ROLE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN TYPE I DIABETIC NEPHROPATHY

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Type I –IDDM is characterized by

- The abrupt onset of symptoms
- Insulinopenia
- Dependence on injected insulin for life
- Proneness to ketoacidosis.
- Confirmed by demonstrating low plasma insulin or C-peptide levels, circulating islet cell antibodies and association with HLA DR3,DR4
- Asparagines for neutral amino acids in position 57 of HLA-DQB chain.

Clinical distinction between type I and type II Diabetes

CRITERIA	IN FAVOUR OF TYPE I	IN FAVOUR OF TYPE II
Age at diagnosis of diabetes	<25 yrs	>40 yrs
Weight at diagnosis	105% of ideal weight	>115%
Ketoacidosis within 2 yrs of following diagnosis	+ +	- -
Long term complications at diagnosis	- -	+ +
Delay between diagnosis and insulin deficiency	- -	+ +
C-peptide	- -	+ +

Diabetic nephropathy

- A major micro vascular complication of diabetes mellitus.

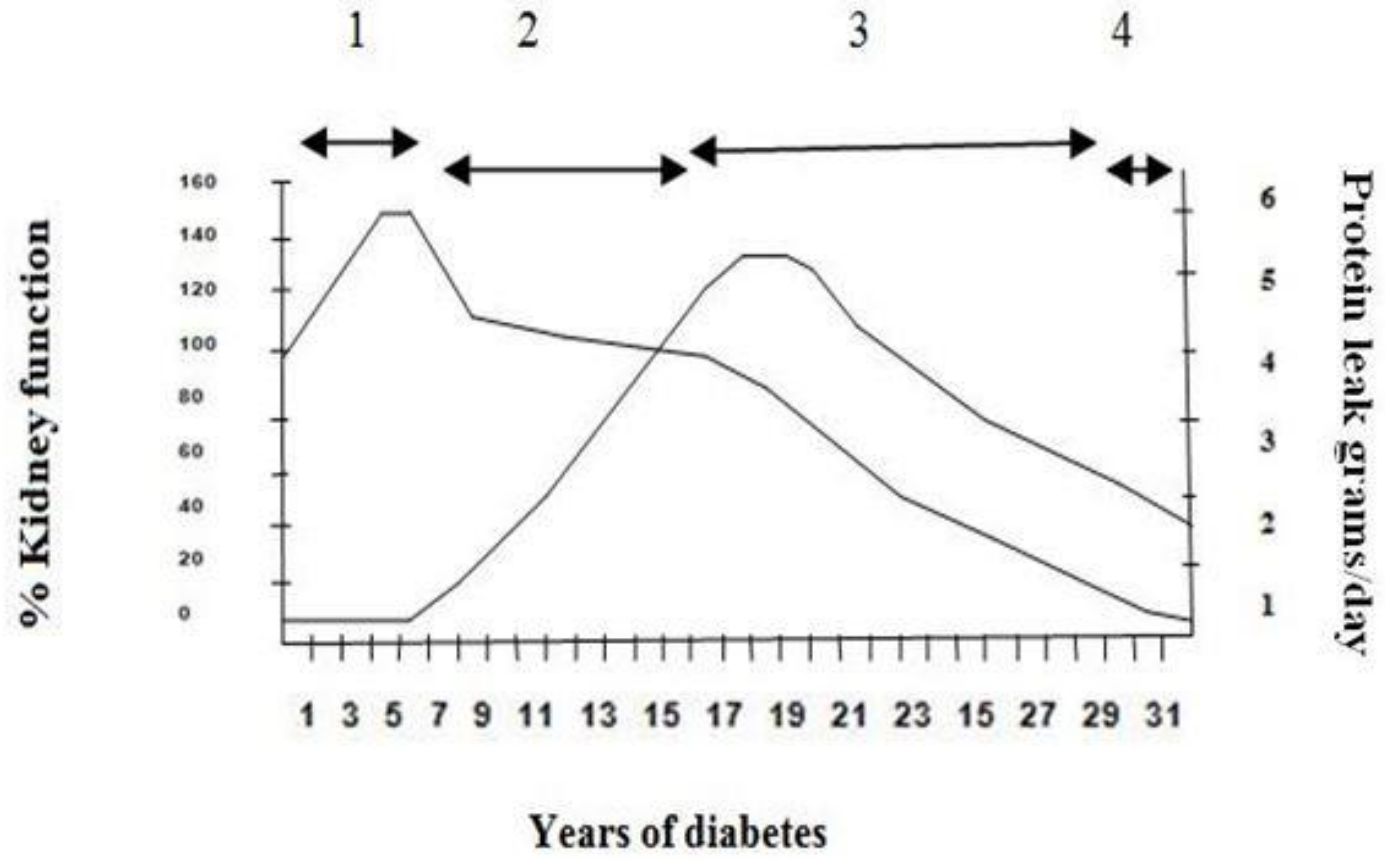
- Major cause of morbidity and mortality in both type I and type II diabetes
- Represent the major cause of ESRD worldwide.

- About 20-40% of all diabetic subjects develop DN

- Diabetic nephropathy represents a continuum from microalbuminuria to macroalbuminuria and finally ESRD.

- There is vital need to identify and target novel pathophysiological pathways to reduce the rising burden of this disease.

A GRAPH SHOWING RELATIONSHIP BETWEEN KIDNEY FUNCTION,PROTEIN LEAK, AND YEARS OF DIABETES



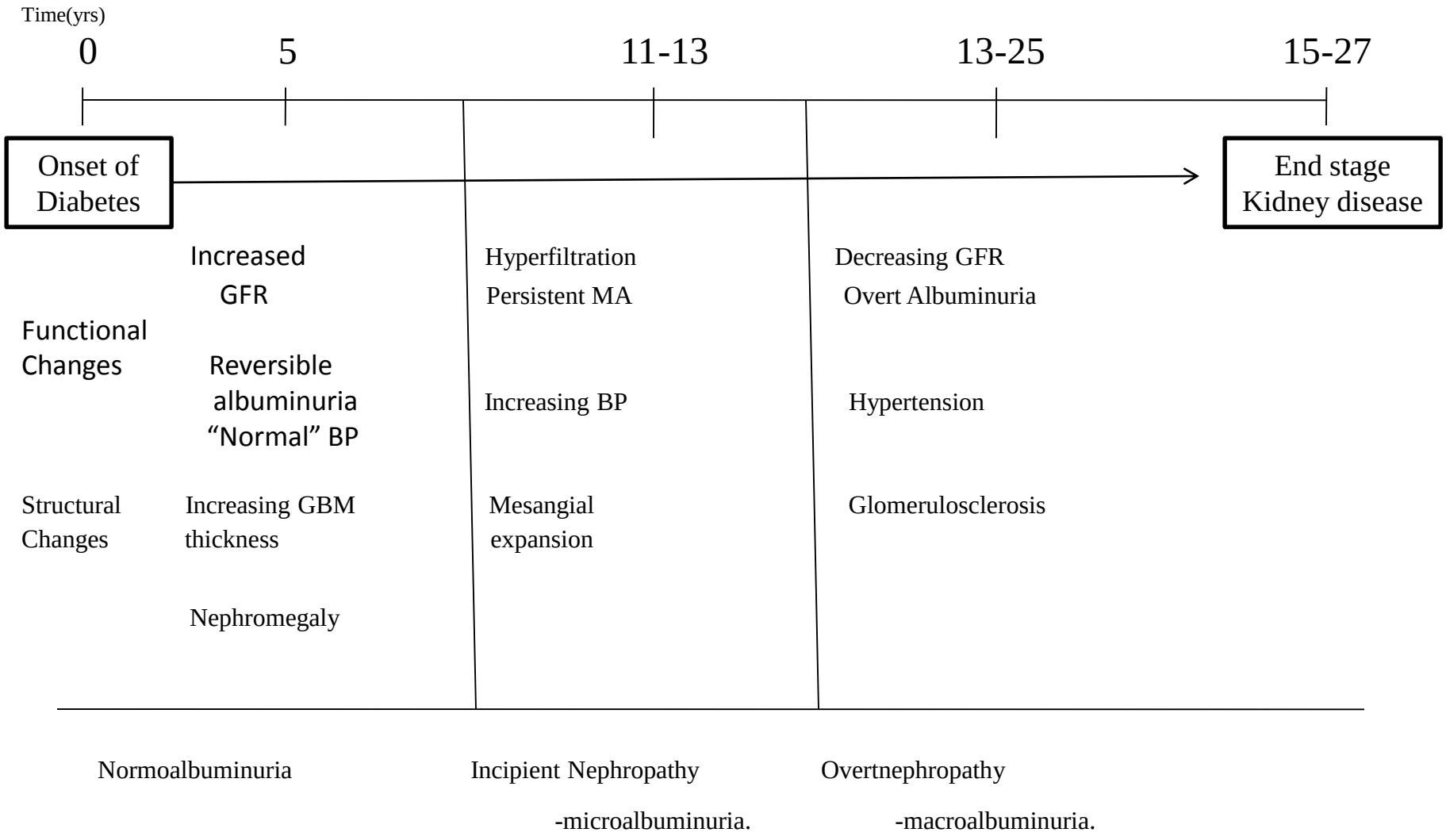
EPIDEMIOLOGY OF DN-

40% OF TYPE I AND 20% OF TYPE II DIABETICS DEVELOP CLINICALLY SIGNIFICANT NEPHROPATHY.

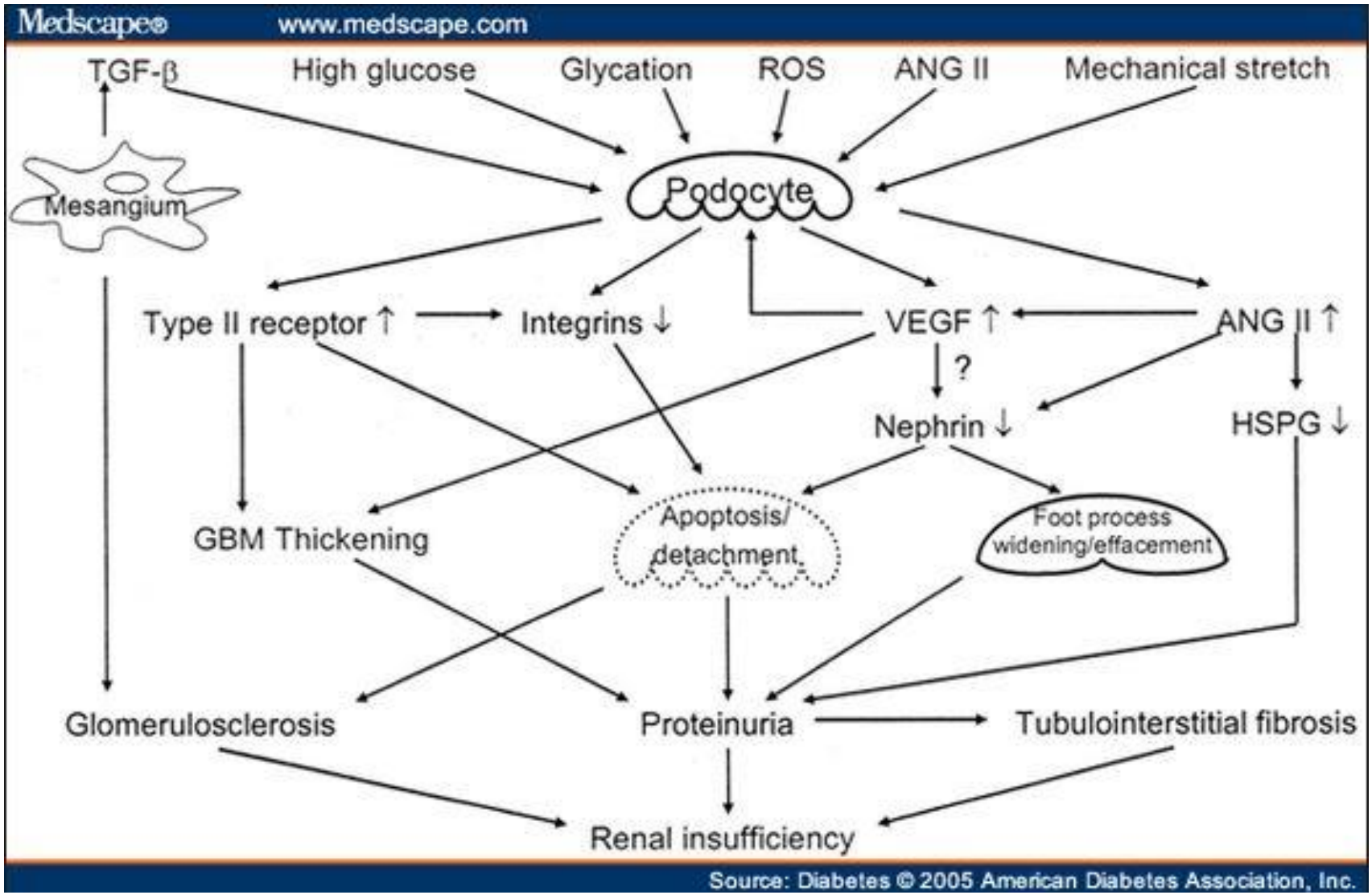
ACCORDING TO Krolewski et al. PATIENTS WITH IDDM HAVE 30%-50% RISK OF DEVELOPING DIABETIC NEPHROPATHY OVER 40 YEAR OF DISEASE.

Krolewski AS, warram JH, christlieb AR, Busik EJ, Khan CR. The changing natural history of nephropathy in type I diabetes. Am Jf Med 1985;785-94.

Natural course of renal disease in Diabetes



PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY-



STAGES OF DIABETIC NEPFROPATHY-

STAGE	GLOMERULAR FILTRATION	ALBUMIN	BP	TIME
RENAL HYPERFUNCTION	ELEVATED	ABSENT	NORMAL	AT DIAGNOSIS
CLINICAL LATENCY	HIGH NORMAL	ABSENT	WITHIN OR ABOVE NORMAL	5-15 YRS
MICROALBUMINURIA	NORMAL	20-200ug/min	INCREASED	10-15 YRS
MICROALBUMINURIA OR PERSISTING PROTEINURIA	DECREASING	200ug/min	-	-
RENAL FAILURE	DIMINISHED	massive	INCREASED	15-30 YRS

MANAGEMENT-

SLOWING THE PROGRESSION OF DN INCLUDES

- **OPTIMISING GLYCAEMIC CONTROL**
- **CONTROL OF HYPERTENSION**
- **USING ACEI AND/OR ARB.**

MANAGEMENT-

- **MEDICINES THAT ARE USED TO TREAT DIABETIC NEPHROPATHY ARE ALSO USED TO CONTROL BLOOD PRESSURE.**

  ACEI SUCH AS

  CAPTOPRIL, LISINOPRIL, RAMIPRILAND ENAPRIL, HAVE BEEN SHOWN TO PROTECT THE KIDNEY FUNCTION IN PEOPLE WITH TYPE I DIABETES.

MANAGEMENT

- **ARBS, SUCH AS**

  CANDESARTAN, IRBESTAN, OSARTAN POTASSIUM, MAY BE GIVEN WITH ACEI TO PROVIDE GREATER PROTECTION OF THE KIDNEY.

Chavers, BM, Billus, N. Eng J Med 1989; 320:966

ROLE OF ACEI

- ACEI Blocks The Conversion of Angiotensin I To Angiotensin II. They Lower Arteriolar Resistant And Increased Venous Capacity, Increased Cardiac Output And Lower Renovascular Resistance.
- First Orally Active ACEI Was Captopril Which Was Discovered In 1975

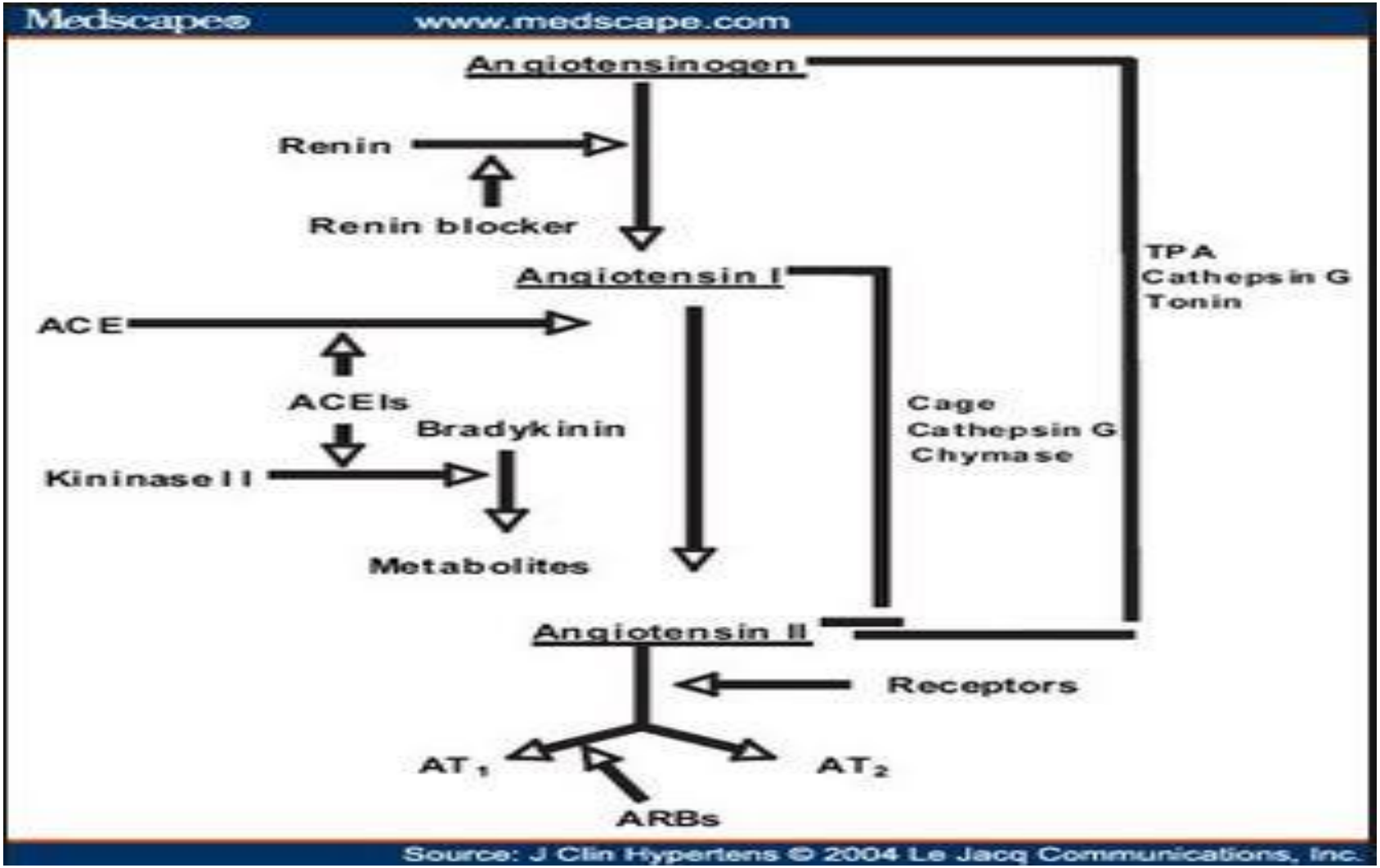
ROLE OF ARB

- THEY BLOCK THE ACTIVATION OF

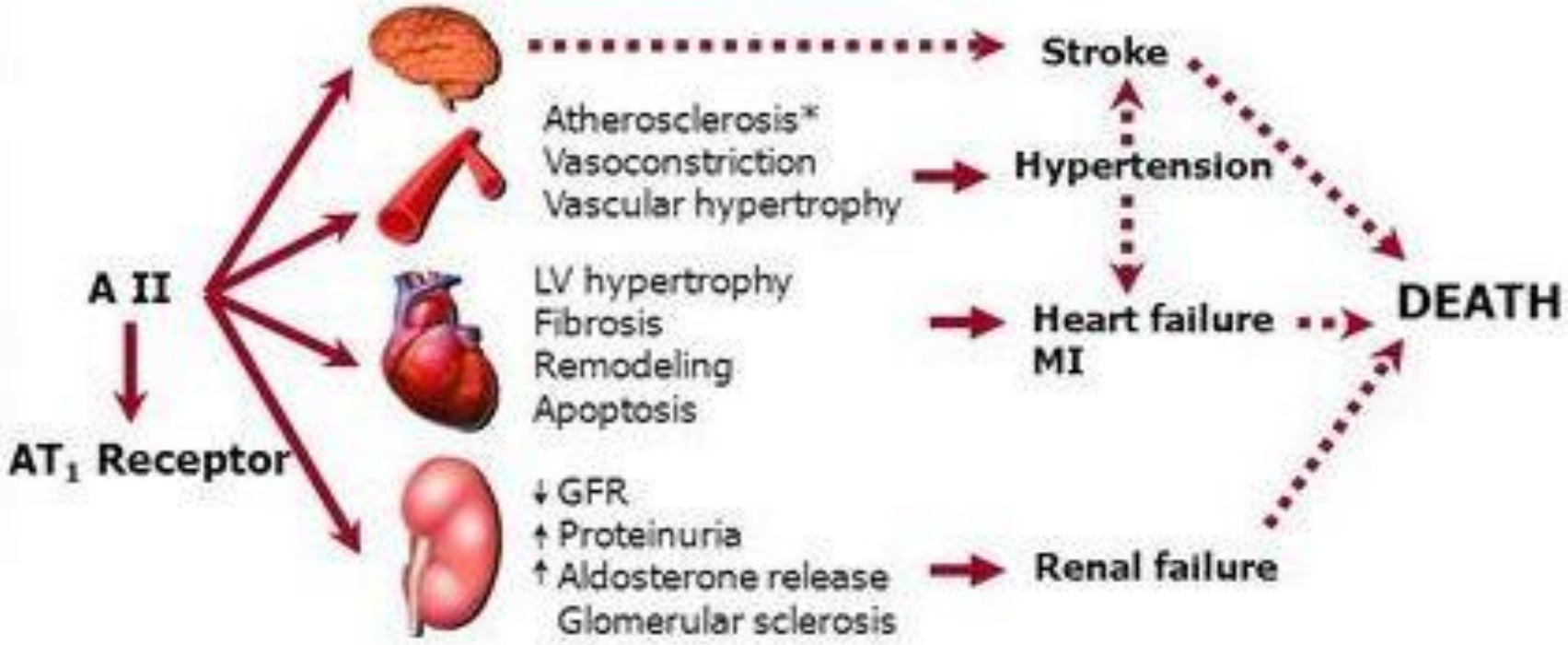
  ANGIOTENSIN II AT AT1

  RECEPTORS. BLOCKADE CAUSES VASODILATATION, REDUCES SECRETION OF VASOPRESSIN, REDUCES PRODUCTION OF AND SECRETION OF ALDOSTERONE.
- FIRST ORALLY ACTIVE ARB WAS LOSARTAN WHICH WAS DISCOVERED IN 1980.

ANGIOTENSIN PATHWAY-



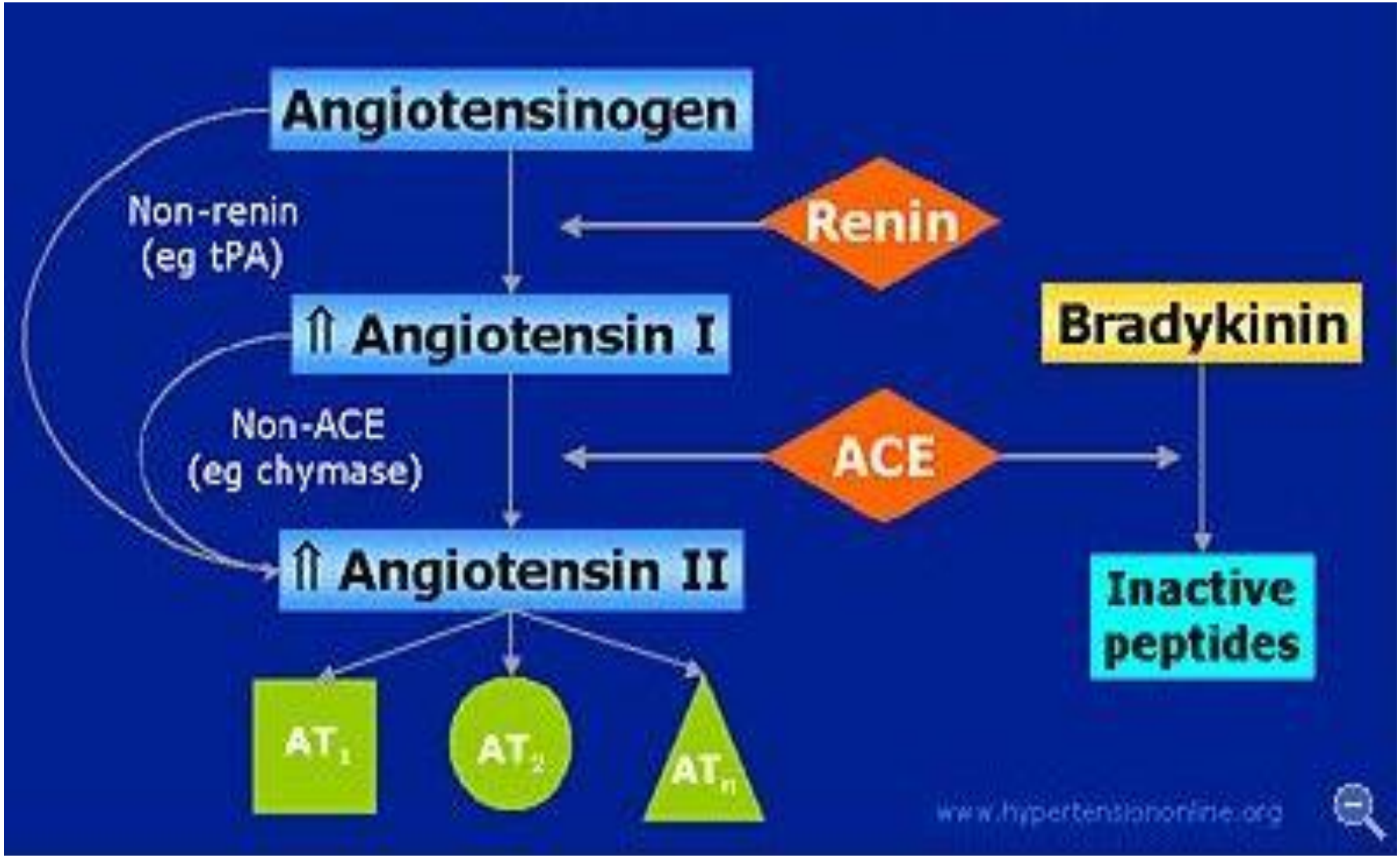
ANGIOTENSIN II PLAYS A CENTRAL ROLE IN ORGAN DAMAGE



*preclinical data

LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

RENIN-ANGIOTENSIN CASCADE

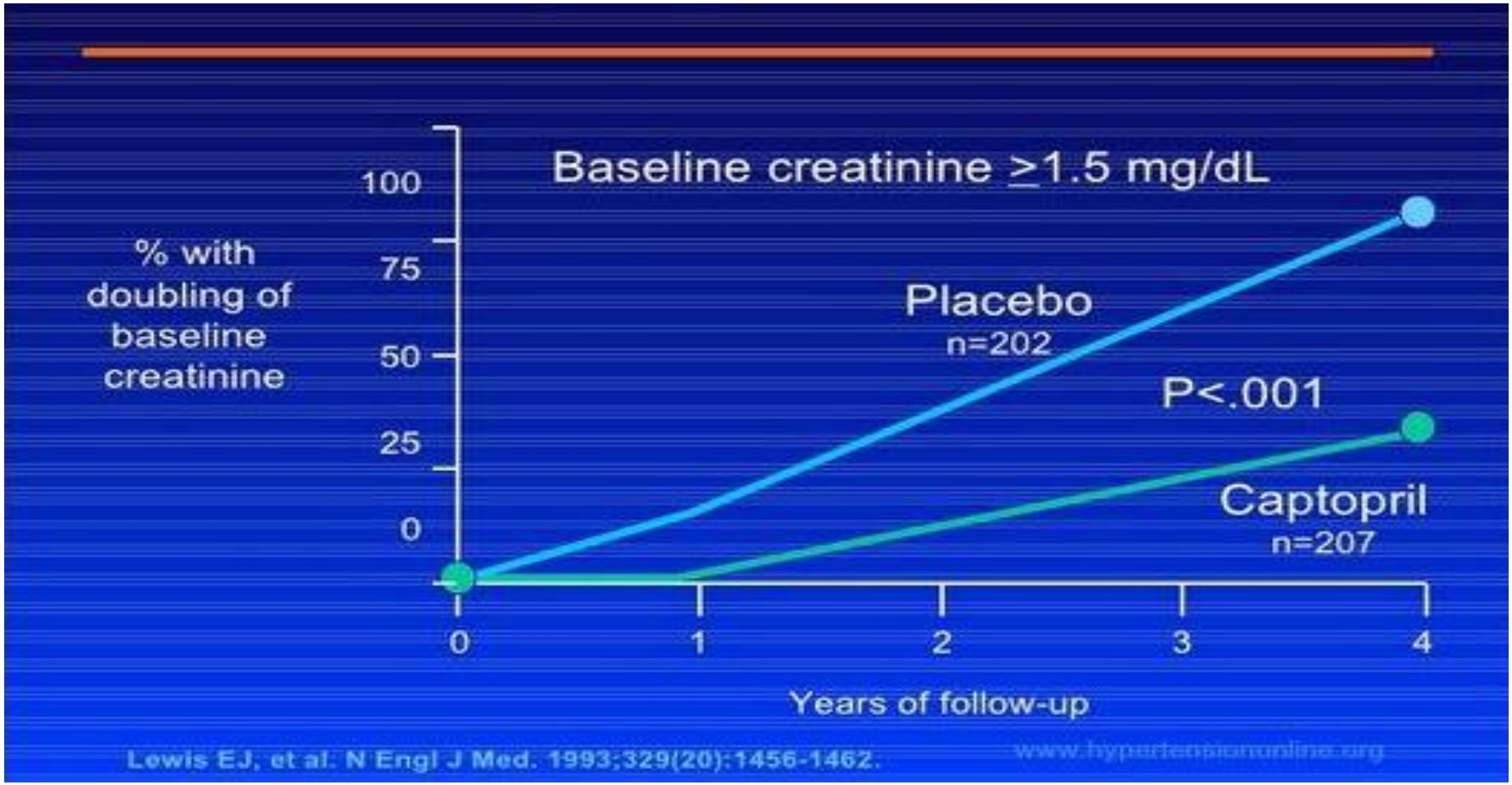


WHAT ARE THE EVIDENCES?

Are The Inhibitors Of Renin- Angiotensin System(ACEIs or ARBs) Really Effective?

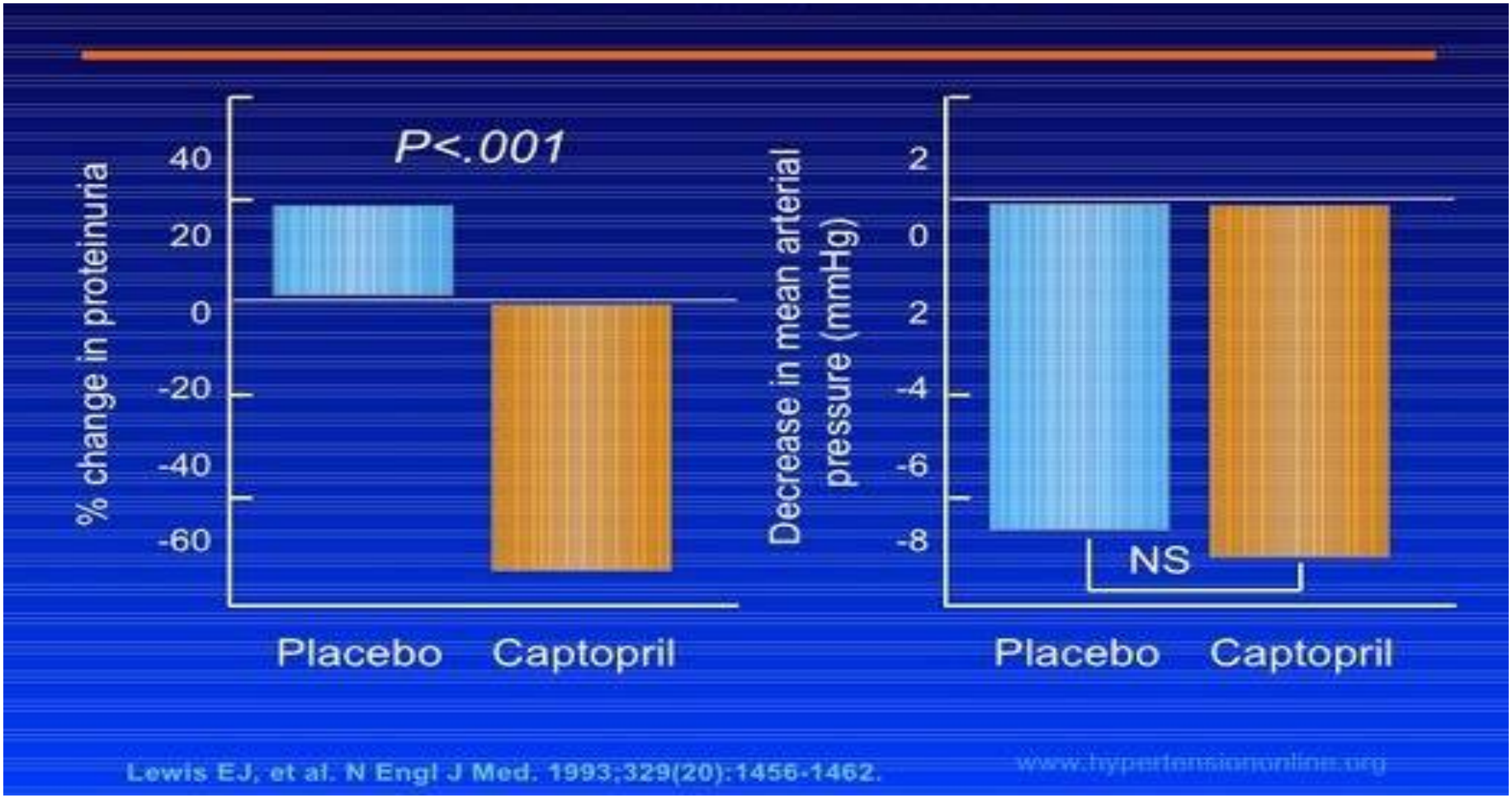
ACE-I Is More Renoprotective Than Conventional Therapy In Type I

Diabetes

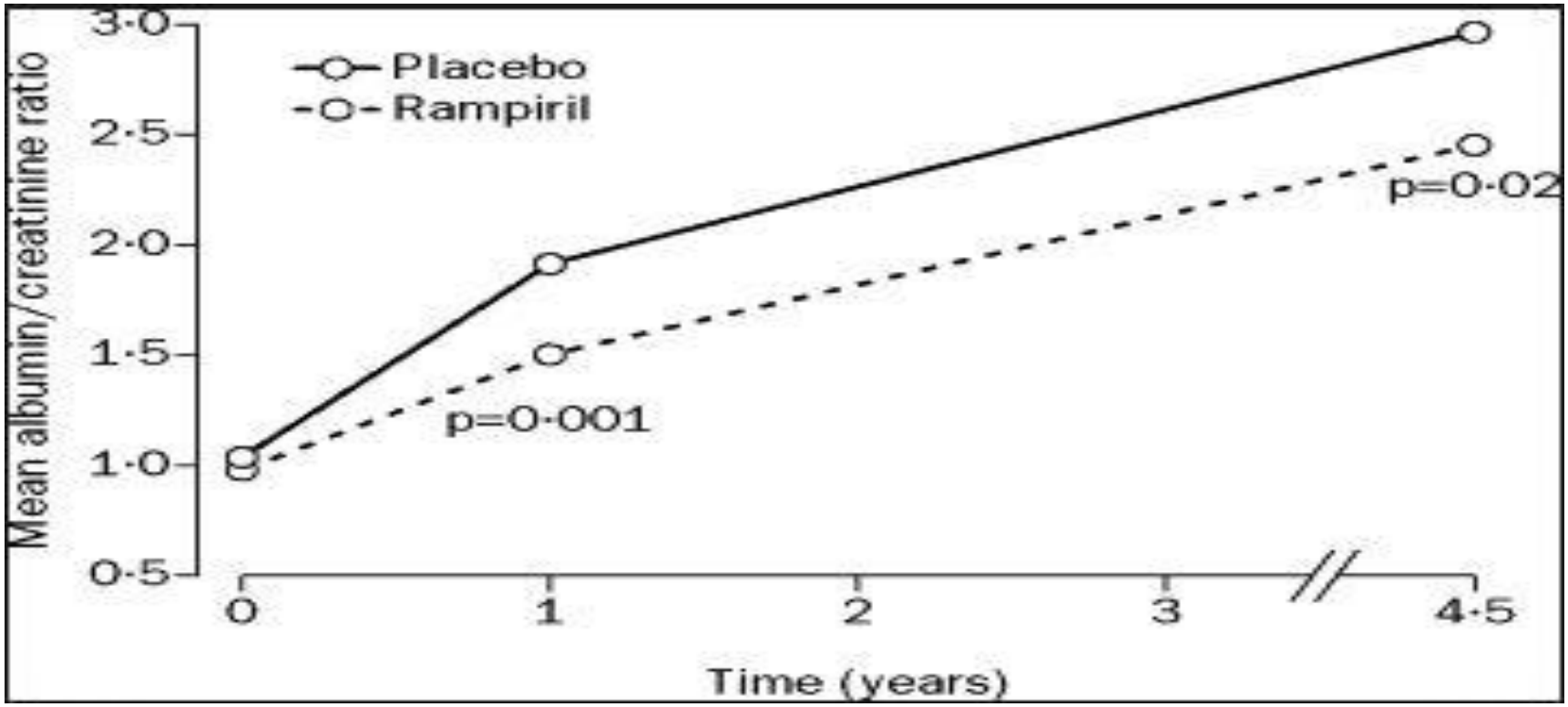


ACE-I Is More Renoprotective Than Conventional Therapy In Type I

Diabetes2

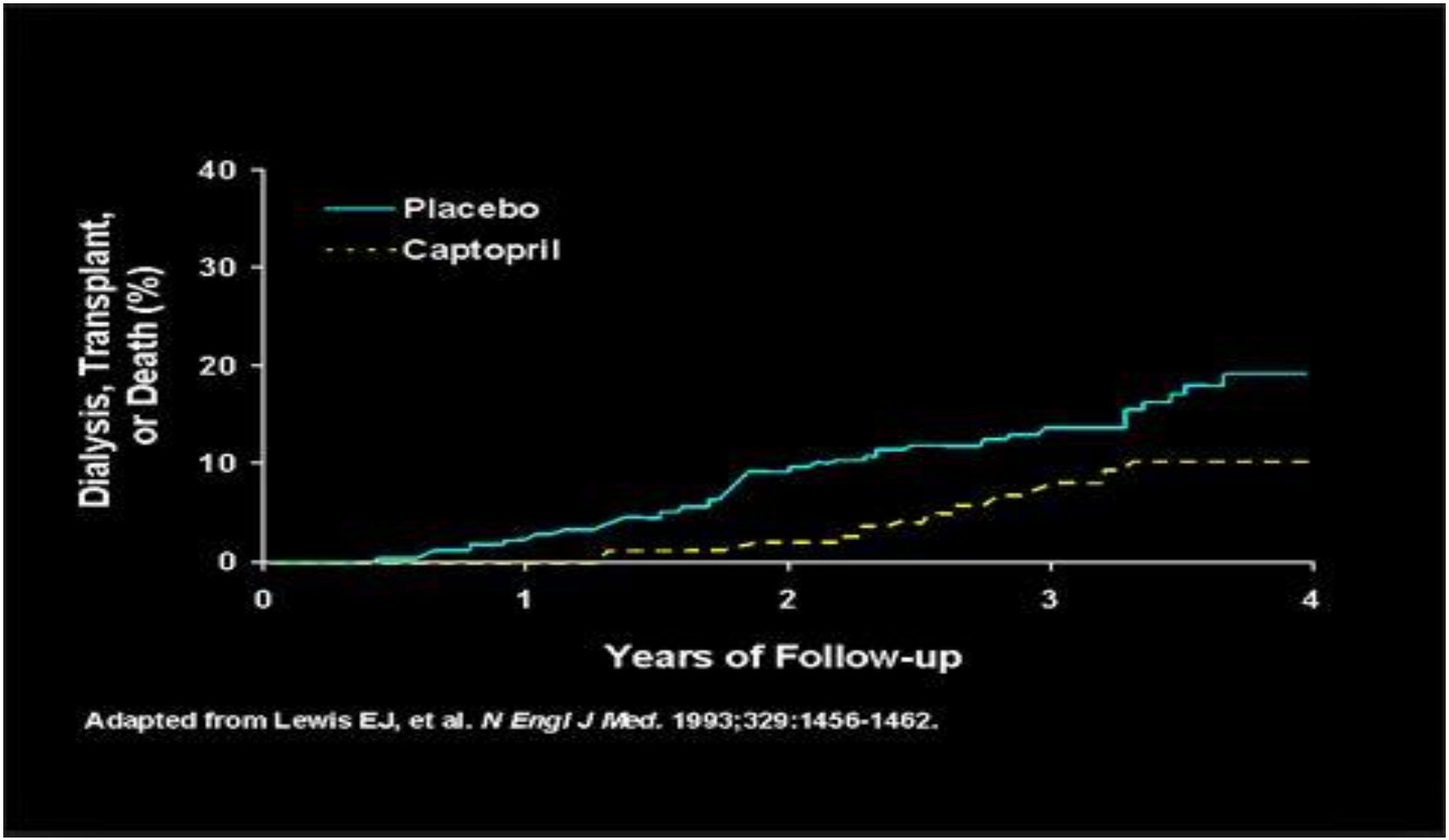


Micro Hope Study (n=3577)



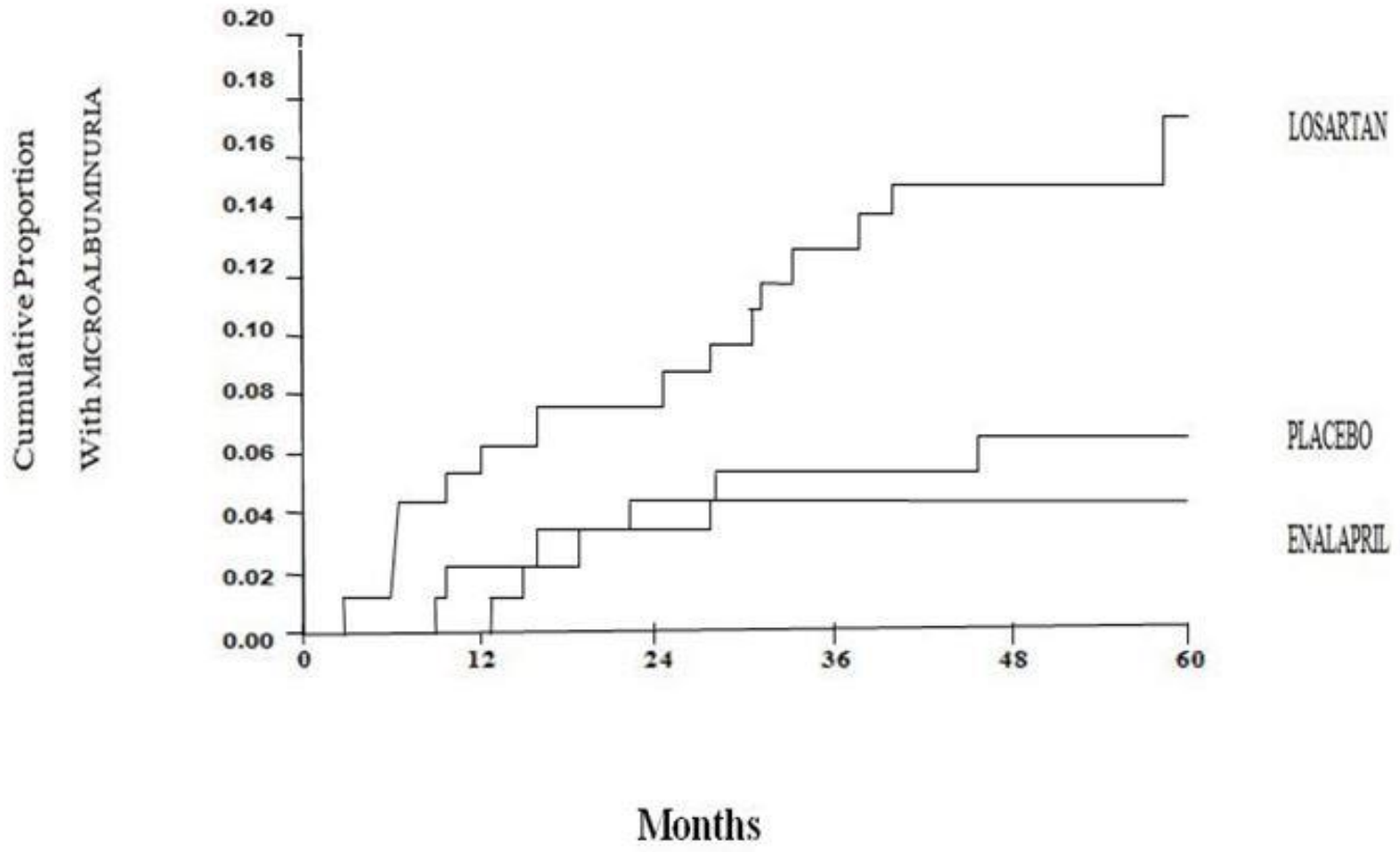
24% greater decrease in progression to overt Nephropathy in the Ramipril group than placebo

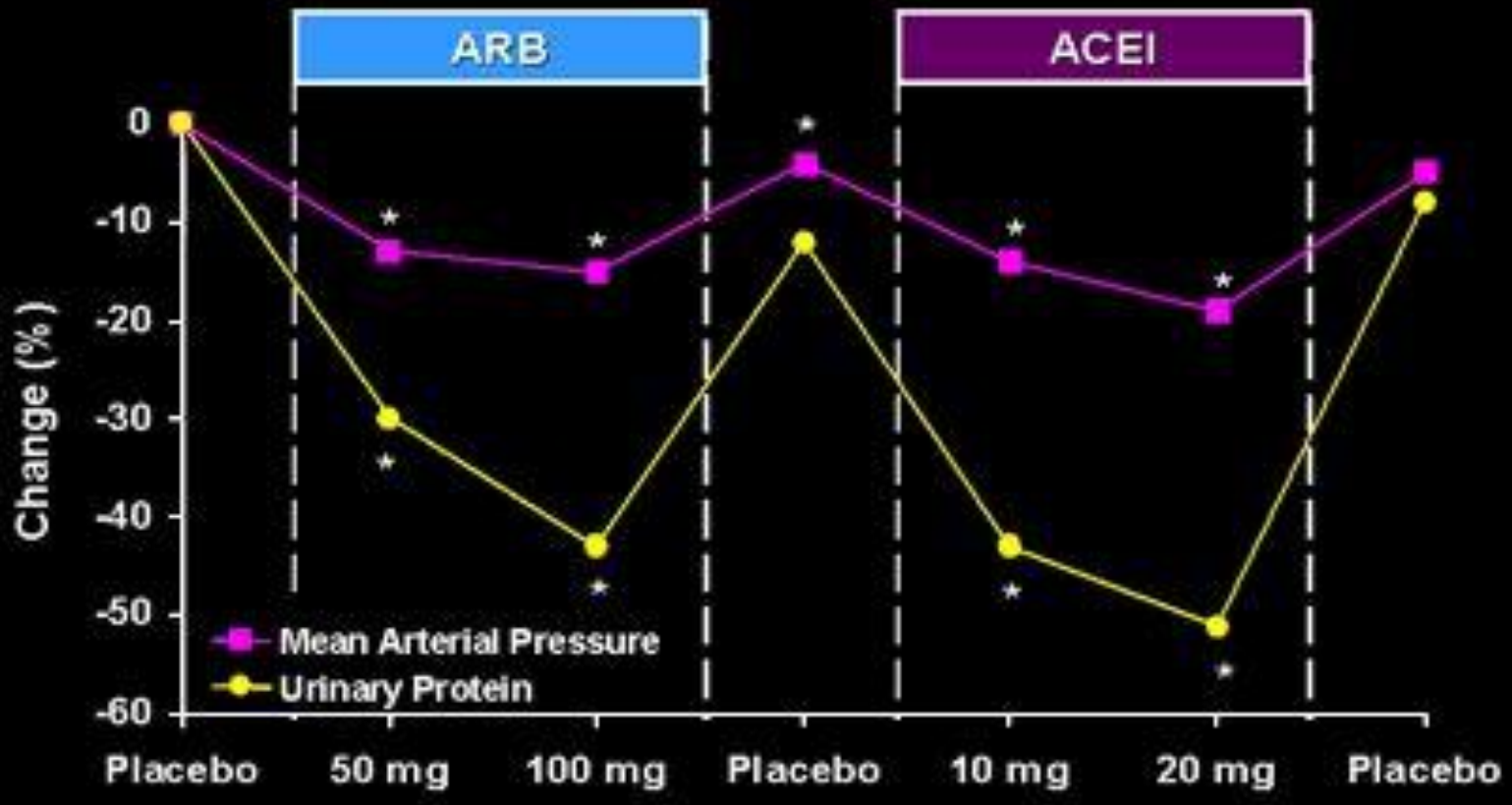
Renoprotective Effect Of Losartan In Diabetic Nephropathy (RENAAL Study, n=1513)



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

Comparison Of Losartan, Enalapril & Placebo On Microalbuminuria





Adapted from Gansevoort RT, et al. *Kidney Int.* 1994;45:861-867.

STUDY	STUDY DESIGN	SAMP-LE SIZE	EXPOSURE	RESULTS	CONCLUTION
Jacobsen et al	RCT Crossover Design.	20	ACEI &/or ARB.	Treatment with benazepril, valsartan or dual blockade significantly reduce albuminuria and BP compared with placebo. Dual blockade induced an additional reduction in albuminuria of 43% (29to 54%) compared with any type of monotherapy.	Dual blockade of the RAS may offer additional renal and cardiovascular protection in type I diabetic patients with DN
Mauer et al	RCT Multi-center Parallel design.	285	ACEI & ARB.	Change in mesangial fractional volume per glomerulus over 5-year period did not differ significantly between Placebo(0.016 units) and Enalapril(0.005,p=0.38) or Losartan group	Early blockade of the renin-angiotensin system in patients with type I diabetes did not slow nephropathy progression.
Lewis et al	RCT Multi-center Parallel design.	409	ACEI.	Total 65 patients reached endpoint, of which 23 were in captopril group and 42 were in pacebo group. Treatment with captopril is associated with 50% reduction of in risk of combined end points of death. Dialysis or renal transplantation.	Captopril protect against deterioration of renal function in IDDM Nephropathy irrespective of BP status. The therapy is effective on patient with established nephropathy rather not as prophylactic treatment.
Agarwal et al	RCT Crossover design.	17	ACEI & ARB.	Increase in GFR was seen 14% by the add-on Losartan therapy and fall of Plasama rennin activity by 32%.	Add on Losartan therapy didn't improve proteinuria or ABP over one month add on therapy.
Schjoedt et al	Clinical audit. Follow-up Study.	227	ACEI or ARB.	With RAS blockade mean decline in UAER of 4% year. 65 patients(29%) progressed to overt Diabetic Nephropathy, about 3.1%/yrs. 29 of them regressed to normo-or microalbuminuria on intensified antihypertensive treatment.	Implementation of RAAS-blocking treatment in type I diabetic patients with microalbuminuria successfully reduced long-term progression to overt Diabetic Nephropathy.
Tarnow et al	RCT Parallel design.	52	ACEI vs Ca antagonist.	GFR declined in a biphasic manner with an initial(0-6months) reduction of 1.3+_0.3ml_min _1_month_1 in the lisinopril group compared with0.2+_0.4ml_min_1_month_1 in the nisoldipine geoup (p_0.01).	Long-term treatment with Lisinopril or Nisoldipine has similar beneficial effects on progression of diabetics nephropathy in hypertensive type I diabetic patients.

STUDY	DRUG	N=	CONCLUTION
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CONCLUTION-

FURTHER STUDIES AS WELL AS REVIEW WITH HOMOGENEOUS SUBJECT EXPSURE AND OUTCOME COULD UNVEIL DEFINITIVE EVIDENCE REGARDING ROLE OF ACEI AND ARB FOR PREVENTION AS WELL AS FOR TREATMENT OF DIABETIC NEPHROPATHY IN IDDM PATIENT.

THANK YOU