

Diabetic Nephropathy 2009

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Diabetic Nephropathy

Clinical Stages

Hyperfunction / Renal Enlargement

- 0-15 years after onset of DM
- GFR normal or increased

Microalbuminuria (Protein: 30-300 mg/d)

- 10-15 years after onset of DM
- GFR normal

Macroalbuminuria (Protein: > 300 mg/d)

- 11-20 years after onset of DM
- GFR decreasing

Progressive CRF / ESRD

- 15-25 years after onset of DM
- GFR < 30 ml/min

Diabetic Nephropathy

Clinical Stages

Hyperfunction / Renal Enlargement

- ~ 50% if DM < 5 years

Microalbuminuria (Protein: 30-300 mg/d)

- 20-30% at 15 years

Macroalbuminuria (Protein: > 300 mg/d)

- 25-45% at 15-20 years

Progressive CRF / ESRD

- 4-17% at > 20 years

Diabetic Nephropathy

Pathological Changes

Mesangial Expansion

- Glycosylation of matrix proteins (AGEs)
- Increased production of matrix proteins

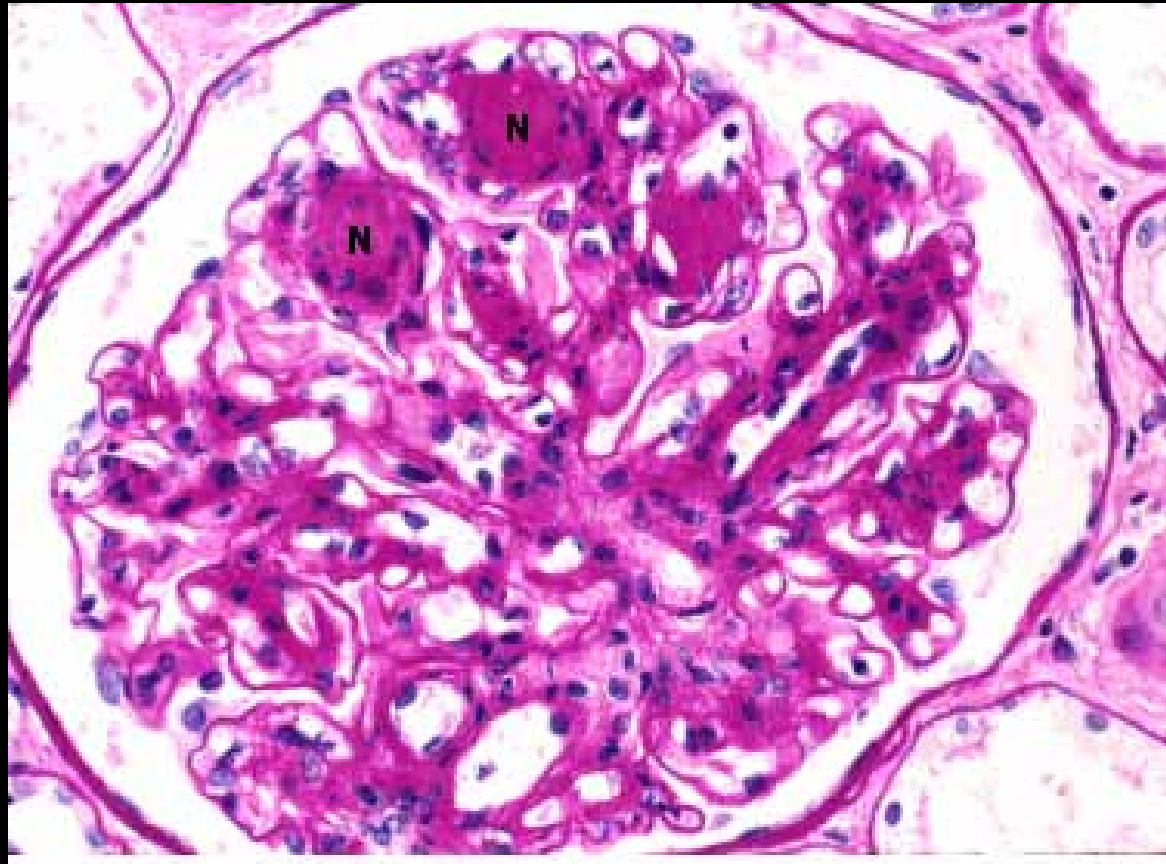
Glomerular Basement Membrane Thickening

- Glycosylation of GBM proteins (AGEs)
- Intraglomerular hypertension (vasodilation)

Glomerular Sclerosis (+/- Nodules)

- Intraglomerular hypertension (vasodilation)
- Ischemic injury (hyaline vascular narrowing)

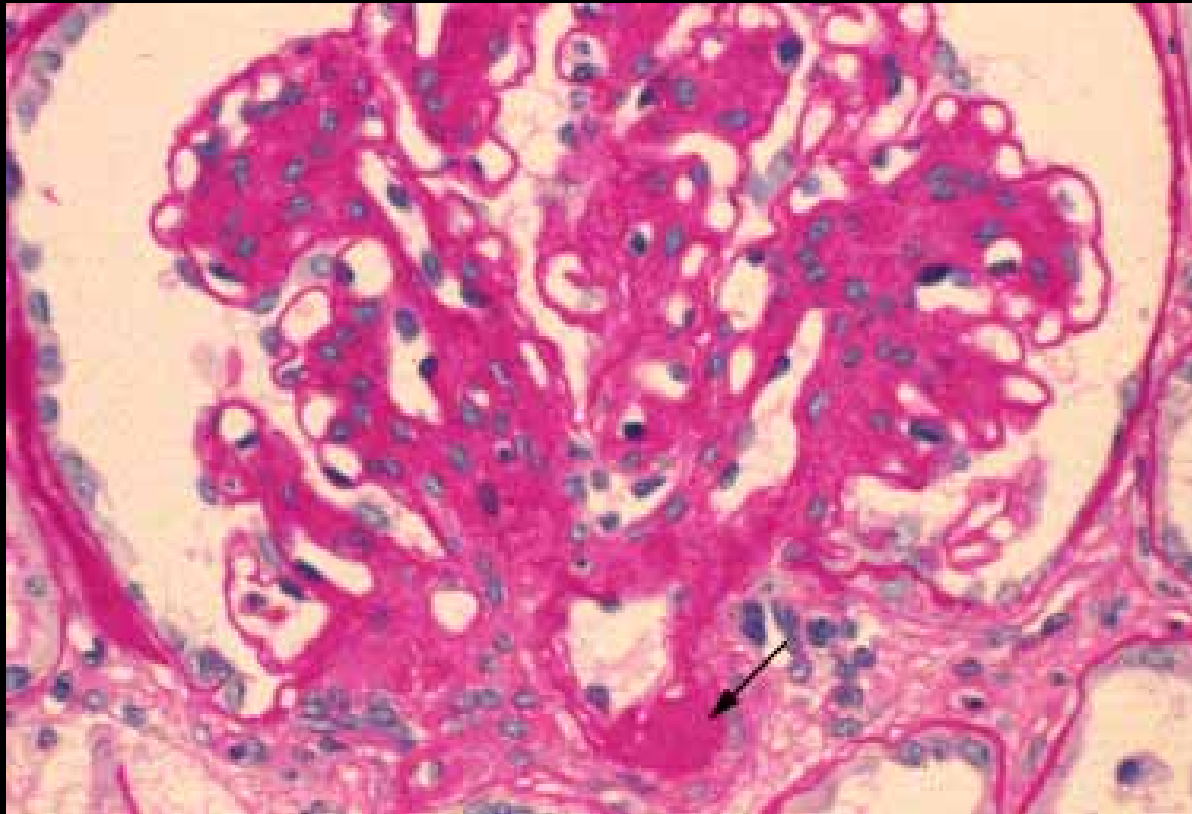
Diabetic Nephropathy



Light Microscopy

Diffuse and nodular glomerulosclerosis. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis

Advanced Diabetic Glomerulosclerosis



Light Microscopy

Diffuse and nodular mesangial expansion and characteristic hyaline thickening of the arteriole at the glomerular hilum (arrow).

Diabetes typically affects both the afferent and efferent arterioles, whereas hypertension typically affects only the afferent arterioles.

Diabetic Nephropathy

Pathogenesis

Renal Hemodynamic Changes

- Vasodilation / Increased Renal Blood Flow
- Glomerular Hypertension and Hyperfiltration
- Systemic Hypertension

Metabolic Alterations

- Activation of Aldose Reductase pathway
- Activation of Protein Kinase C pathway
- Glycosylation of Renal Proteins (AGEs)

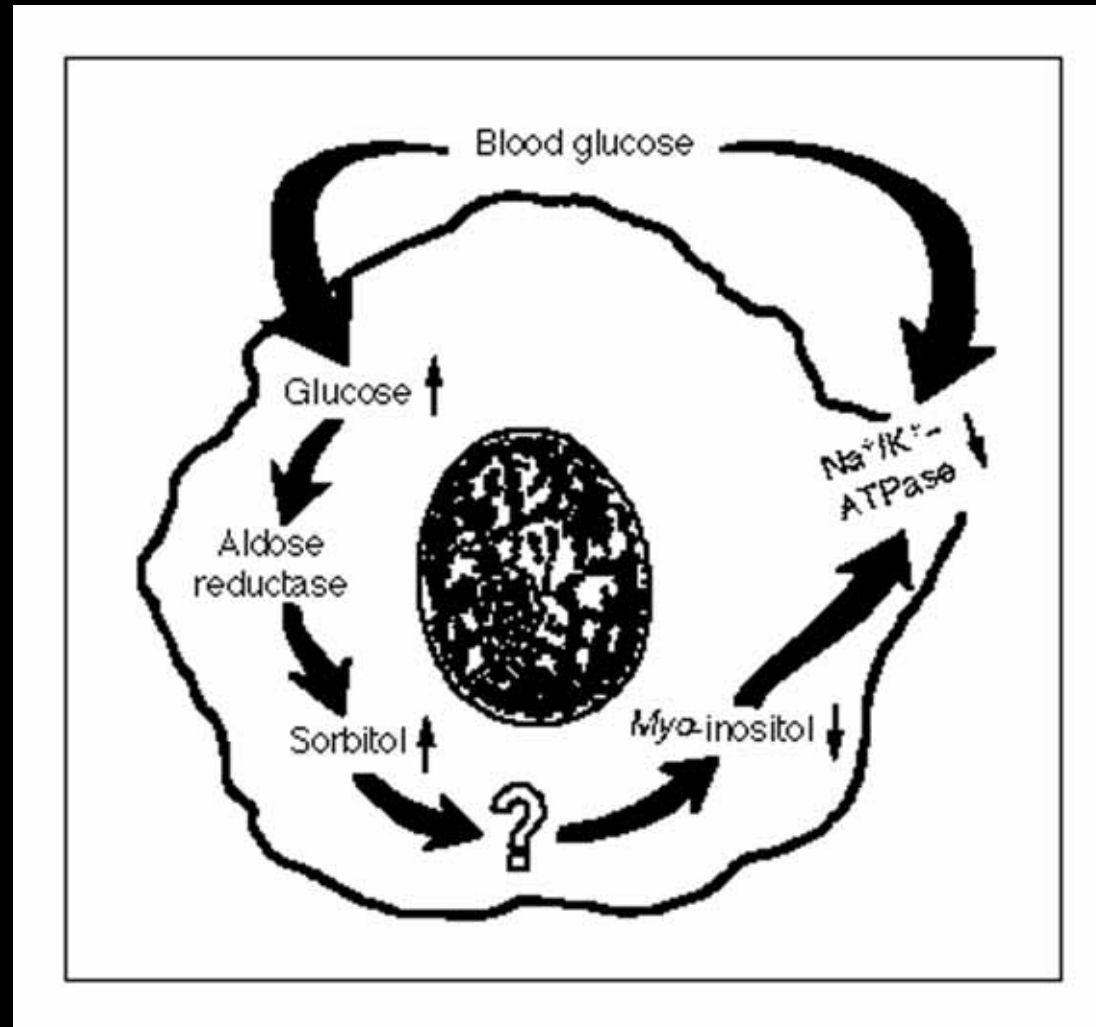
Growth Factor and Cytokine Changes

- AII, TGF- β , IGF-1, PDGF, CTGF, Eicosanoids

Oxidative Stress

Genetic Susceptibility

Aldose Reductase Pathway

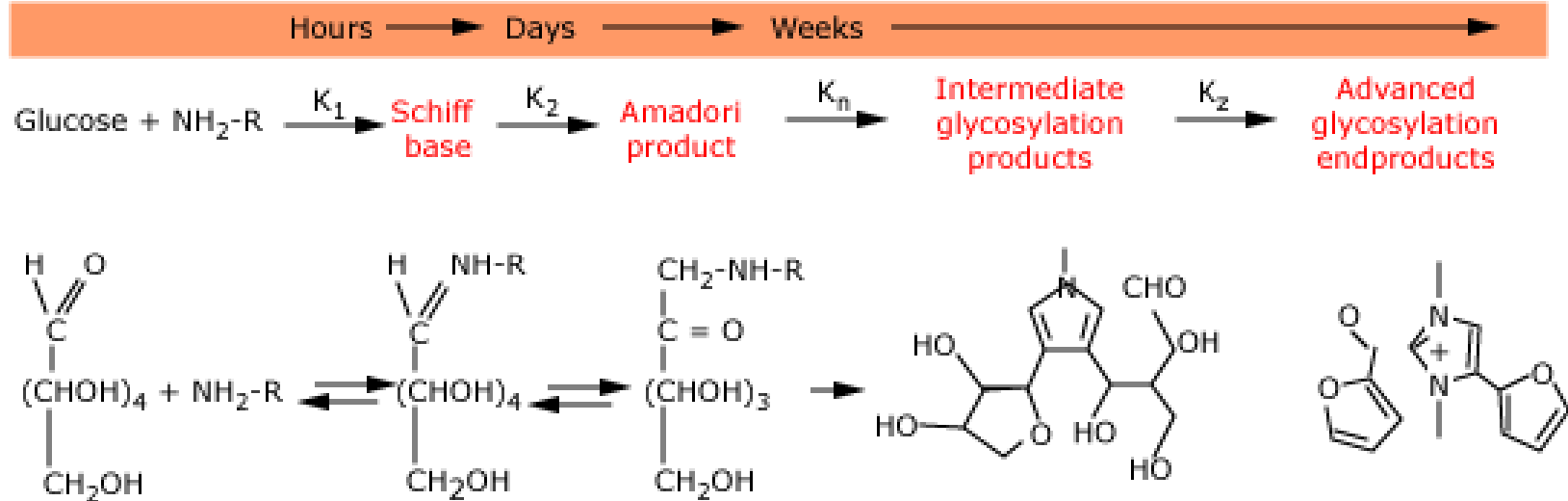


Clark C and Lee D. N Engl J Med 1995;332:1210



The NEW ENGLAND
JOURNAL of MEDICINE

Advanced Glycosylation End Products



Adapted from: Bucala R, Drug Development Research 1994; 32:77

Diabetic Nephropathy

Genetic Susceptibility

Candidate genes

- ACE gene (DD polymorphisms)
- AII gene (AA haplotype)
- Aldose Reductase gene (Z-2 allele)

Clinical Practice Recommendations: ADA 2009

Nephropathy Screening

Type 1 DM: ≥ 5 years duration of DM, test urine albumin excretion (UAE) annually (E).

Type 2 DM: test UAE annually (E).

Measure Albumin/Creatinine Ratio (preferred method): random spot urine sample (E).

Measure Serum Creatinine: at least annually in adults with DM regardless of UAE and use to estimate GFR and stage of chronic kidney disease, if present (E).

Urine Protein Measurement

Significance of Findings

	Spot Urine (ug/mg Cr)	24 Hr Urine (mg/24 h)	Timed Urine (ug/min)
Normal	< 30	< 30	< 20
Microalbuminuria	30-299	30-299	20-199
Macroalbuminuria	> 300	> 300	> 200

Evidence that Proteinuria is Not Due to Diabetes

- **Acute onset of renal disease**
- **Onset of proteinuria < 5 years after onset of DM**
- **Active urine sediment with RBCs or cellular casts**
- **Absence of retinopathy or neuropathy**

Diabetic Nephropathy

Treatment Strategies

Glucose Control

- All patients

Blood Pressure Control

- Patients with BP > 130/80

Proteinuria Reduction

- Patients with microalbuminuria

Lipid Reduction

- Patients who exceed lipid goals

Investigational

- Aldose Reductase inhibition
- Protein Kinase C inhibition
- Advanced Glycosylation End-product inhibition

Diabetic Nephropathy

Treatment Strategies

→ Glucose Control

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Lipid Reduction

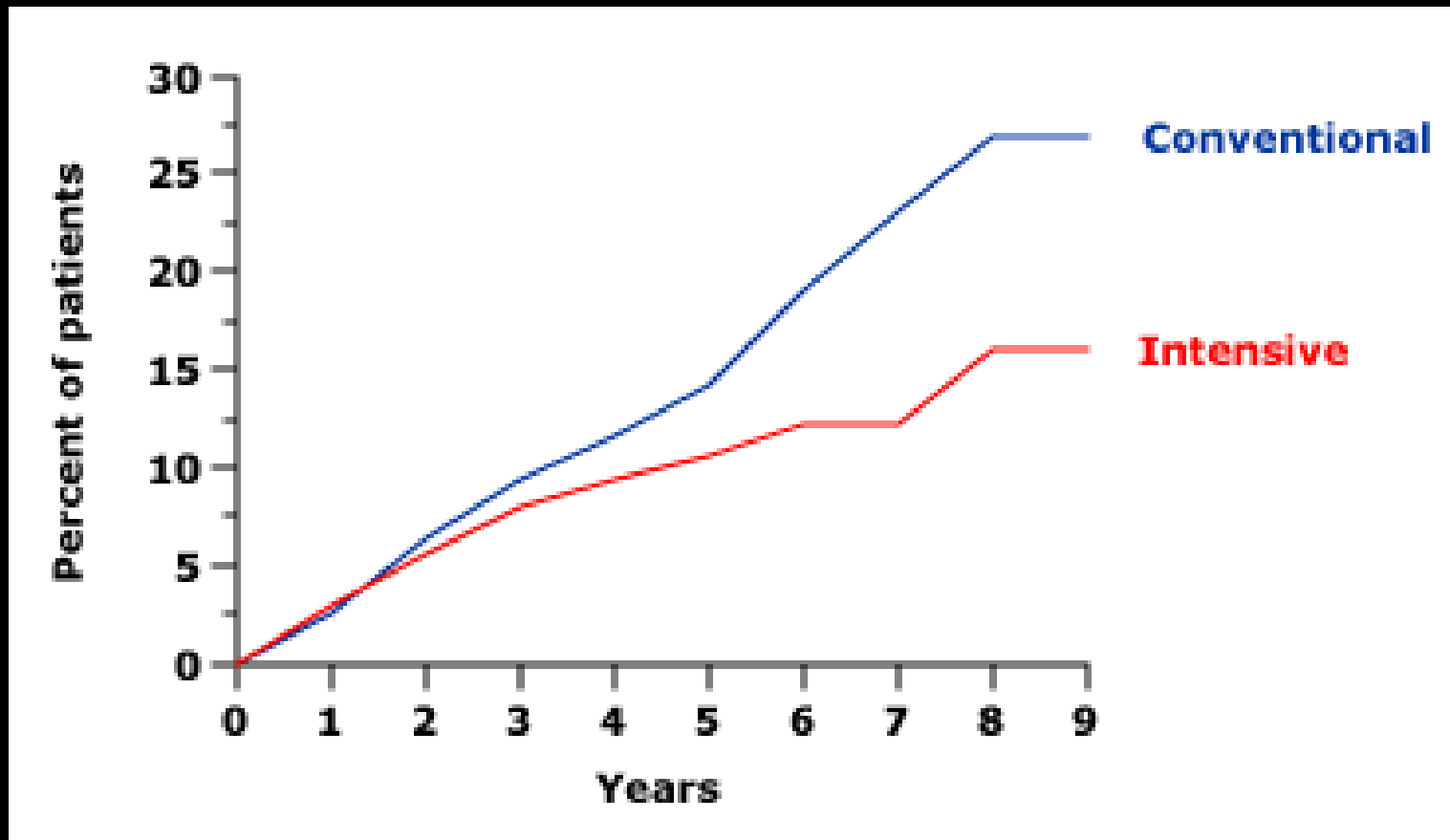
- Patients who exceed lipid goals

Investigational

- Aldose Reductase inhibition
- Protein Kinase C inhibition
- Advanced Glycosylation End-product inhibition

Glucose Control in Type 1 DM

Effect on Microalbuminuria Development



DCCT Group, N Engl J Med 1993; 329:977

Glycemic Control

Microvascular Complications

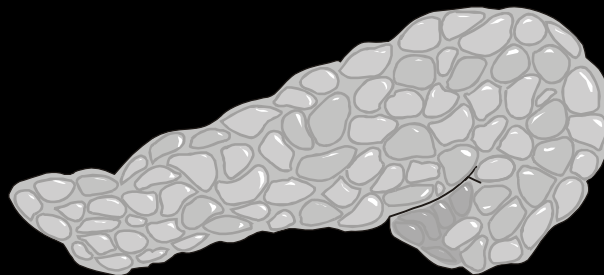
Study	A1C %	Retinopathy	Nephropathy	Neuropathy
DCCT	9 v 7	↓ 76%	↓ 54%	↓ 60%
UKPDS	8 v 7	↓ 17-21%	↓ 24-33%	
Kumamoto	9 v 7	↓ 69%	↓ 70%	↓ (ss)
ADVANCE	7.3 v 6.5		↓ 21%	

Clinical Practice Recommendations: ADA 2009

Glucose Control

Lowering A1C to below or around 7% reduces microvascular and neuropathic complications of Type 1 and Type 2 DM. Therefore, for microvascular disease prevention, **the A1C goal for nonpregnant adults is < 7% (A).**

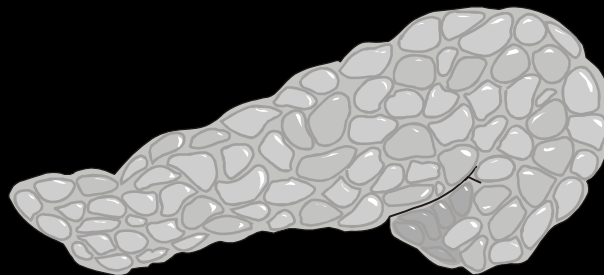
Type 1 Diabetes Mellitus Pathophysiology



Absolute Insulin Deficiency
Autoimmune Beta Cell Destruction

Type 1 Diabetes Mellitus Treatment

Physiologic Insulin Therapy



Absolute Insulin Deficiency
Autoimmune Beta Cell Destruction

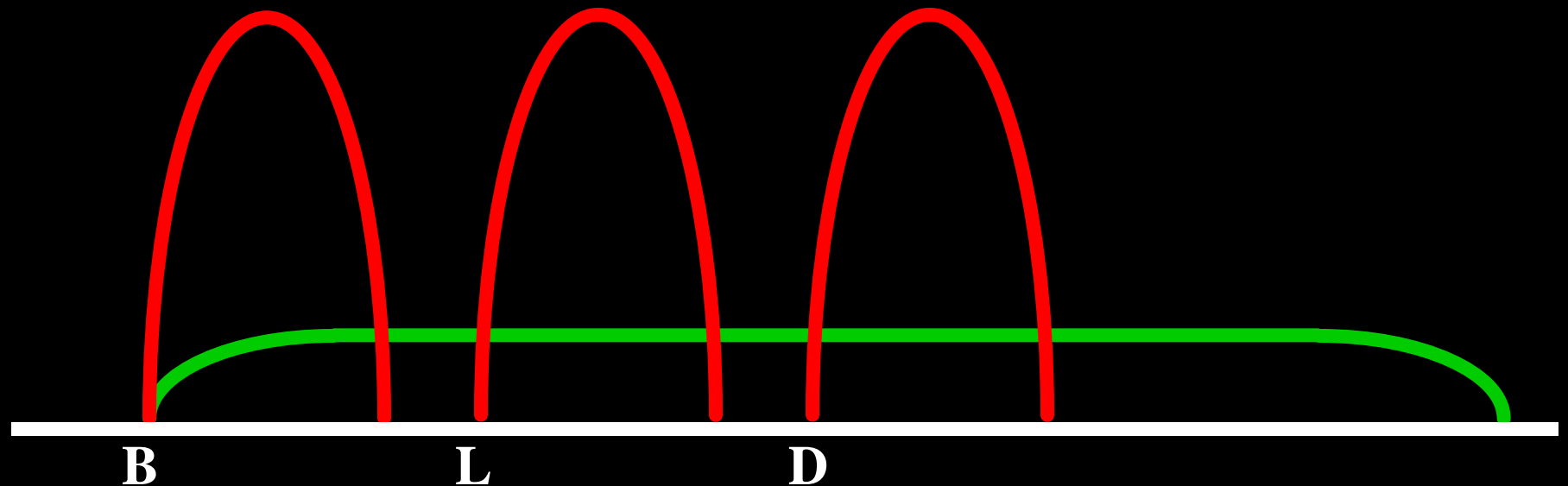
Basal Bolus Insulin Regimen



Glargine / Detemir / CSII

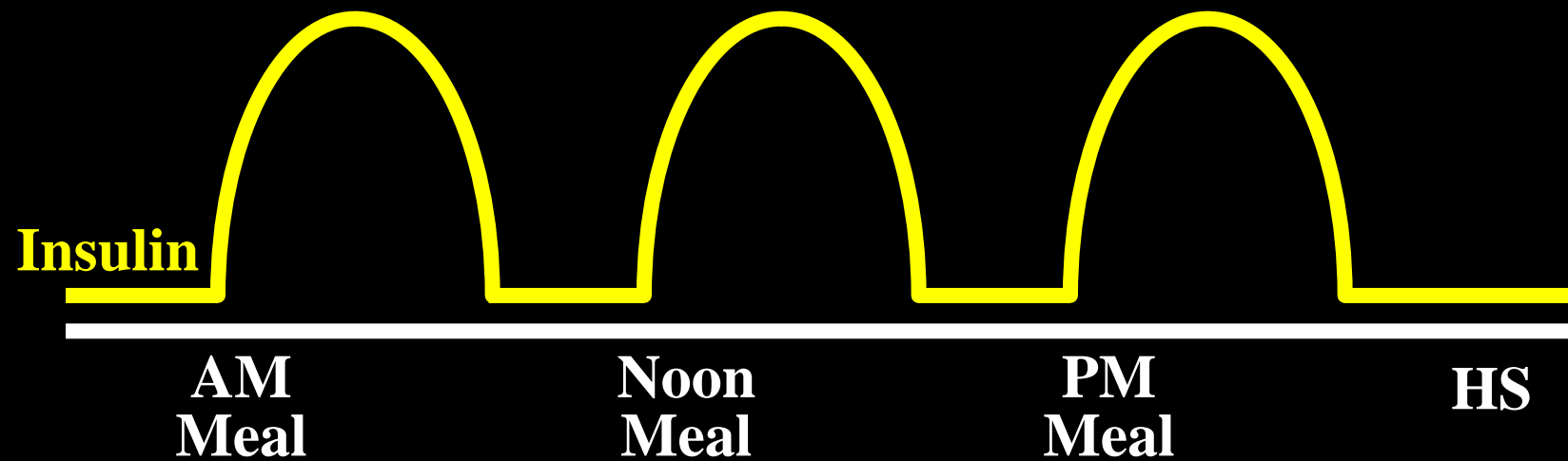


Lispro / Aspart / Glulisine



Basal amount ~ 50%
Bolus amount ~ 50%

Physiological Insulin Administration Insulin Pump Therapy (CSII)



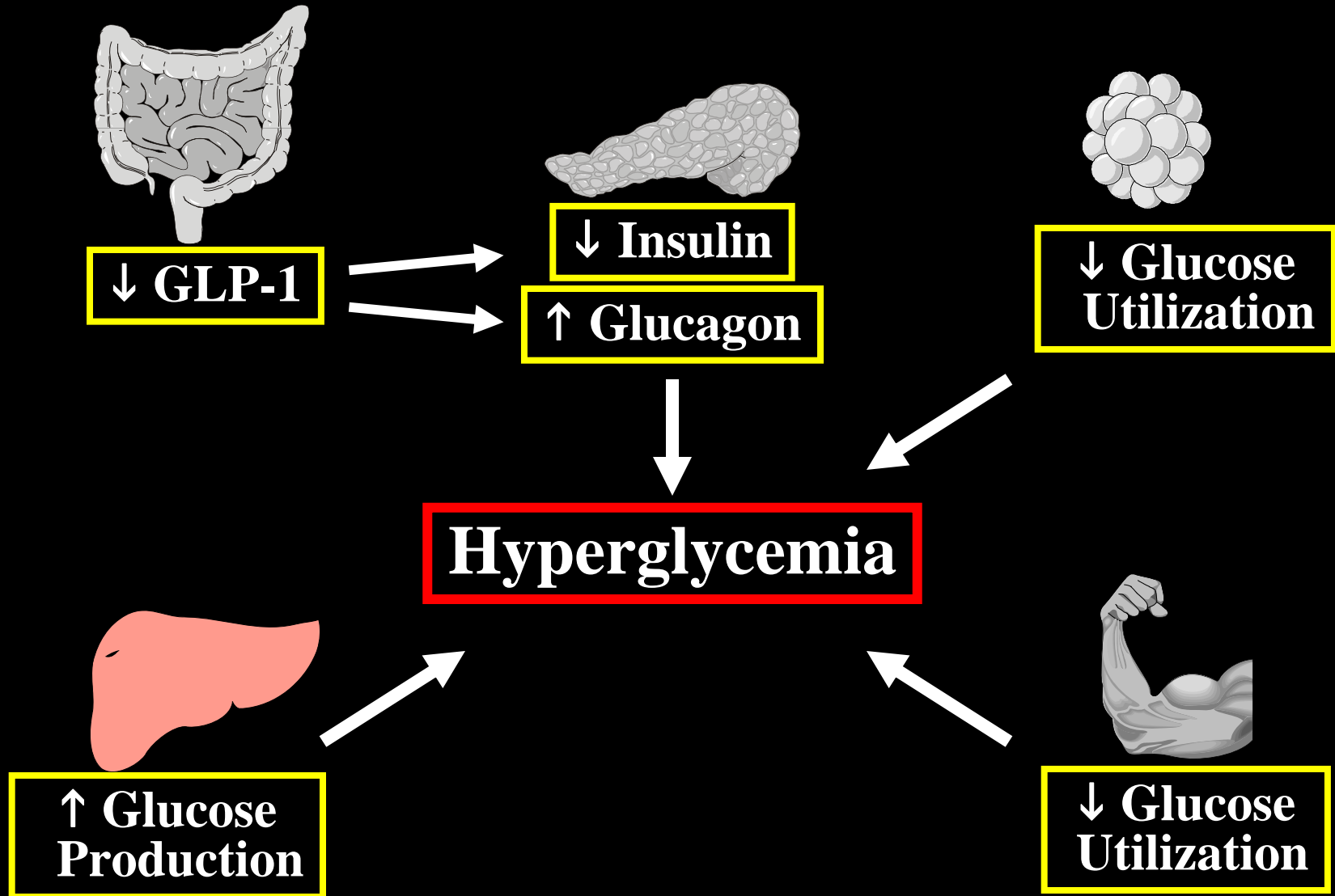
Insulin Therapy

Chronic Renal Failure

GFR (ml/min)	Insulin Dose Adjustment
> 50	None
10-50	↓ 25%
< 10	↓ 50%

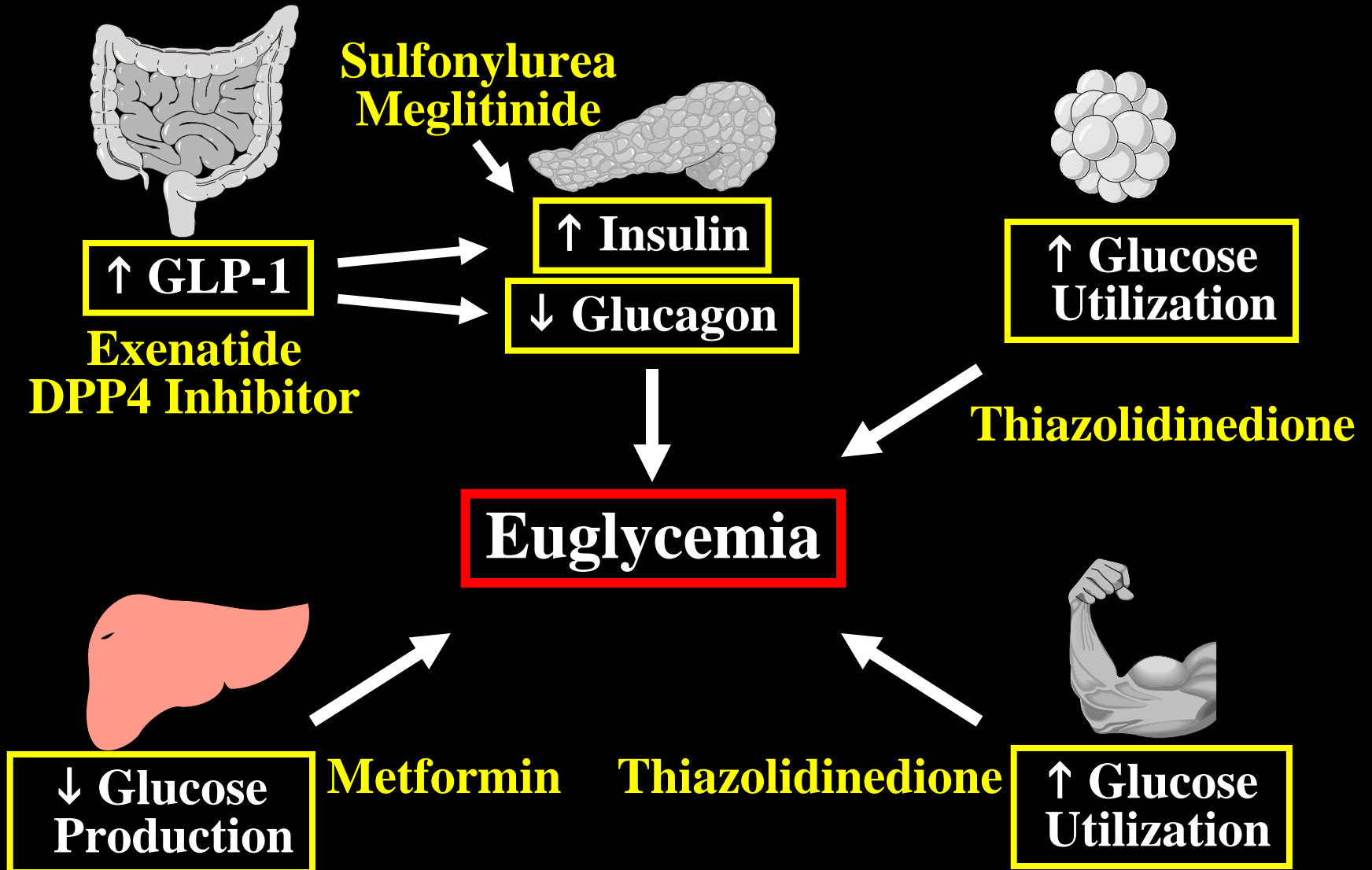
Type 2 Diabetes Mellitus

Pathophysiology



Type 2 Diabetes Mellitus

Pathophysiology Based Treatment



Type 2 Diabetes Mellitus

Lifestyle Intervention + Metformin

3 Months: A1C \geq 7.0

Basal Insulin
Best Efficacy

Sulfonylurea
Low Cost

Exenatide
Weight loss

Pioglitazone
No Hypoglycemia

DPP4 Inhibitor
Weight Neutral

3 Months: A1C \geq 7.0

Basal Bolus Insulin

Basal Insulin

Sulfonylurea

Exenatide

Pioglitazone

DPP4 Inhibitor

3 Months: A1C \geq 7.0

Basal Bolus Insulin

Basal Insulin

Basal Bolus Insulin

DC Insulin Secretagogues

+/- Insulin Sensitizers

MTM Algorithm
Adapted from
ADA 2008

Oral Diabetes Medications

Chronic Renal Failure

Class	Metabolism	Renal Excretion	Recommend
<u>Biguanides</u>			
Metformin	None	Active drug	Against
<u>Sulfonylureas</u>			
Glipizide	Liver	Inactive metabolites	OK
Glyburide	Liver	Weak metabolites	Caution
Glimepiride	Liver	Active metabolites	Against
<u>Meglitinides</u>			
Repaglinide	Liver	< 10% excreted	OK
Nateglinide	Liver	Active metabolites	Caution
<u>Thiazolidinediones</u>			
Pioglitazone	Liver	Active metabolites	Against
Rosiglitazone	Liver	Inactive metabolites	Against
<u>DPP4 Inhibitors</u>			
Sitagliptin	Liver		OK

Diabetic Nephropathy

Treatment Strategies

Glucose Control

- All patients

→ Blood Pressure Control

- Patients with BP > 130/80

Proteinuria Reduction

- Patients with microalbuminuria

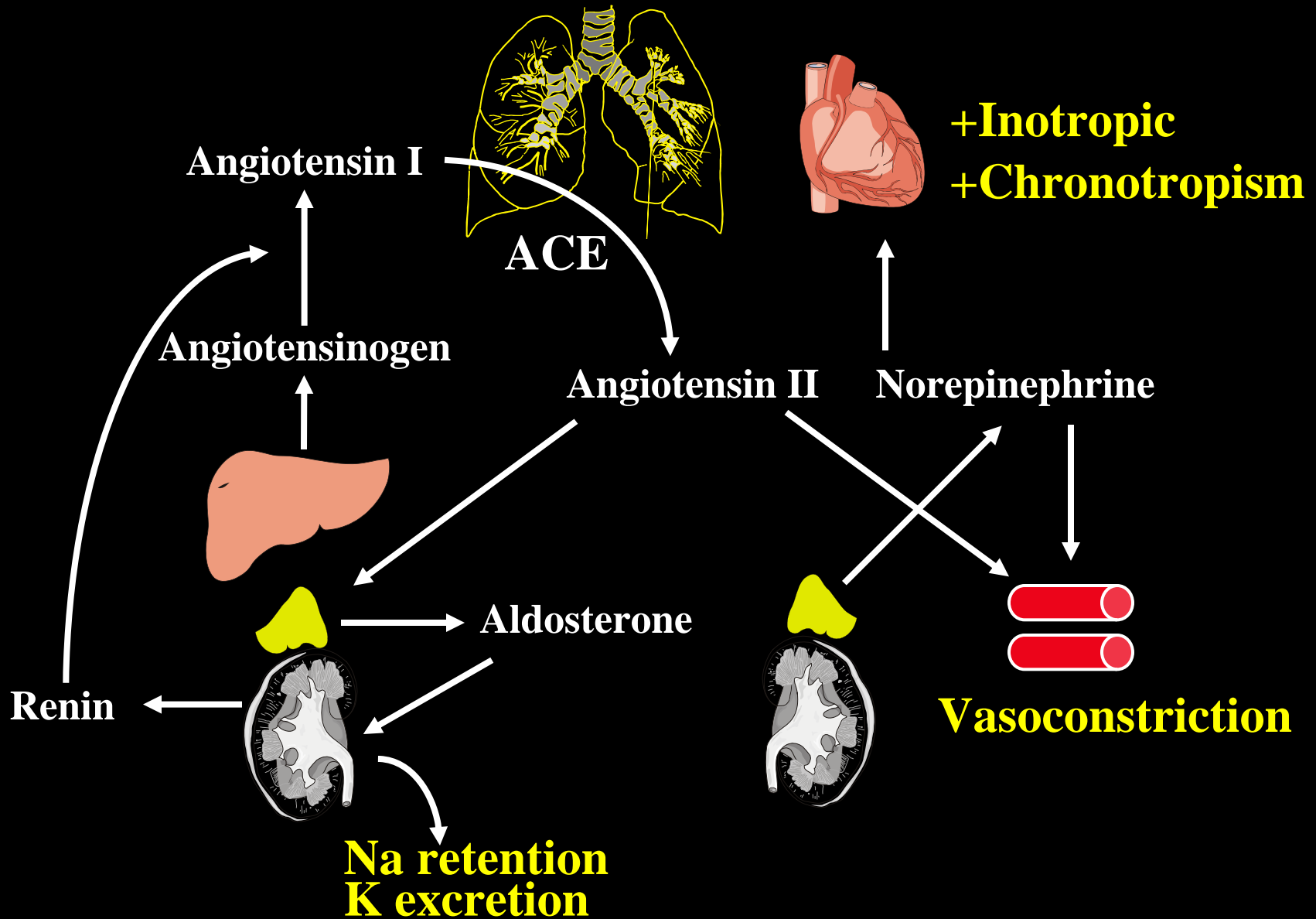
Lipid Reduction

- Patients who exceed lipid goals

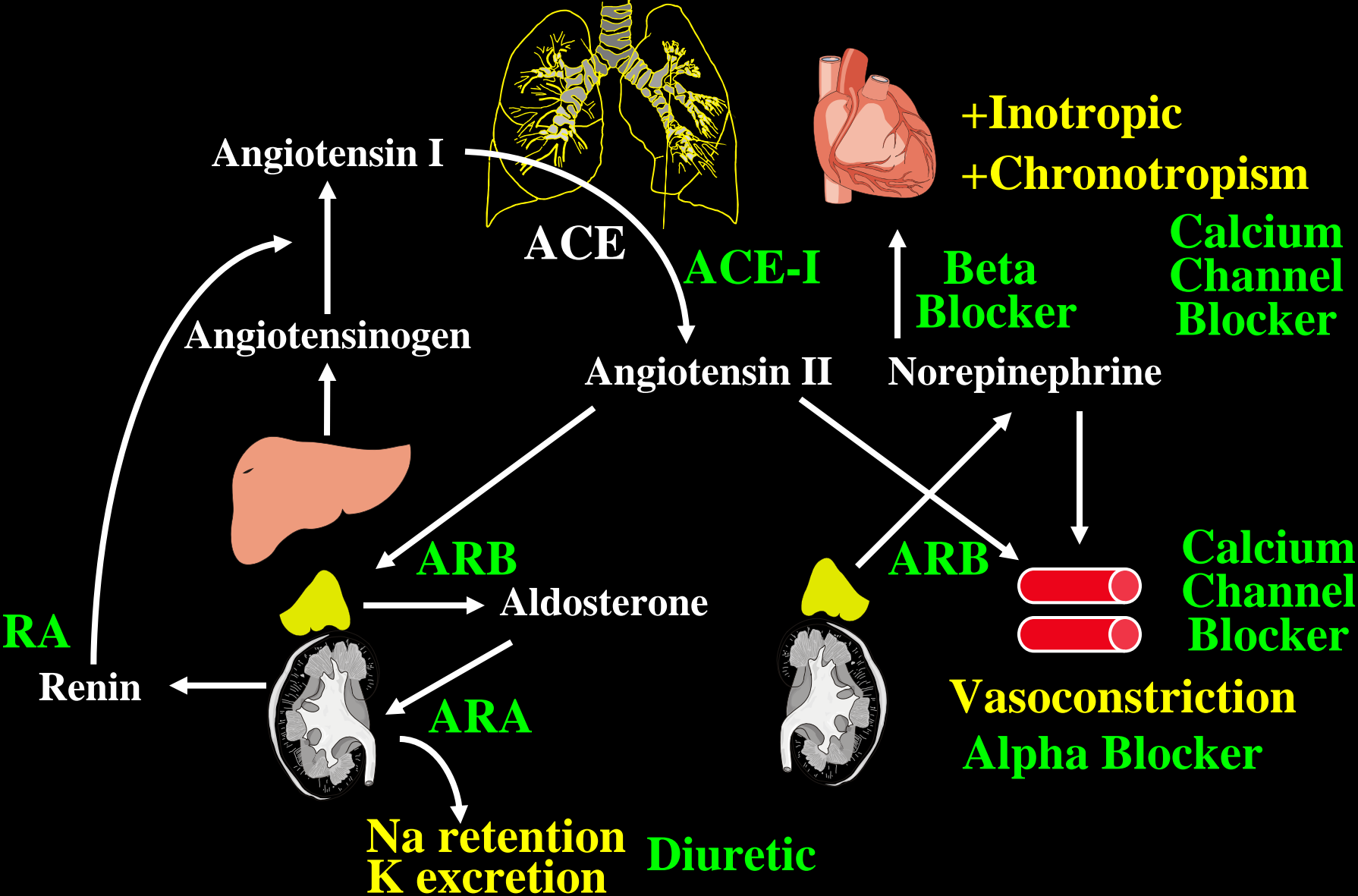
Investigational

- Aldose Reductase inhibition
- Protein Kinase C inhibition
- Advanced Glycosylation End-product inhibition

Blood Pressure Regulation



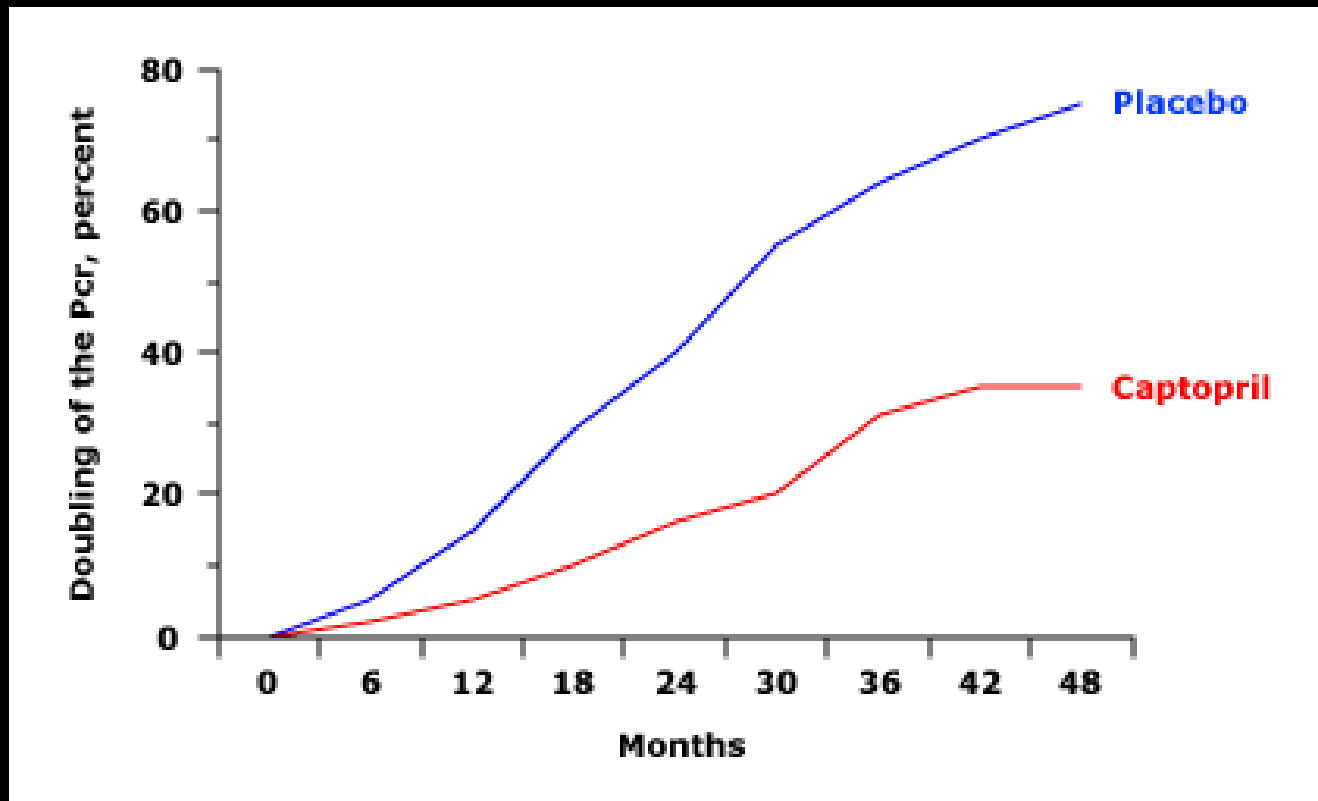
Blood Pressure Medications



ACE-I Therapy in Type 1 DM

Effect on Nephropathy Progression

Type 1 DM, Overt Proteinuria and Creatinine ≥ 1.5 mg/dl
RCT: Captopril vs Placebo for 4 years

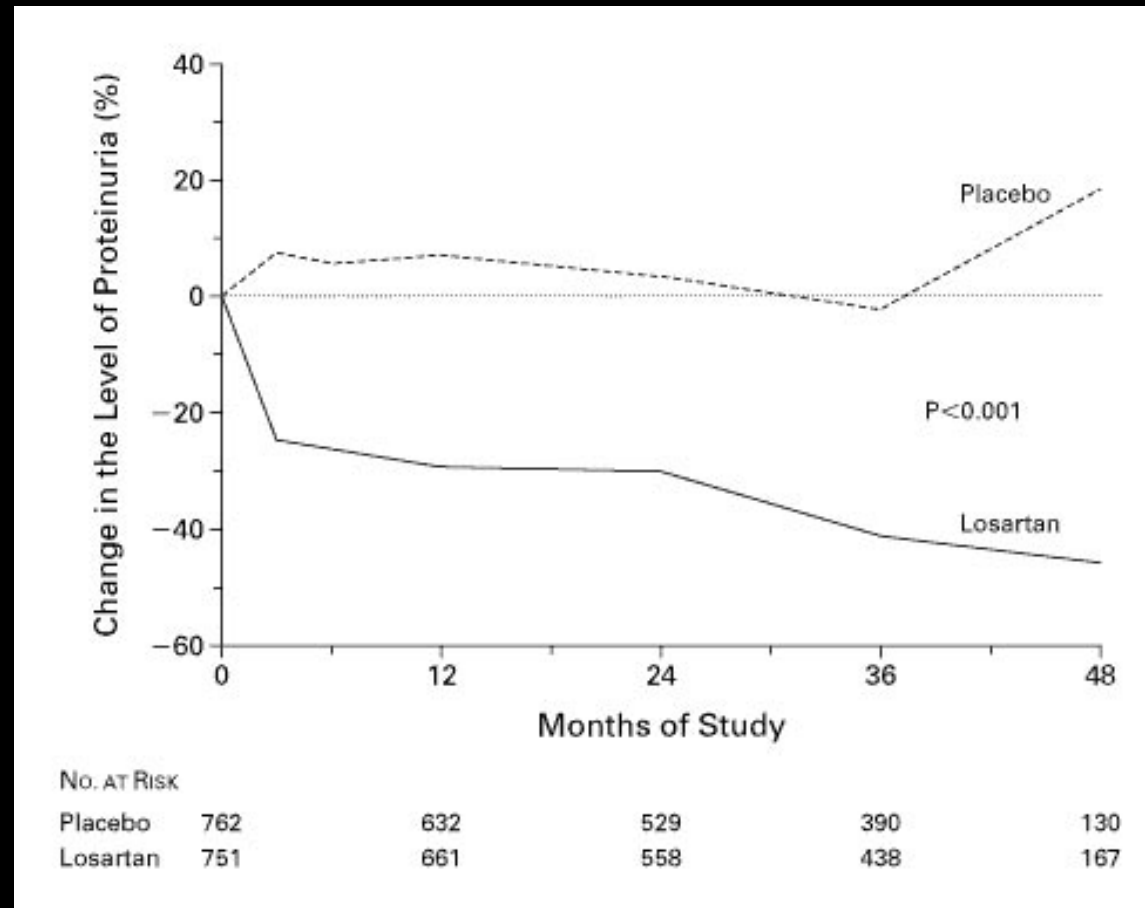


Placebo

Captopril

ARB Therapy in Type 2 DM Effect on Nephropathy Progression

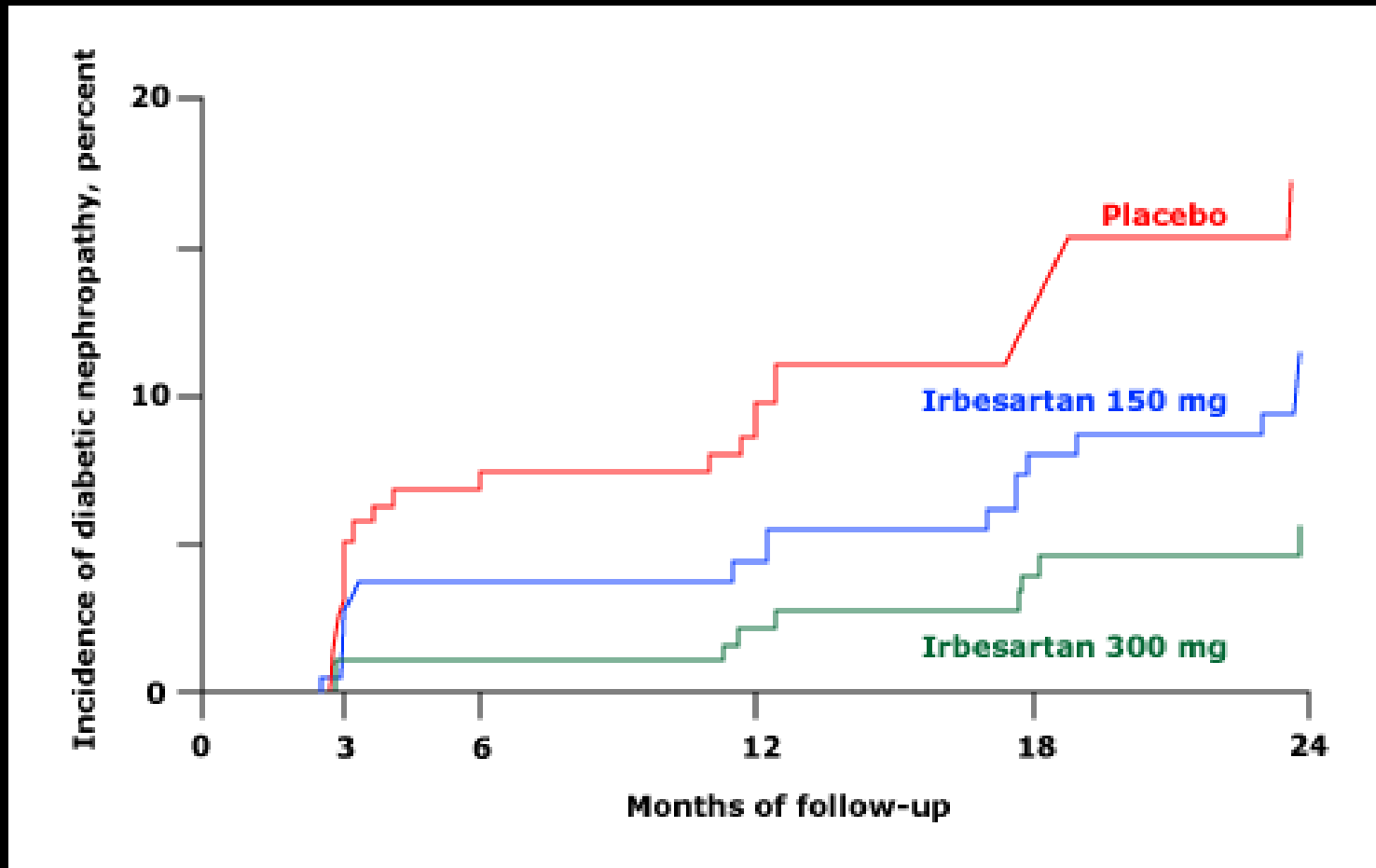
Median Changes in Proteinuria from Base Line



Placebo

Losartan

ARB Therapy in Type 2 DM Effect on Nephropathy Progression



Placebo

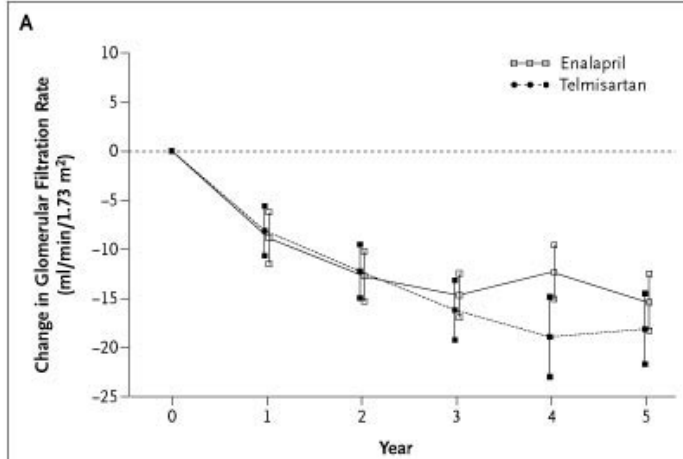
**Irbesartan
150 mg**

**Irbesartan
300 mg**

ACE-I vs ARB in Type 2 DM

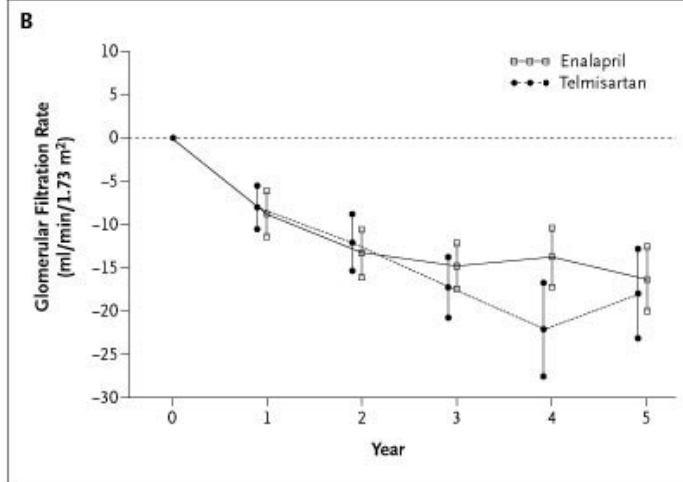
Effect on Nephropathy Progression

Δ in GFR



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

	0	1	2	3	4	5
Enalapril	103 (0)	110 (22)	113 (23)	113 (40)	113 (39)	
Telmisartan	86 (0)	99 (23)	102 (21)	102 (31)	103 (41)	



GFR

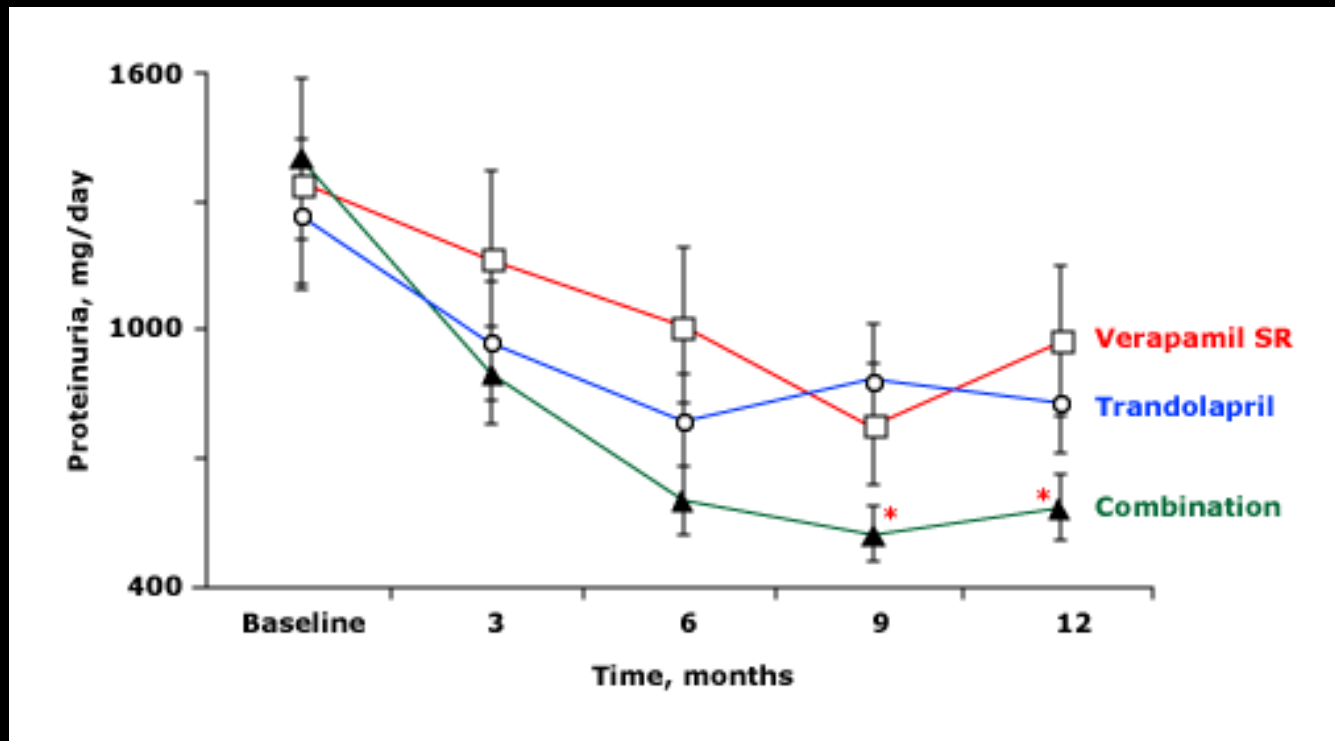
Enalapril
Telmisartan

Enalapril
Telmisartan

ACE-I + NDHP-CCB in Type 2 DM

Effect on Nephropathy Progression

Type 2 DM, Overt Proteinuria and Hypertension
RCT: Trandolapril, Verapamil, or Both for 1 year



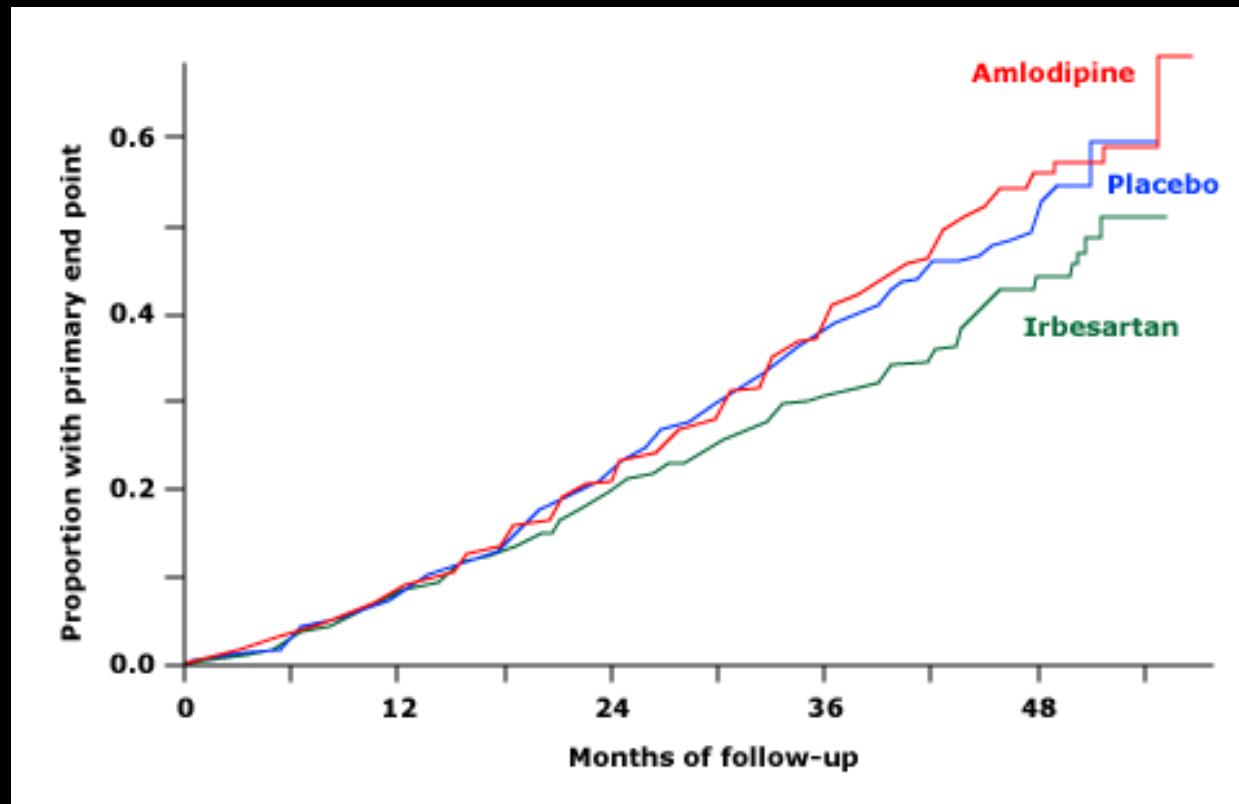
Verapamil SR
Trandolapril
Combination

ARB vs DHP-CCB Therapy in Type 2 DM

Effect on Nephropathy Progression

Type 2 DM, Overt Proteinuria and Hypertension
RCT: Irbesartan vs Amlodipine vs Placebo for 4 years

**Doubling of Serum Creatinine,
Development of ESRD or Death**



Amlodipine

Placebo

Irbesartan

Clinical Practice Recommendations: ADA 2009

Nephropathy Treatment: Supporting Evidence

Type 1 DM Patients with Hypertension and Any Degree of Albuminuria: ACE inhibitors have been shown to delay the progression of nephropathy (A).

Type 2 DM Patients with Hypertension and Micro-albuminuria: ACE inhibitors and ARBS have been shown to delay progression to macroalbuminuria (A).

Type 2 DM Patients with Hypertension, Macro-albuminuria, and Serum Creatinine ≥ 1.5 mg/dl: ARBs have been shown to delay the progression of nephropathy (A).

Clinical Practice Recommendations: ADA 2009

Hypertension Treatment

Pharmacological therapy for patients with diabetes and hypertension should include either an **ACE Inhibitor** or **Angiotensin Receptor Blocker (ARB)**(C).

BP Goal: < 130/80

If needed to achieve BP goal, add a **thiazide diuretic** if the **eGFR \geq 30 ml/min** and a **loop diuretic** if the **eGFR < 30 ml/min (C)**.

Multiple drug therapy (2 or more agents at maximal doses) is generally required to achieve BP targets (B).

If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be closely monitored (E).

Diabetic Nephropathy

Treatment Strategies

Glucose Control

- All patients

Blood Pressure Control

- Patients with BP > 130/80

→ Proteinuria Reduction

- Patients with microalbuminuria

Lipid Reduction

- Patients who exceed lipid goals

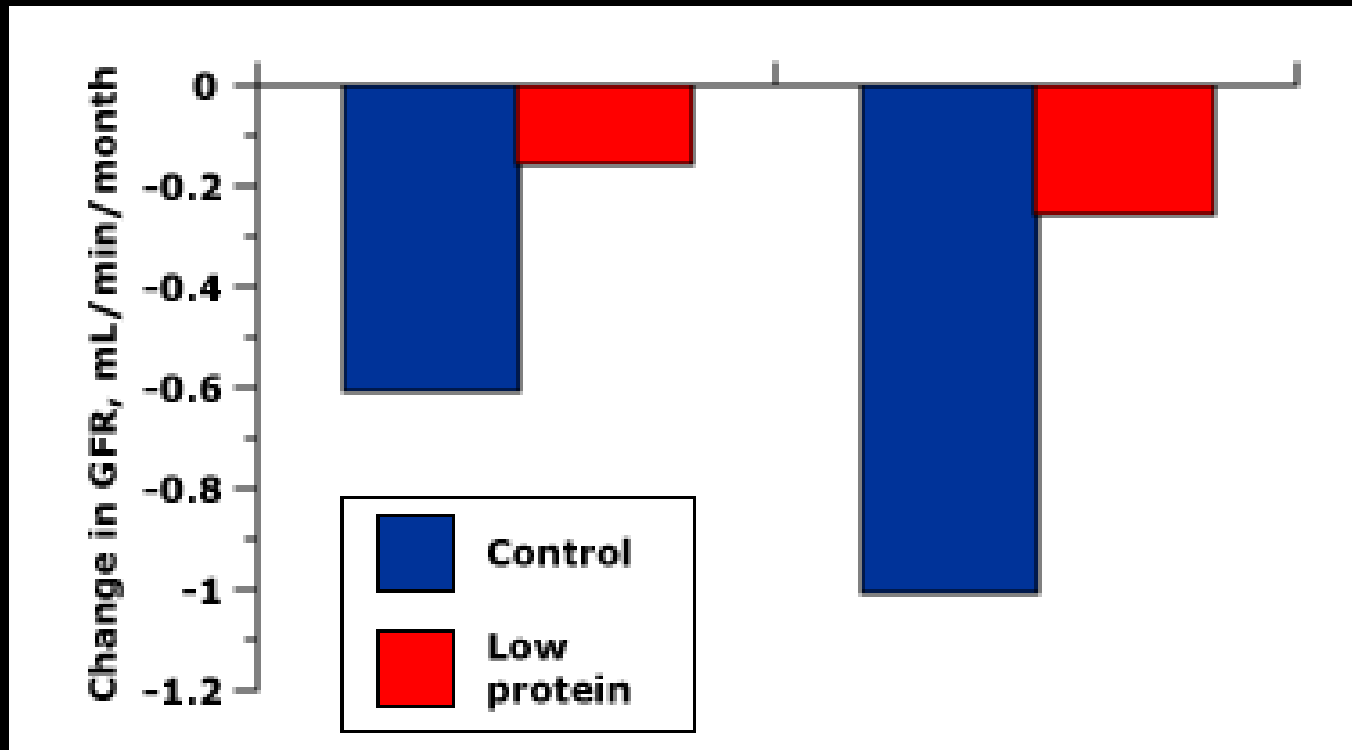
Investigational

- Aldose Reductase inhibition
- Protein Kinase C inhibition
- Advanced Glycosylation End-product inhibition

Low Protein Diet and DM Nephropathy

Effect on Nephropathy Progression

Patients with Diabetic Nephropathy
Protein Restriction (0.6 mg/kg/day) vs Control for 3 years



Walker J, Lancet 1989; 2:1411
Zeller K, N Engl J Med 1991; 324:78

Clinical Practice Recommendations: ADA 2009 Nephropathy Treatment

Reduction of protein intake to **0.8-1.0 g/kg/day** in those with early stages of CKD and to **0.8 g/kg/day** in those with later states of CKD is recommended (B).

Diabetic Nephropathy

Treatment Strategies

Glucose Control

- All patients

Blood Pressure Control

- Patients with BP > 130/80

Proteinuria Reduction

- Patients with microalbuminuria

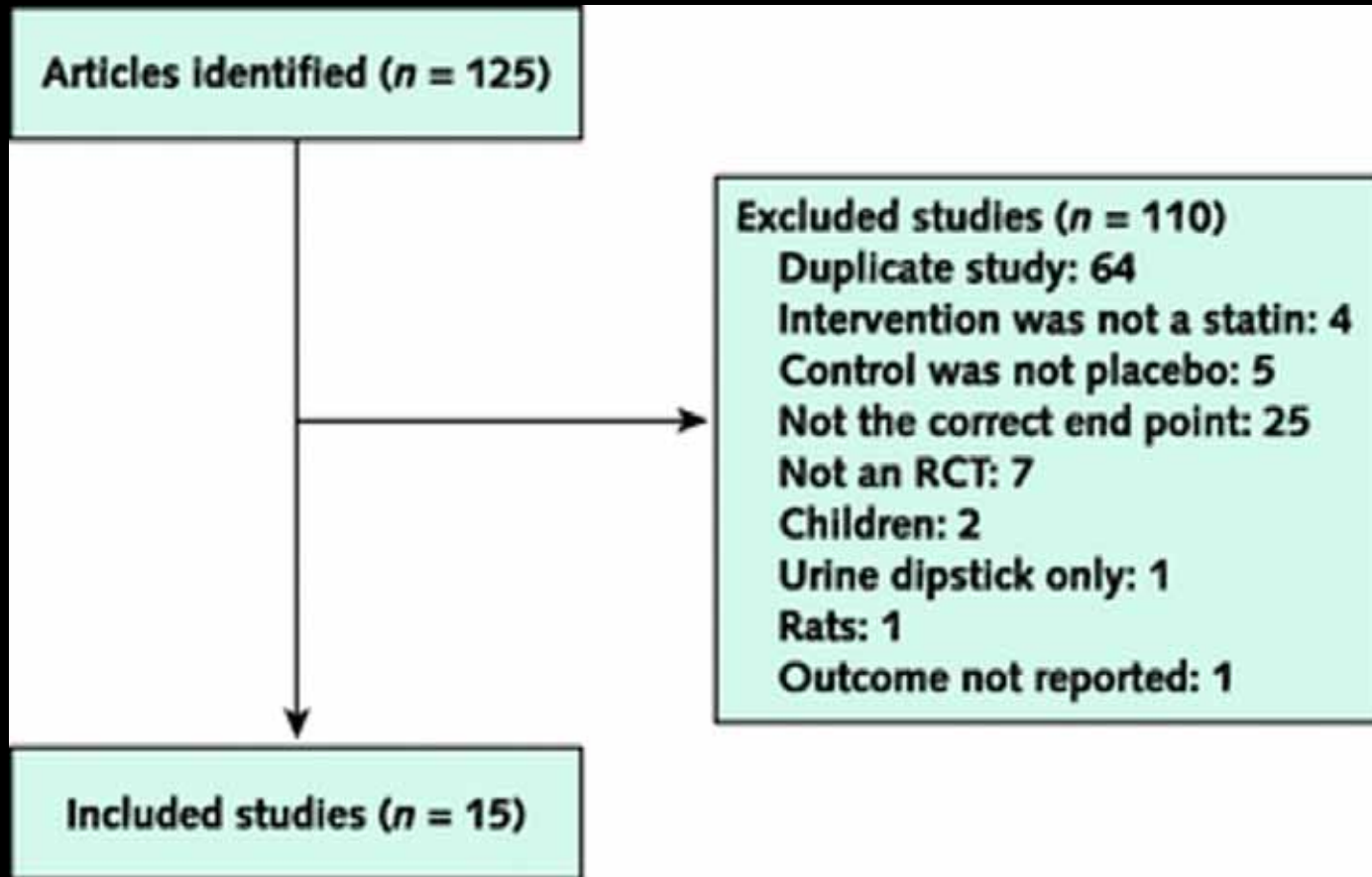
→ Lipid Reduction

- Patients who exceed lipid goals

Investigational

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Statin Therapy DM Nephropathy

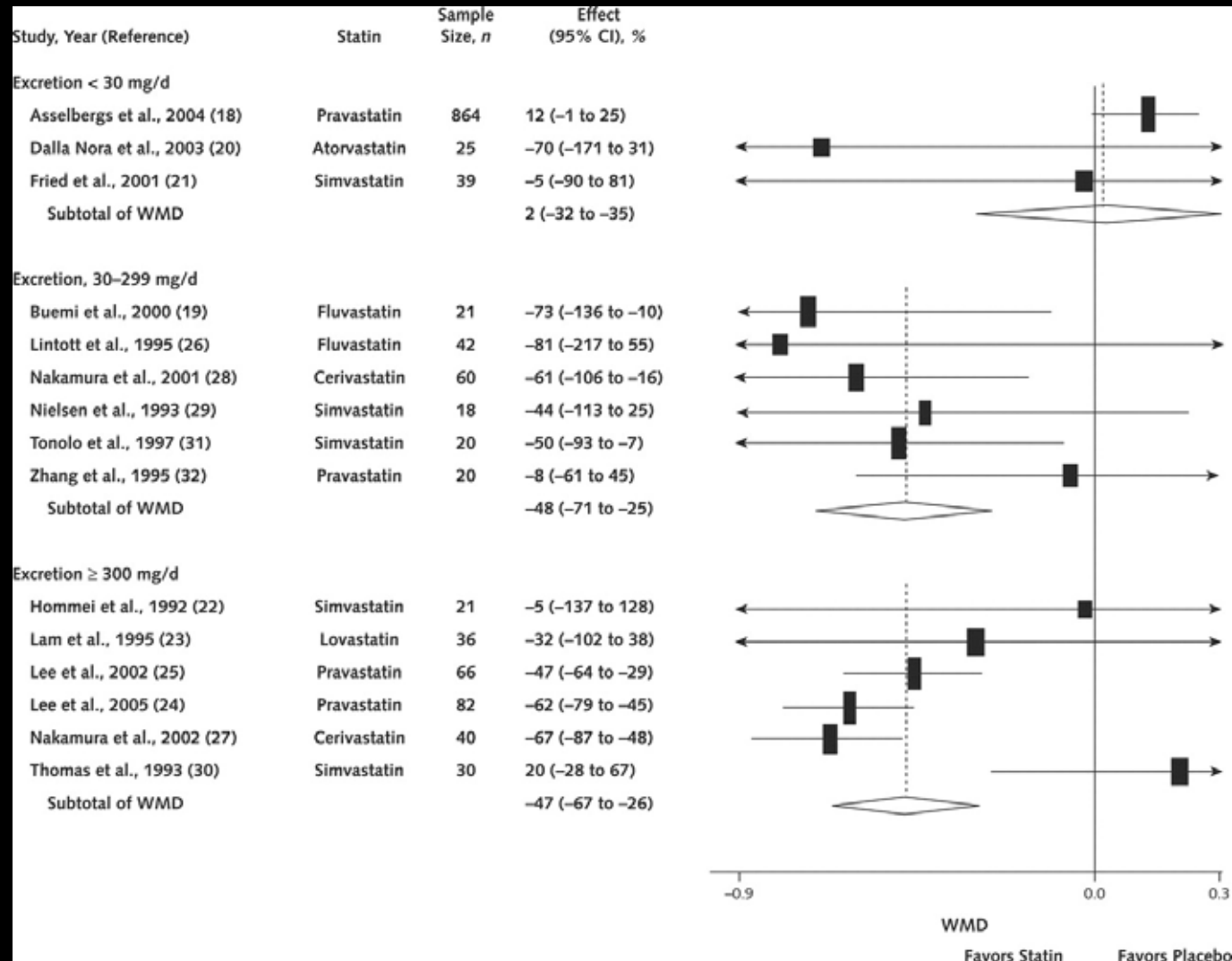


Statin Therapy DM Nephropathy

**Excretion
< 30 mg/d**

**Excretion
30-299 mg/d**

**Excretion
> 300 mg/d**



Individual and pooled results of 15 RCT's examining the effect of statins

Douglas K, Ann Intern Med 2006;145:117

Clinical Practice Recommendations: ADA 2009

Dyslipidemia Treatment Goals

Without Overt CVD: LDL goal: < 100 mg/dl (A).

With Overt CVD: LDL goal: < 70 mg/dl (optional) (B)

Alternative Goal: ↓ LDL by 30-40% if unable to reach targets on maximally tolerated statin therapy (A)

TG < 150 mg/dl (C)

HDL > 40 (men) and > 50 (women) (C)

Combination therapy using statins and other lipid agents may be considered but has not been evaluated in outcome studies for CVD outcomes or safety (C)