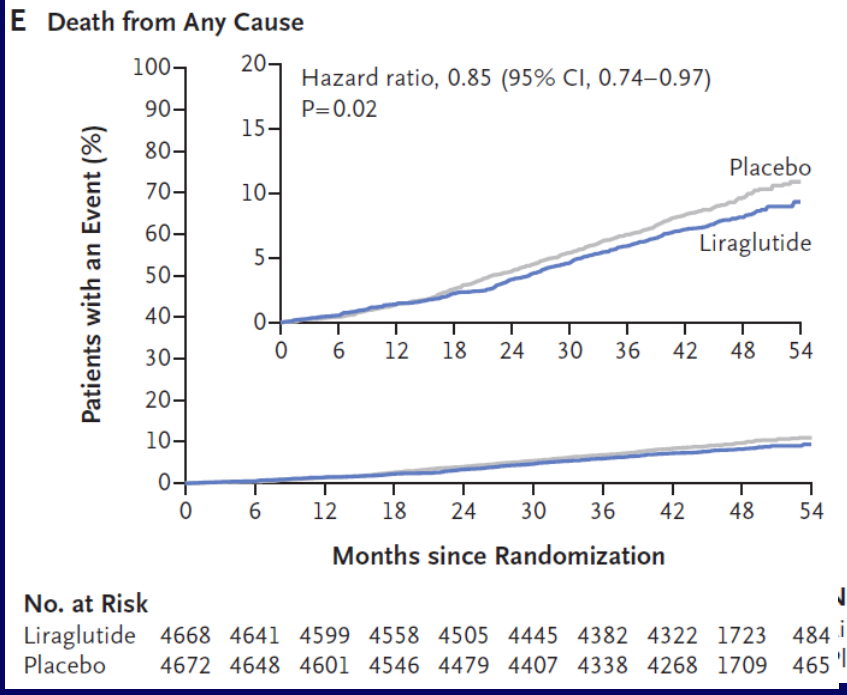
- Multicenter, double-blind, placebo-controlled trial at 410 sites in 32 countries.
- 9,340 Patients with type 2 diabetes who were at high risk for cardiovascular disease were randomly assigned, in a 1:1 ratio, to receive liraglutide or placebo.

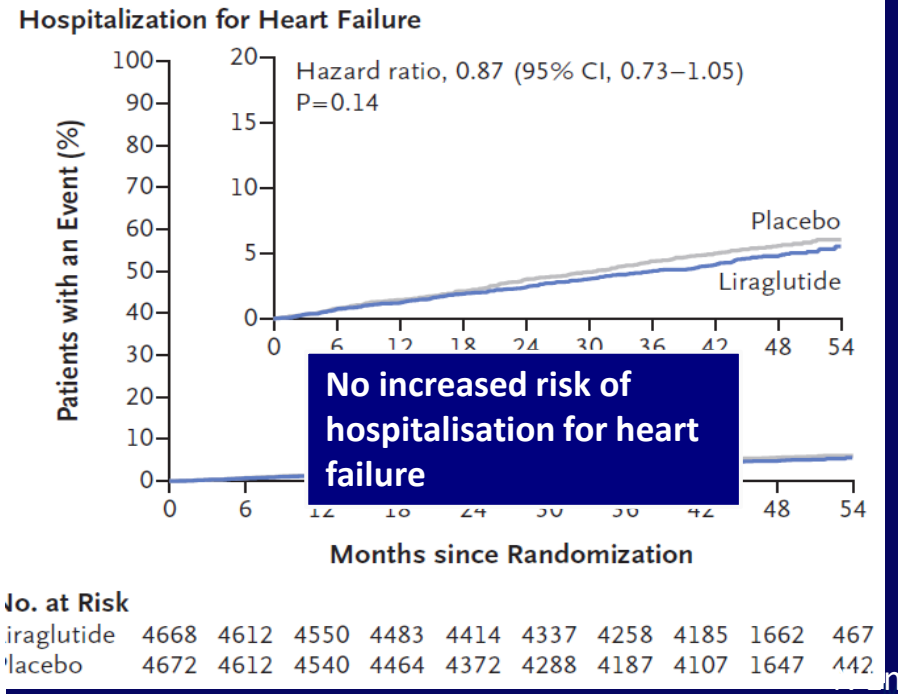
CONCLUSIONS : In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

N Engl J Med 2016; 375:311-322

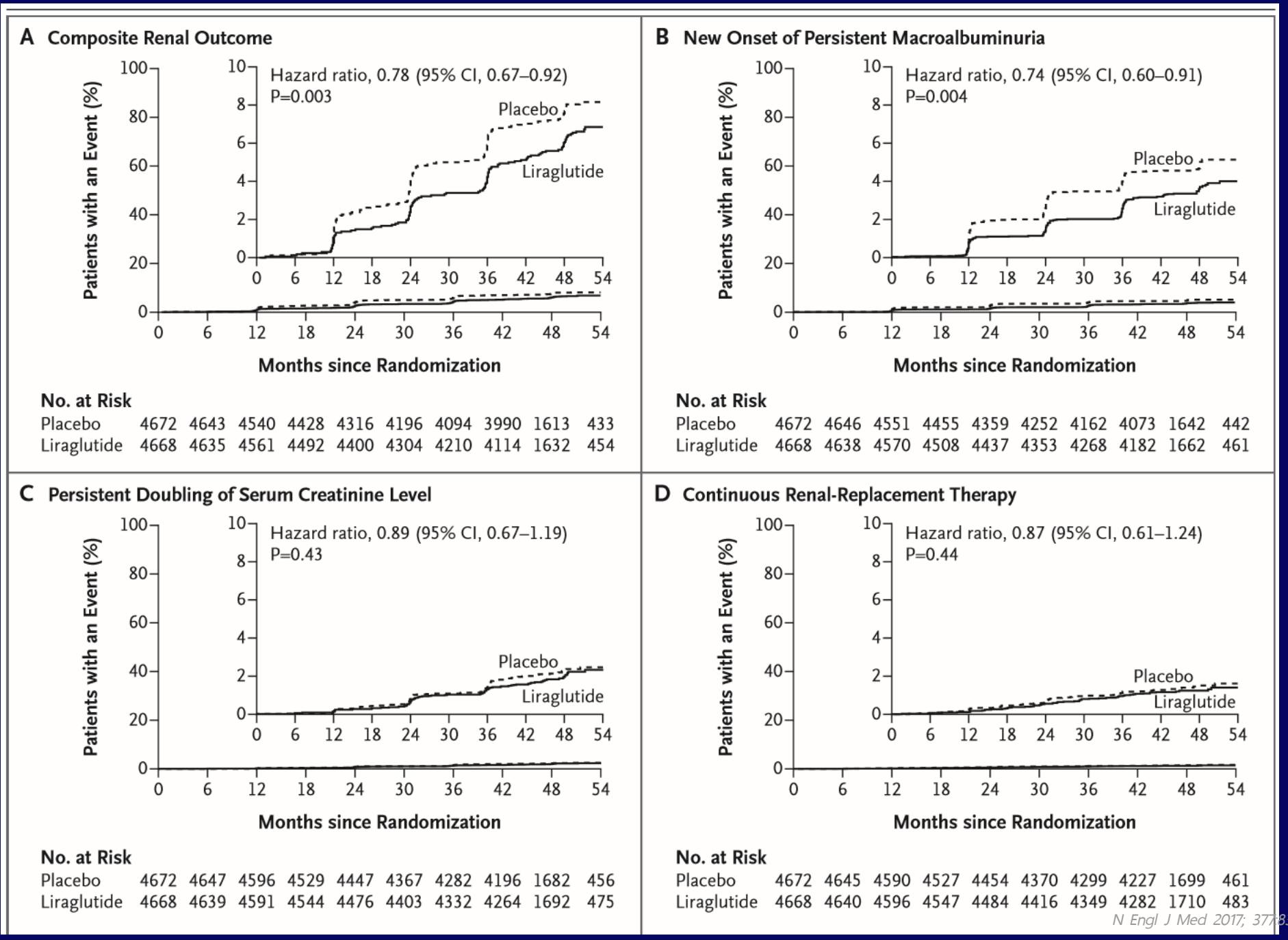








N Engl J Med 2016; 375:311-322



Time to first renal event

- **Macroalbuminuria,**
- **doubling of serum Cr *and* eGFR ≤45,**
- **ESRD,**
- **renal death**

N Engl J Med 2017; 377:839-848DOI: 10.1056/NEJMoa1616011

Thank you for your attention