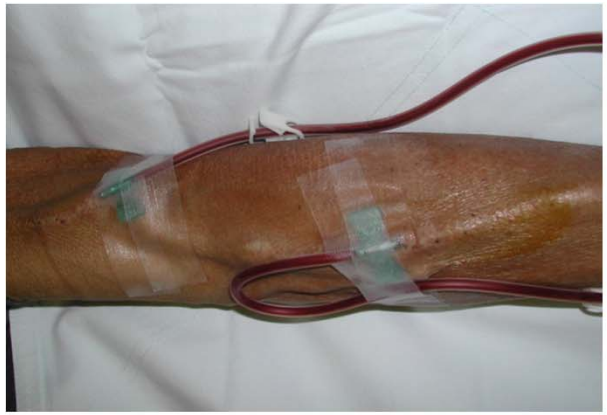
2011년도 대한심장학회 춘계학술대회

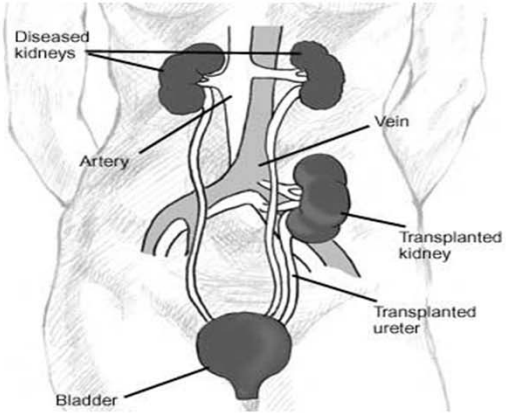
Renal Protection in Hypertensive Patients

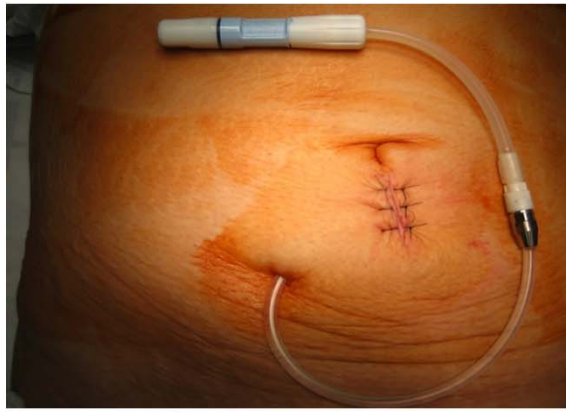
Korea University Medical College, Ansan Hospital

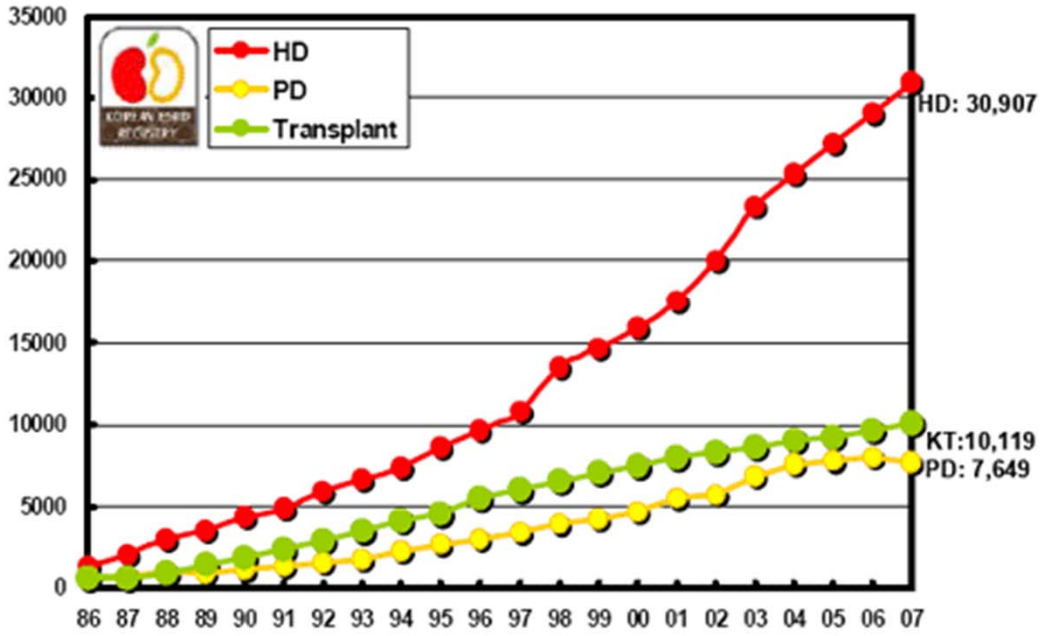
Young Sun Kang

신대체 요법 현황 (대한신장학회)



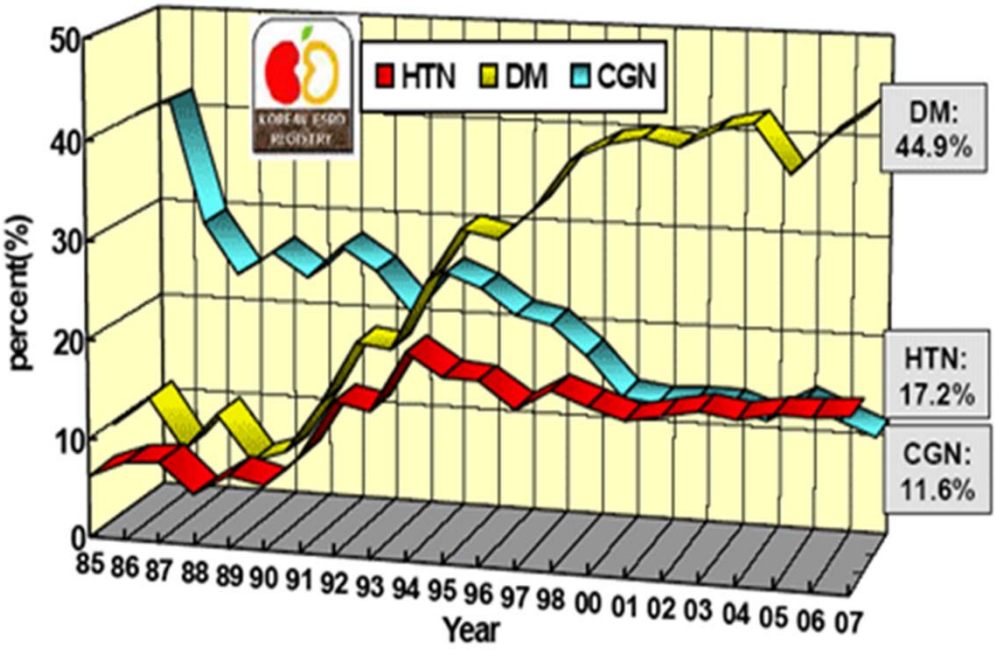






말기 신부전 환자의 원인질환

- 당뇨 (44.9%)
- 고혈압 (17.2%)
- 사구체신염 (11.6%)

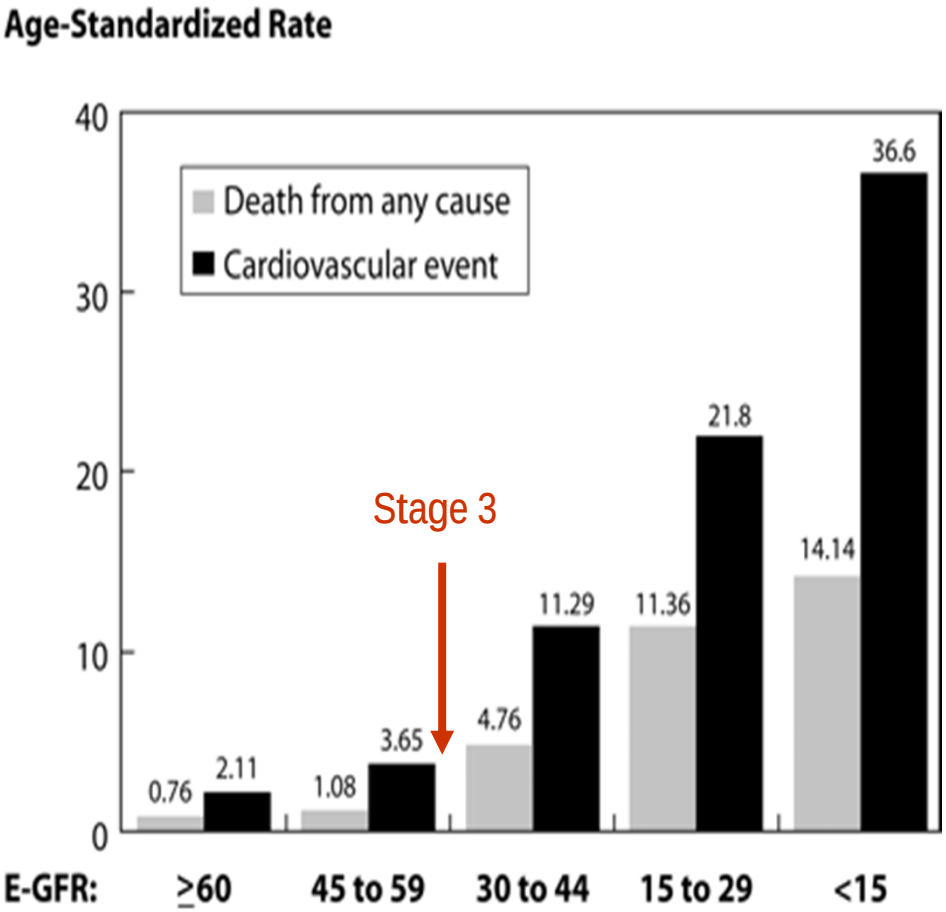


->고혈압성 신질환 (27.5%)

by USRDS(US renal data system,2009)

-> 만성신질환 의 60-100% 가 고혈압.

Hypertension and Kidney



만성 신질환은 심혈관 질환의 독립적인 원인인자이다.

- **Chronic kidney disease is a multiplier of cardiovascular disease**

DuBose, T. D. J Am Soc Nephrol 2007;18:1038-1045

초기 만성신질환 수는 **ESRD** 환자의 **80**배가 넘는다.

Case

- 60y man, worsening peripheral edema
- Coronary disease, Af, type 2 diabetes
- BP 160/100 mmHg
- serum Cr 1.8 mg/dl, urinalysis: prot(+)
- Echo: dilated LV, EF(45%)
- Px. furosemide, β-blocker, ACEi,
  low-dose aspirin, statin, insulin

Contents…

1. Goals for Reduction of BP and Proteinuria
2. Nephroprotective Antihypertensive Therapies

Summary-1

- Hypertension is a strong independent risk factor for ESRD.
- Treatment target for BP reduction is nephroprotective

  < 140/90mmHg (EH, no evidence of renal disease)
  < 130/80 mmHg (CKD and/or diabetes)

Summary-2

- Maximal RAAS inhibition in proteinuria !
  (*** monitor serum Cr, K level)

- Chronic proteinuric nephropathies

  - ACE inhibitors, angiotensin II receptor blockers(ARB)

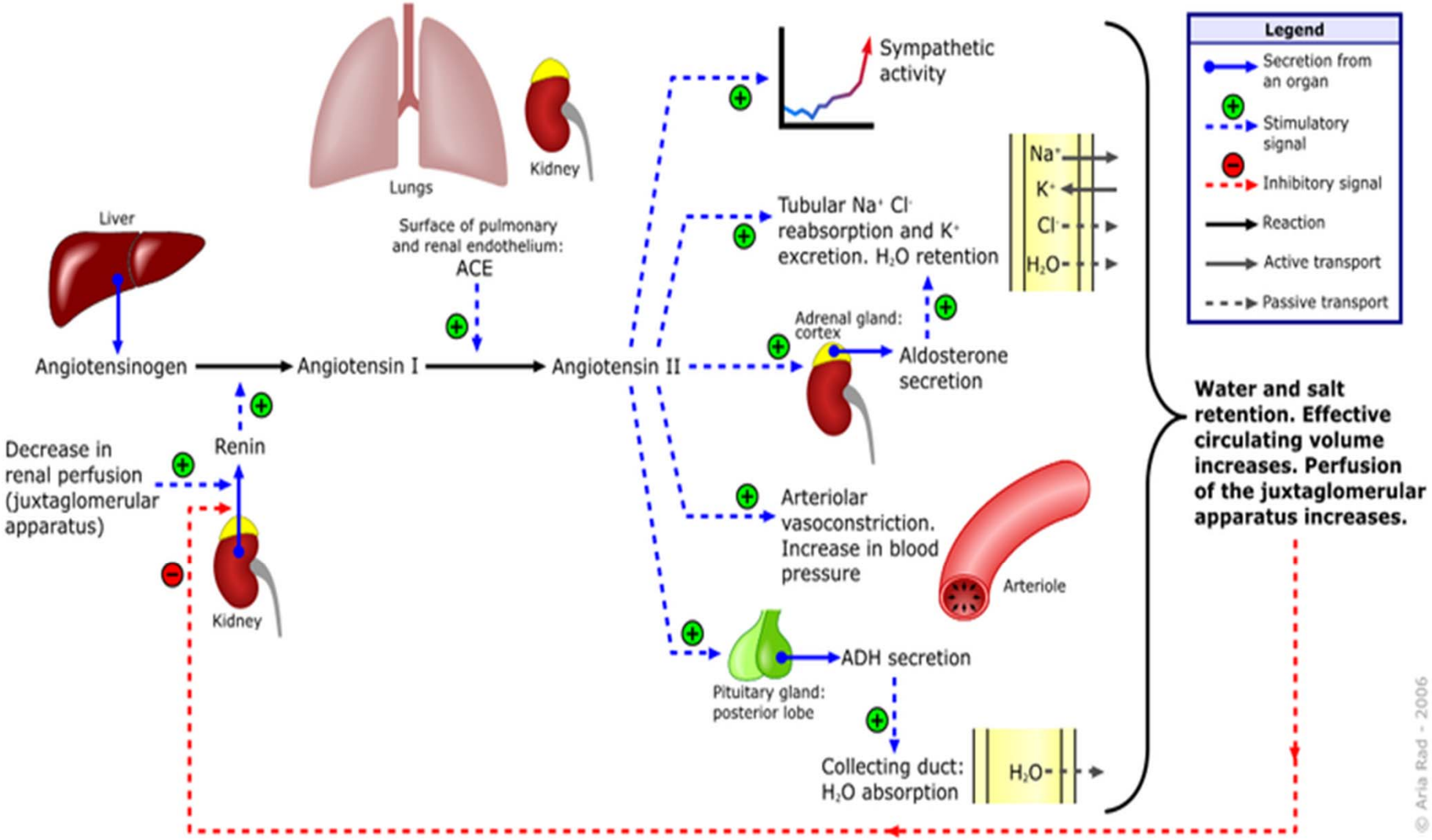
    -> first-line therapy

(nephroprotective effect over other antihypertensive effect)

Summary-3

- No evidence of superior nephroprotection is available for new RAAS inhibitors compared with ACE i and ARB, but encouraging results (add-on therapy)
- Aldosterone antagonists , direct renin inhibitors(DRI)
- CCB, β-blocker, diuretics
- Vitamin D, VDRA

Renin-angiotensin-aldosteron system

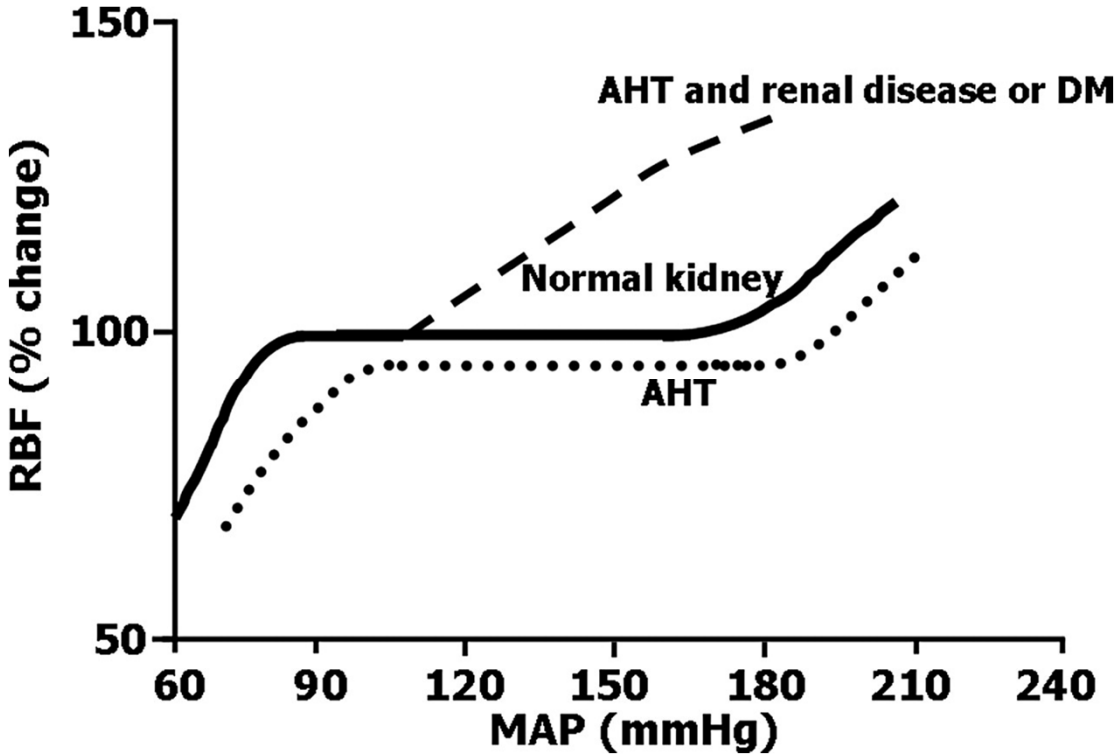


Mechanism of progression

- Systemic hypertension
- Intraglomerular hypertension
- Glomerular hypertrophy ; glomerular growth
- DM, cyanotic heart dis, obesity
- Hyperlipidemia
- Reactive oxygen species
- Cytokines and growth factors
- Proteinuria

Hypertension and Kidney

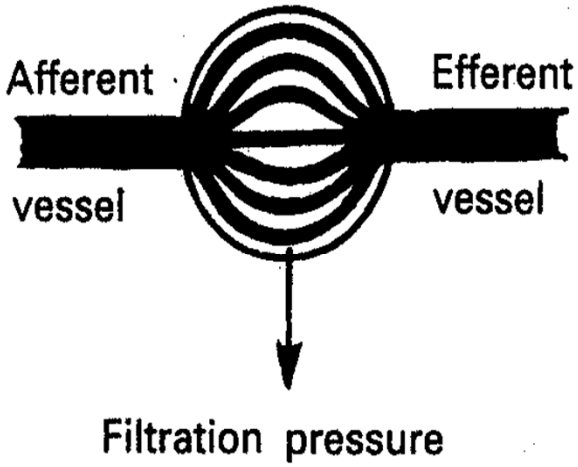
- Relationships between renal blood flow and systemic BP



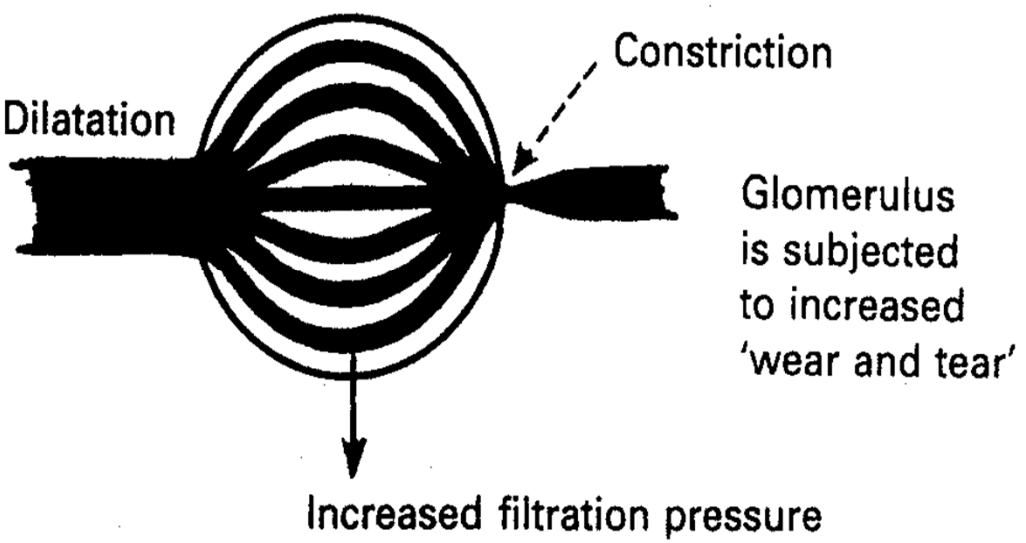
Ravera M et al. JASN 2006;17:S98-S103

Intraglomerular pressure

Normal Glomerulus



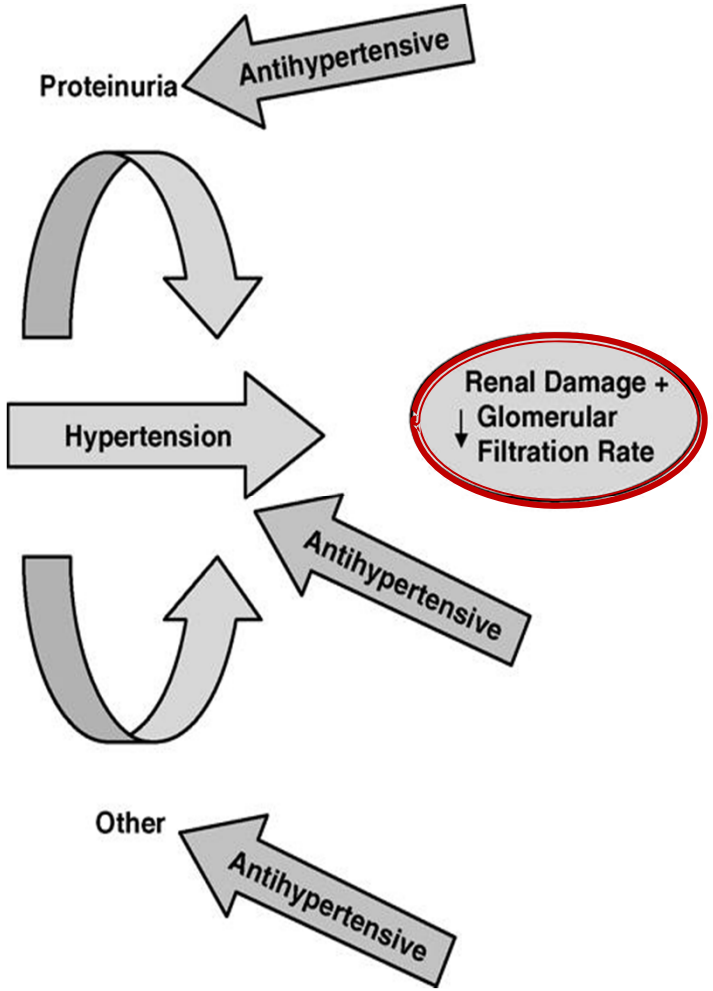
Compensatory hypertrophy

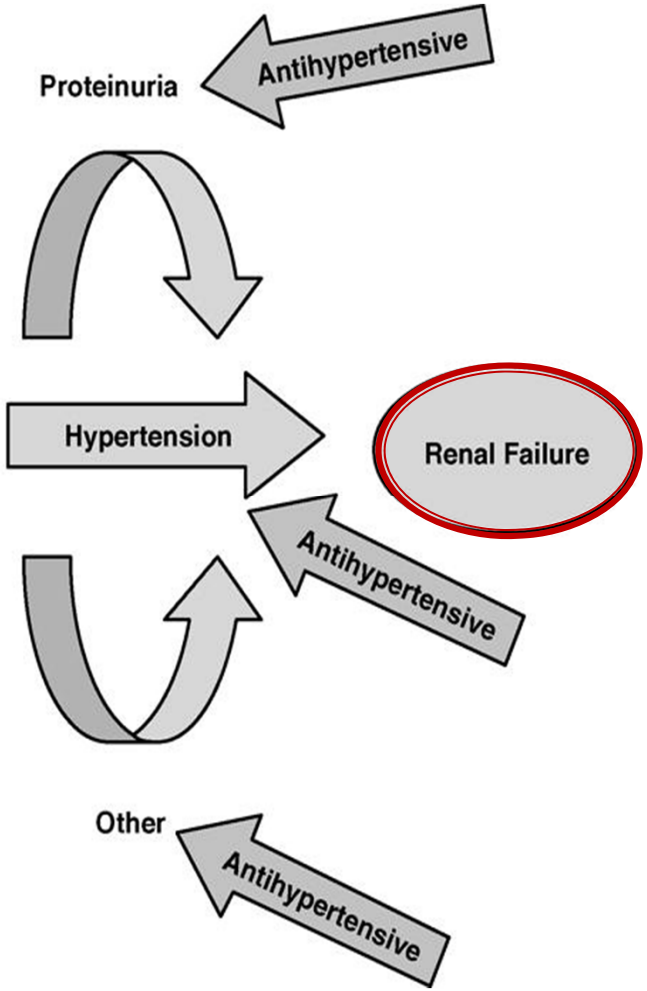


Reducing BP to protect the kidney

Proteinuria

BP control





Albuminuria

- **Microalbuminuria(MA)**

  : 30-300 mg/day
  or 20-200 μg/min
  or dipstick (-/trace/+)

- **Macroalbuminuria**

  : >300 mg/day
  or 200 μg/min

A marker of endothelial dysfunction, which is associated with worsening kidney function

Reducing BP to protect the kidney

- **Macroalbuminuria: reduction > 30% - 39-72% risk reduction for dialysis –** *(Captopril trial,NEJM 1993)(AASK trial –JAMA 2001)(RENAAL,NEJM 2001)(IDNT, NEJM 2001)*

- **Early reduction in microalbuminuria was associated with a greater reduction in CV events –***LIFE trial (2005)*

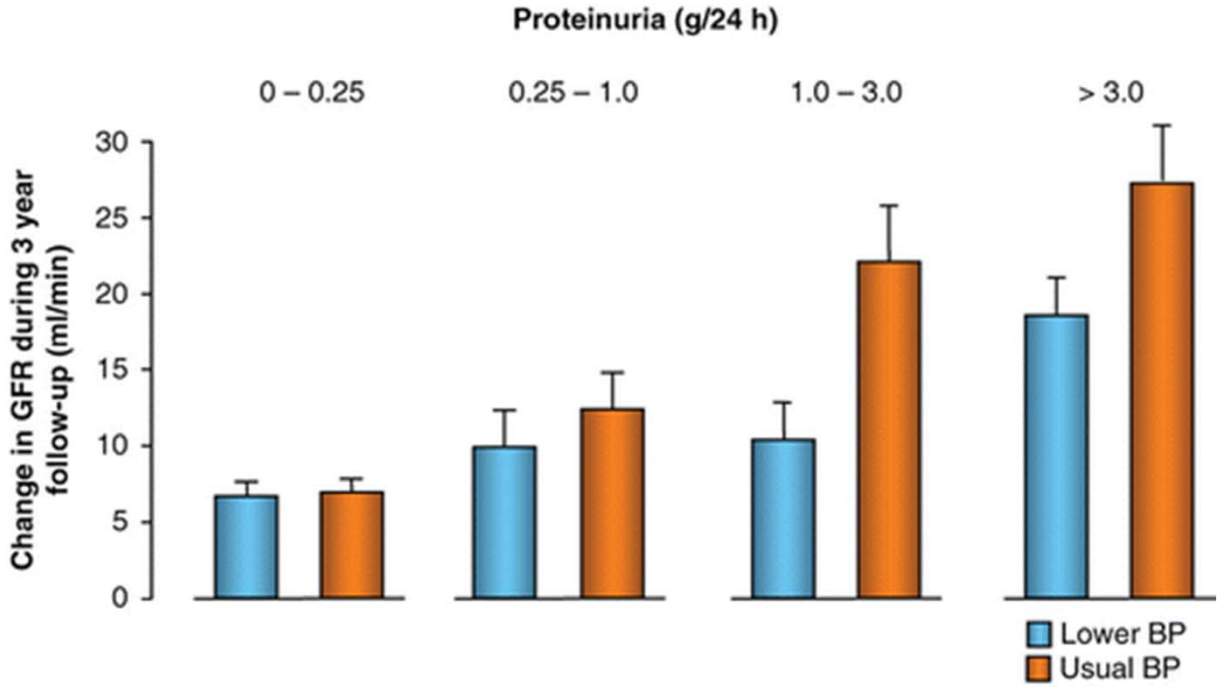
Current published guidelines for goal BP in kidney disease or diabetes

Group	Goal BP (mmHg)	Initial therapy
ADA (2009)	< 130/80	ACE Inhibitor/ARB +diuretic
ESH (2007)	< 130/80	ACE Inhibitor/ARB
KDOQI –NKF (2004)	< 130/80	ACE Inhibitor/ARB +diuretic
JNC 7 (2003)	< 130/80	ACE Inhibitor/ARB +diuretic
Am Diabetes Assoc (2003)	< 130/80	ACE Inhibitor/ARB +diuretic
Canadian HTN Soc (2002)	< 130/80	ACE Inhibitor/ARB +diuretic
Am Diabetes Assoc (2002)	< 130/80	ACE Inhibitor/ARB +diuretic
Natl Kidney Fdn-CKD (2002)	< 130/80	ACE Inhibitor/ARB +diuretic
Natl Kidney Fdn (2000)	< 130/80	ACE Inhibitor +diuretic
British HTN Soc (1999)	< 140/80	ACE Inhibitor
WHO/ISH (1999)	< 130/85	ACE Inhibitor
JNC Vl (1997)	< 130/85	ACE Inhibitor

- **BP reduction : different strategies for pts at different risk!**
- **J –curve: SBP < 120mmHG-> RISK of CV events**

Reducing BP to protect the kidney

- **Blood pressure control, proteinuria, and the progression of renal disease. The (MDRD) modification of diet in renal disease study:** *Ann Intern Med 1995;123:754-62*



Reducing BP to protect the kidney

- **The AASK trial :** *N Engl J Med 2010;363:918-29*
  - **benefit of intensive BP control(< 130/80 mmHg) in CKD with urine Prot/Cr ratio> 0.22**

Renoprotective antihypertensive drugs ?

1. ACE inhibitors
2. Angiotensin II receptor blockers
3. Aldosterone antagonists
4. Renin inhibitors
5. CCB: NDCCB *vs* DCCB
6. β-adrenergic blockers

ACE inhibitors

- Hemodynamic effect through dilation of efferent arterioles, reduced capillary pressure
- Direct molecular effect

- The Collaborative Captopril Study *N Engl J Med 1993;329:1452-62*
  ; The effect of ACE inhibition on type 1 diabetic nephropathy

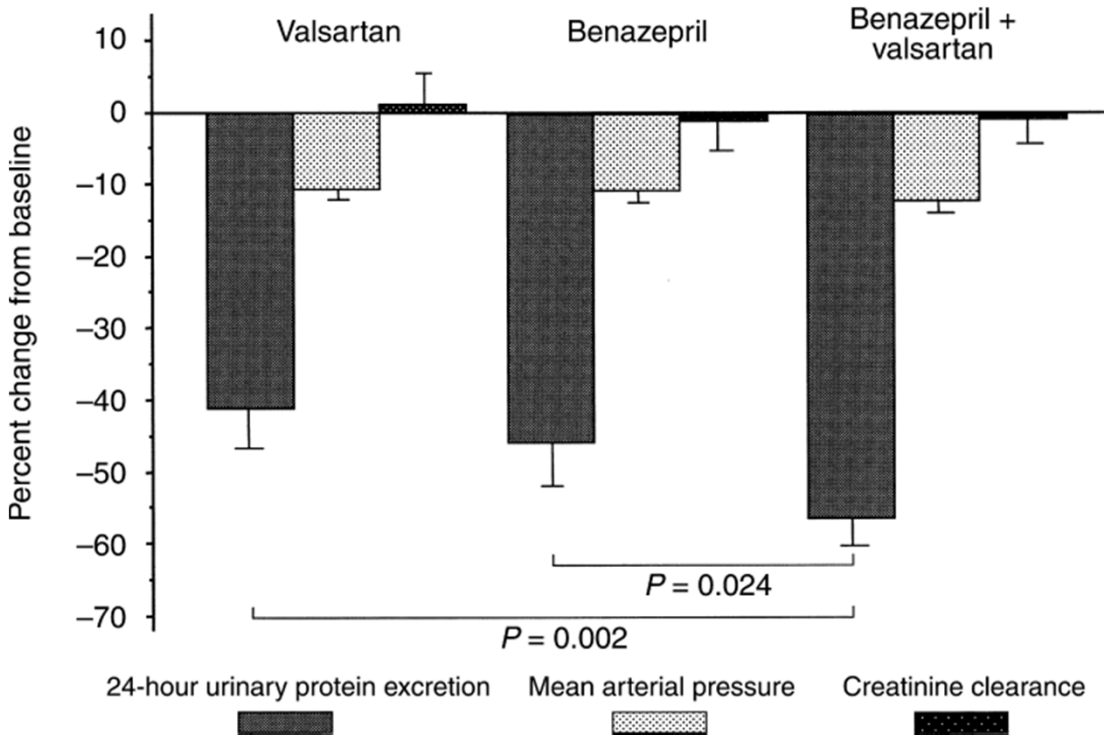
- APRI (ACE inhibition in progressive renal insufficiency) study *N Engl J Med 1996;334:939-45*
  ; Effect of the ACE inhibitor benazepril on the progression of chronic renal insufficiency

Angiotensin II receptor blocker

- RENAAL (reduction of endpoints in type 2 DM with the AT II antagonist losartan) trial: decreased urinary protein excretion(35%), doubling serum Cr, ESRD, or death(22%)

- INDT (irbesartan in diabetic nephropathy trial): reduced doubling serum Cr, ESRD or death

Combination of ACEi and ARB



In humanic chronic nephropathies; Kindey Int 2003;63:1094-103

Combination of ACEi and ARB

- **ONTARGET (ongoing telmisartan alone and in combination with ramipril global endpoint) trial:**

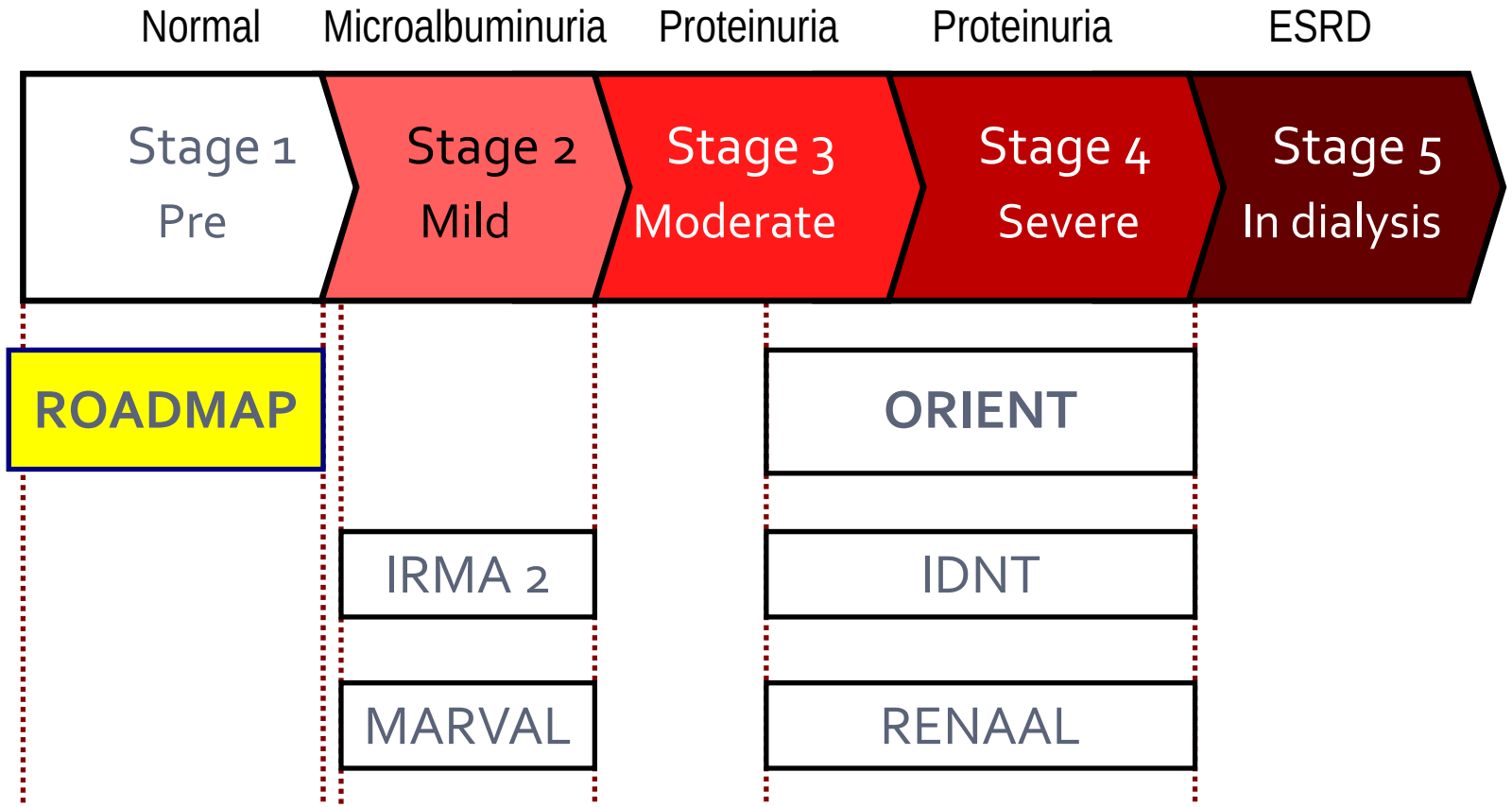
Lancet 2008;372:547-53

- 25,620 pts with atherosclerotic vascular disease
- 6982 diabetic and end-organ damage
- only 4% overt proteinuria
- over 56 m. – no effect on renal outcome,
combined tx -> renal insufficiency, hyperK

ROADMAP

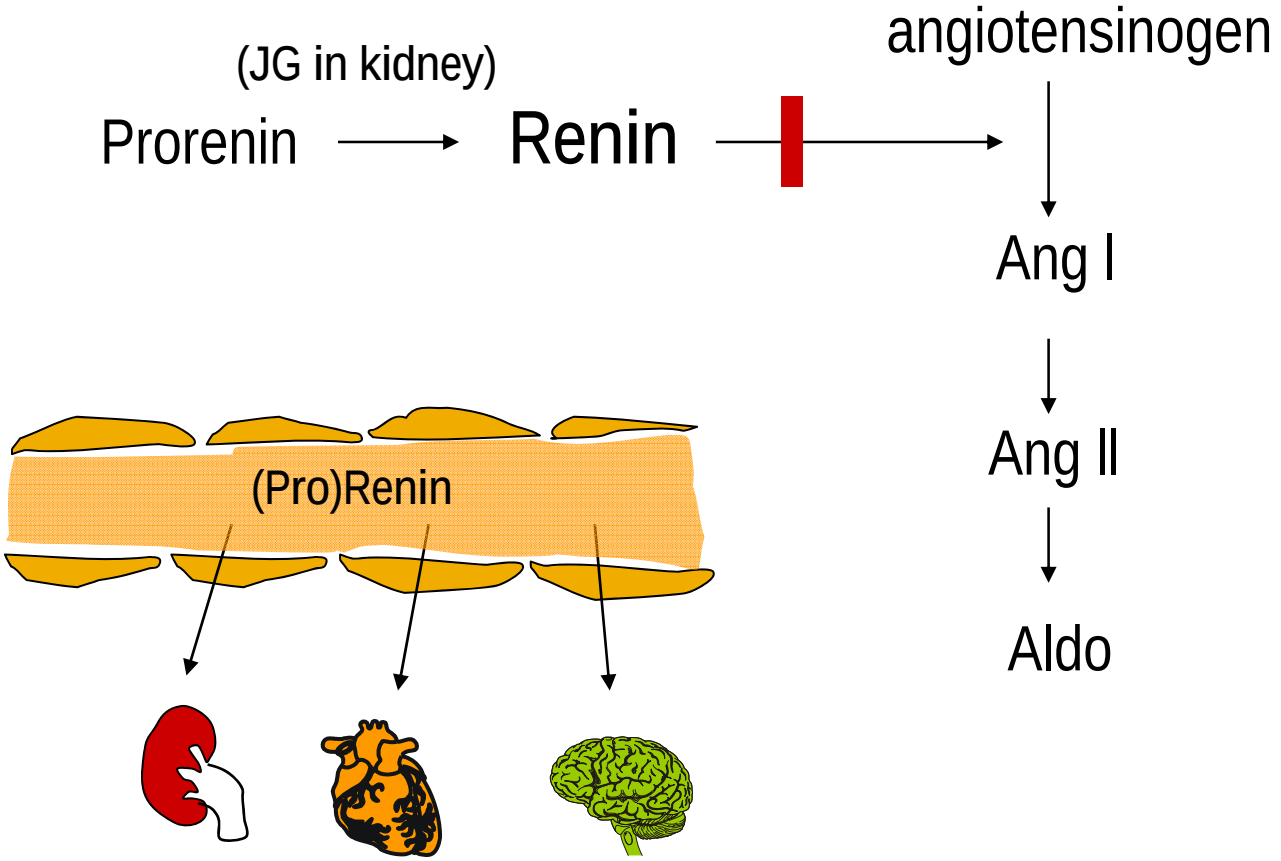
Randomised **O**lmesartan **A**nd **D**iabetes **M**icro**A**lbuminuria **P**revention **S**tudy

- *Diabetic Nephropathy and Outcomes Studies*

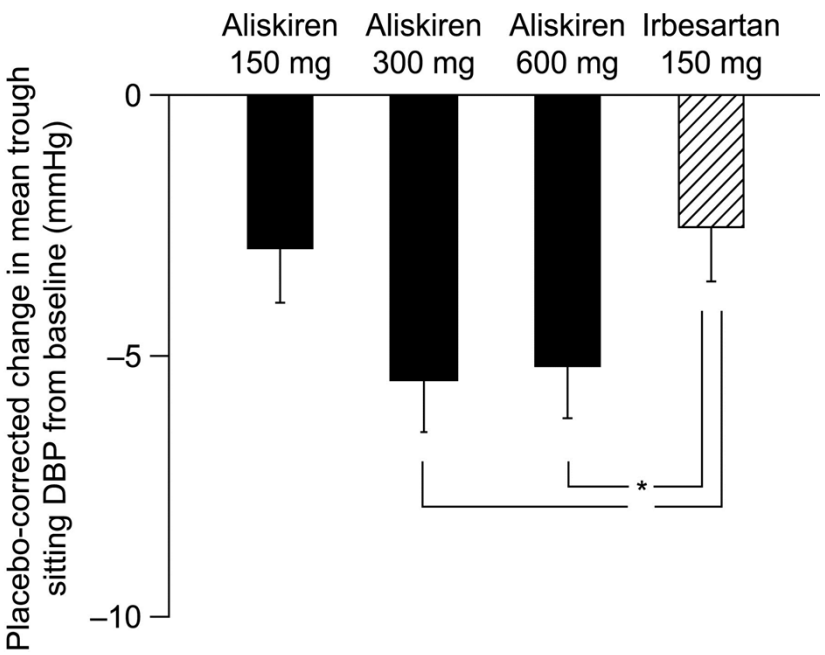


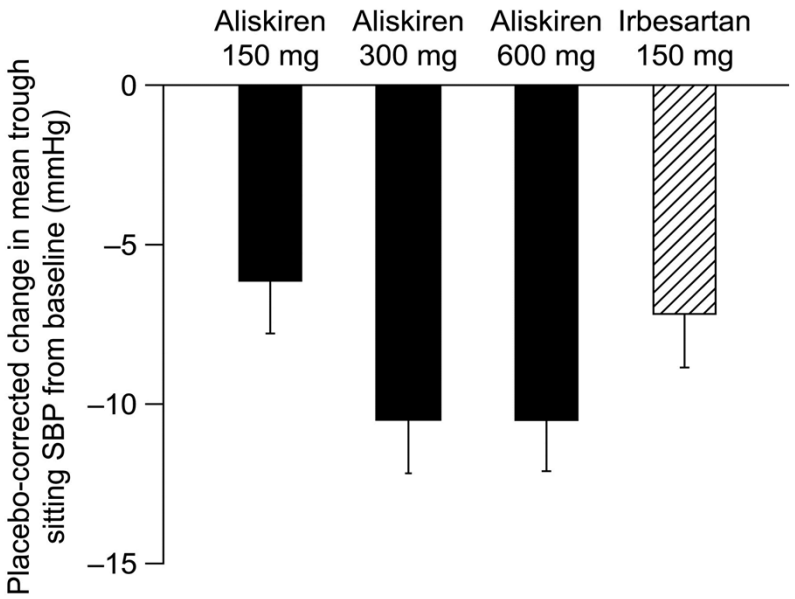
N Engl J Med 2011;364:907-17

Direct Renin Inhibitors



Direct Renin Inhibitors



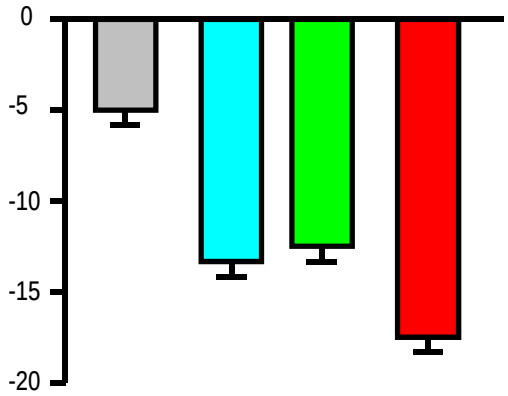


8 weeks

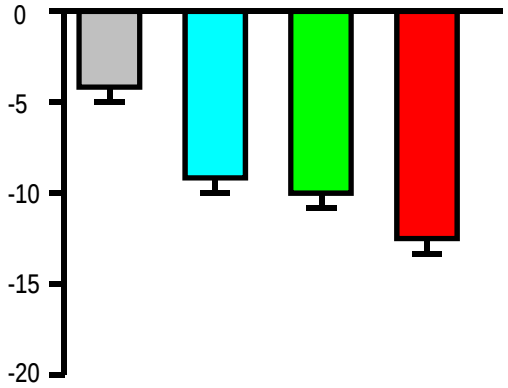
Gradman, A. H. et al. Circulation 2005;111:1012-1018

Direct Renin Inhibitors

Change from baseline mean sitting systolic pressure(mmHg)



Change from baseline mean sitting diastolic pressure(mmHg)



Placebo Aliskiren Valsartan Aliskiren / valsartan

8 weeks

Suzanne Oparil, Steven A Yarows et al. Lancet, 2007;370:221-229

Direct Renin Inhibitors

- **AVOID (aliskiren combined with losartan in type 2 diabetes and nephropathy):** *N Engl J Med. 2008 Jun 5;358(23):2433-46*

  - Renoprotective effects, independent of its blood-pressure–lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended renoprotective treatment

- **ALTITUDE (aliskiren trial in type 2 diabetes)**
  : Cardio-renal endpoints

Aldosterone antagonists

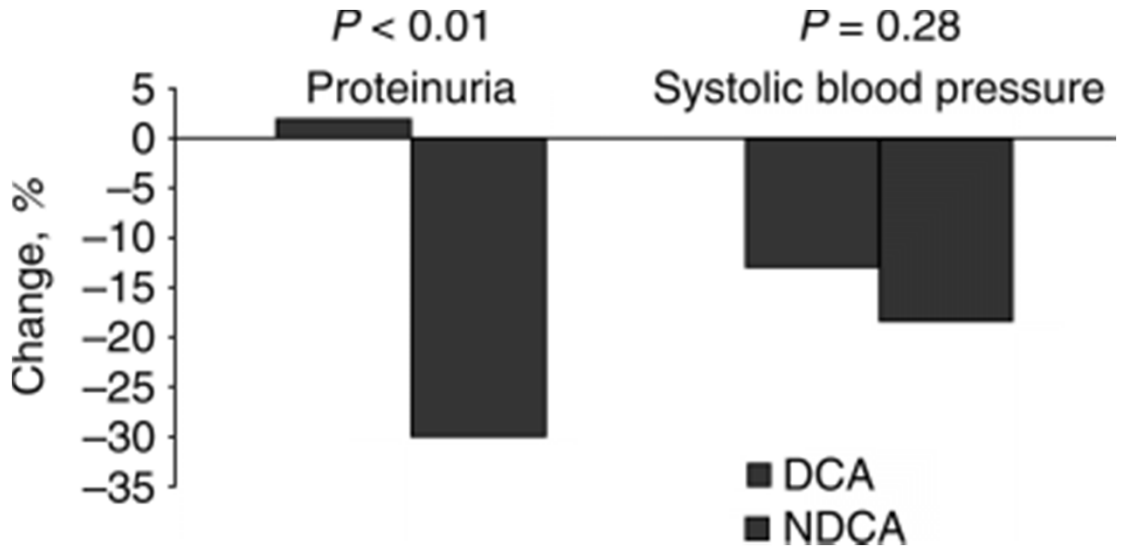
- Heart failure or post-MI
- ASCOT-BPLA: significant BP reduction
- Aldosterone antagonist alone or in combination with ACEi or ARB: proteinuria reduction in type 1, 2 diabetes
- Risk of hyperkalemia

Renoprotective antihypertensive drugs ?

1. ACE inhibitors
2. Angiotensin II receptor blockers
3. Aldosterone antagonists
4. Renin inhibitors
5. **CCB: NDCCB *vs* DCCB (T-type > L-type)**
6. β-adrenergic blockers

CCB: NDCCB *vs* DCCB

- **The change in proteinuria and systolic blood pressure**



Kidney Int . 2004;65:1991-2002

Renoprotective properties of CCB

Type of renal insufficiency	Study (year)	CA type	Comparator	Proteinuria reduction	Decline in GFR/CrCl	Risk of doubling of serum creatine, ESRD or death
Diabetic	Bakris (1996)	Non-DHP (verapamil/diltiazem)	ACE-I (lisinopril)	NS	NS	
	Bakris (1997)	Non-DHP (verapamil SR)	BB (atenolol)	>	<	
	IDNT (2001)	DHP (amlodipine)	Placebo	NS	NS	NS
	IDNT (2001)	DHP (amlodipine)	ARB (irbesartan)	<	>	>
	ABCD (2000)	DHP (nisoldipine)	ACE-I (enalapril)	NS	NS	
	ABCD (2002)	DHP (nisoldipine)	ACE-I (enalapril)	NS	NS	
	RENAAL (2003)	DHP (at baseline or in placebo arm)	No DHP			>
		DHP + ACE-I (at baseline or in losartan arm)	ACE-I (losartan)			<
Non-diabetic	Sys-Eur (2001)	DHP (nitrendipine)	Placebo	>		
	AASK (2001)	DHP (amlodipine)	ACE-I (ramipril)	<	NS	>
	AASK (2002)	DHP (amlodipine)	BB (metoprolol)		NS	
	Nephros (2001)	DHP + ACE-I (felodipine)	ACE-I (ramipril)	NS	NS	
	Syst-Eur (2001)	DHP (nitrendipine)	Placebo	>		
	ALLHAT (2003)	DHP (amlodipine)	Diuretic (chlorthalidone)		<	
	REIN (1998)	DHP (in entire study)	No DHP (in entire study)	<	>	
		DHP (in ACE-I arm)	DHP (in placebo arm)	>	NS	

d/t more impairment in renal autoregulation & glomerular pressure transmission

Gashti CN, Curr Opin Nephrol Hypertens 2004;13:155-161

DCCB (amlodipine)

- **The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial :** *Lancet. 2010 Apr 3;375(9721):1173-81.*

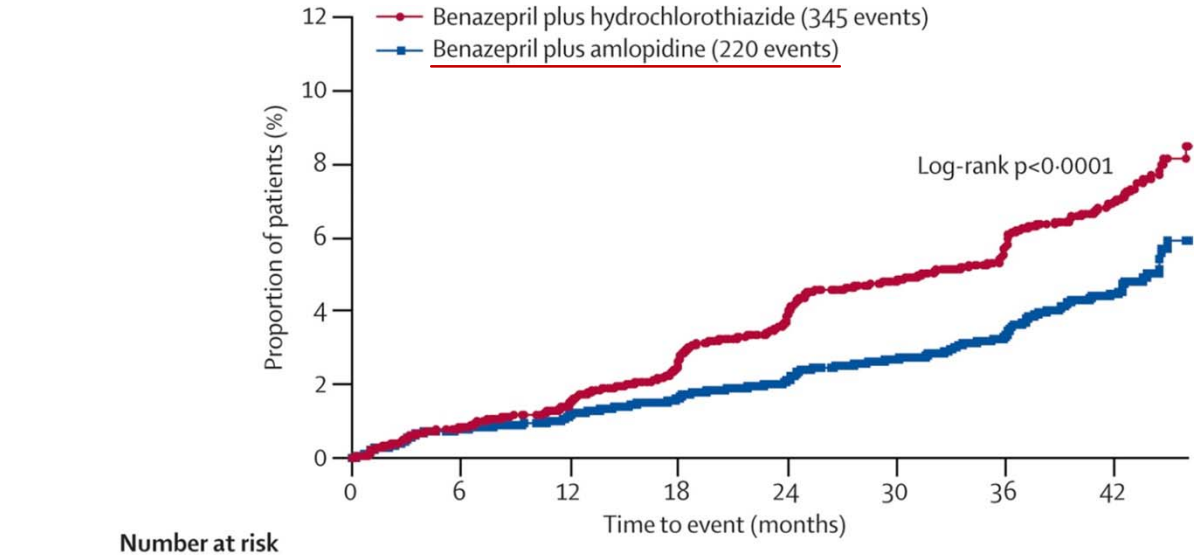
- **Initial antihypertensive therapy with benazepril+amlodipine >benazepril+hydrochlorothiazide ->reducing cardiovascular morbidity, mortality**

- **11,506 patients in five countries (USA, Sweden, Norway, Denmark, and Finland)**
- **terminated early (mean follow-up 2.9 years)**

ACEi+DCCB *vs* ACEi+diuretics

End points : CKD(doubling serum Cr, dialysis, eGFR < 15mL/min/1.73m2)
CV deaths

benazepril +amlodipine *vs* **benazepril +hydrochlorothiazide**



ACCOMPLISH trial ; *Lancet. 2010 Apr 3;375(9721):1173-81*

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β-adrenergic blockers

- α-, β-blockers, carvedilol >> atenolol
- Antihypertensive, antiproteinuric, antioxidative effects
- Reduced risk of CV mortality and morbidity

Salt restriction and diuretics

- Salt restriction enhances the antihypertensive and antiproteinuric efficacy of ACEi and ARB

- Diuretics: thiazides(25-75mg) for GFR>30ml/min
  Loop diuretics for GFR<30ml/min

Treatment of HTN in CKD patients-(1)

- Proteinuria is a risk factor for progression of renal disease and CVD in CKD, it should be monitored to assess response to medications

- Optimal BP goal: < 140/90mmHg, <130/80mmHg in diabetes or renal disease pts

Treatment of HTN in CKD patients –(2)

- Patients with CKD with spot urine protein/Cr ratio of >200mg/g should be treated with moderate to high doses of ACE inhibitors or ARBs even if they are not hypertensive
- In uncontrolled HTN, the addition of CCB and β-blockers should be considered.
- Most patients with CKD should be treated with a diuretic and sodium restriction.

Messages !

- **Acute serum Cr elevation > 35% with ACEi or ARB**
  - Volume depletion
  - Heart failure
  - Renal artery stenosis

- **Hyperkalemia should managed**
  - Low K diet
  - Dosing diuretics
  - Avoid NSAIDs

Case

- 60y man, worsening peripheral edema
- Coronary disease, Af, type 2 diabetes
- BP 160/100 mmHg
- serum Cr 1.8 mg/dl, urinalysis: prot(+)
- Echo: dilated LV, EF(45%)
- Px. furosemide, β-blocker, ACEi,
  low-dose aspirin, statin, insulin