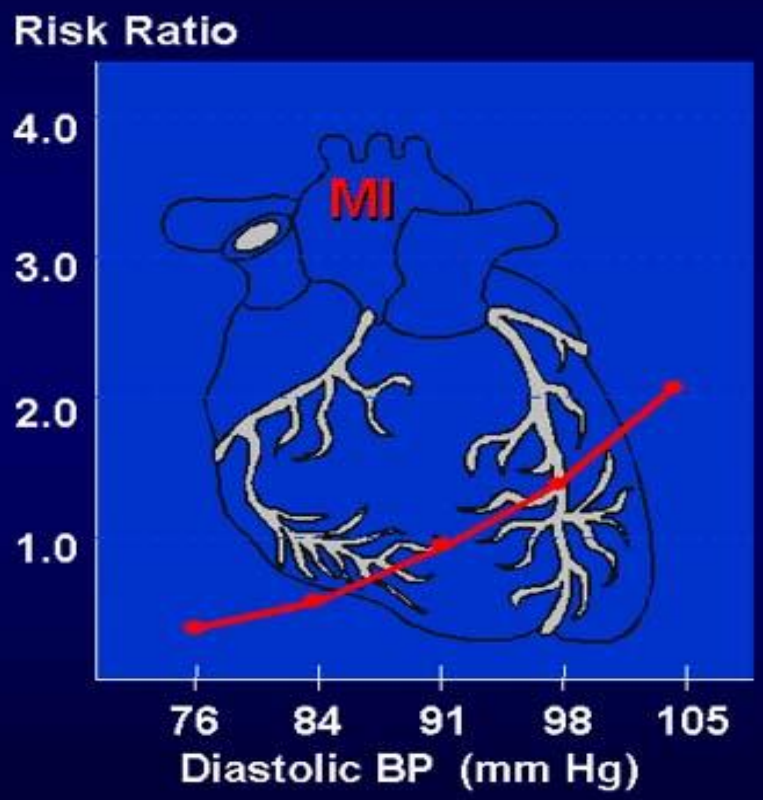
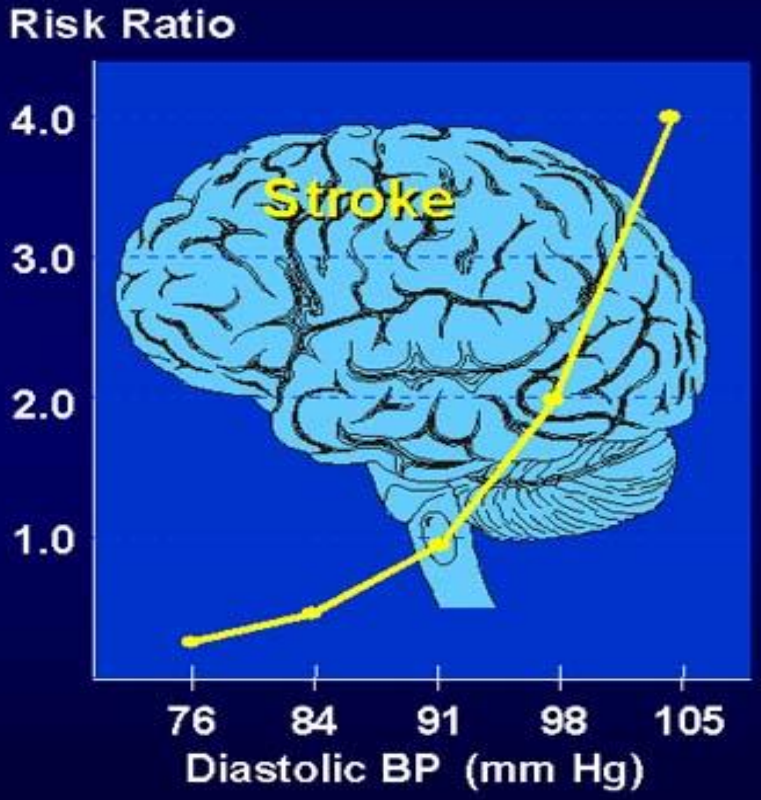
DRUGS IN HYPERTENSION

Principles of drug therapy

Prof Asita de Silva

Stroke, Coronary Heart Disease, and Blood Pressure



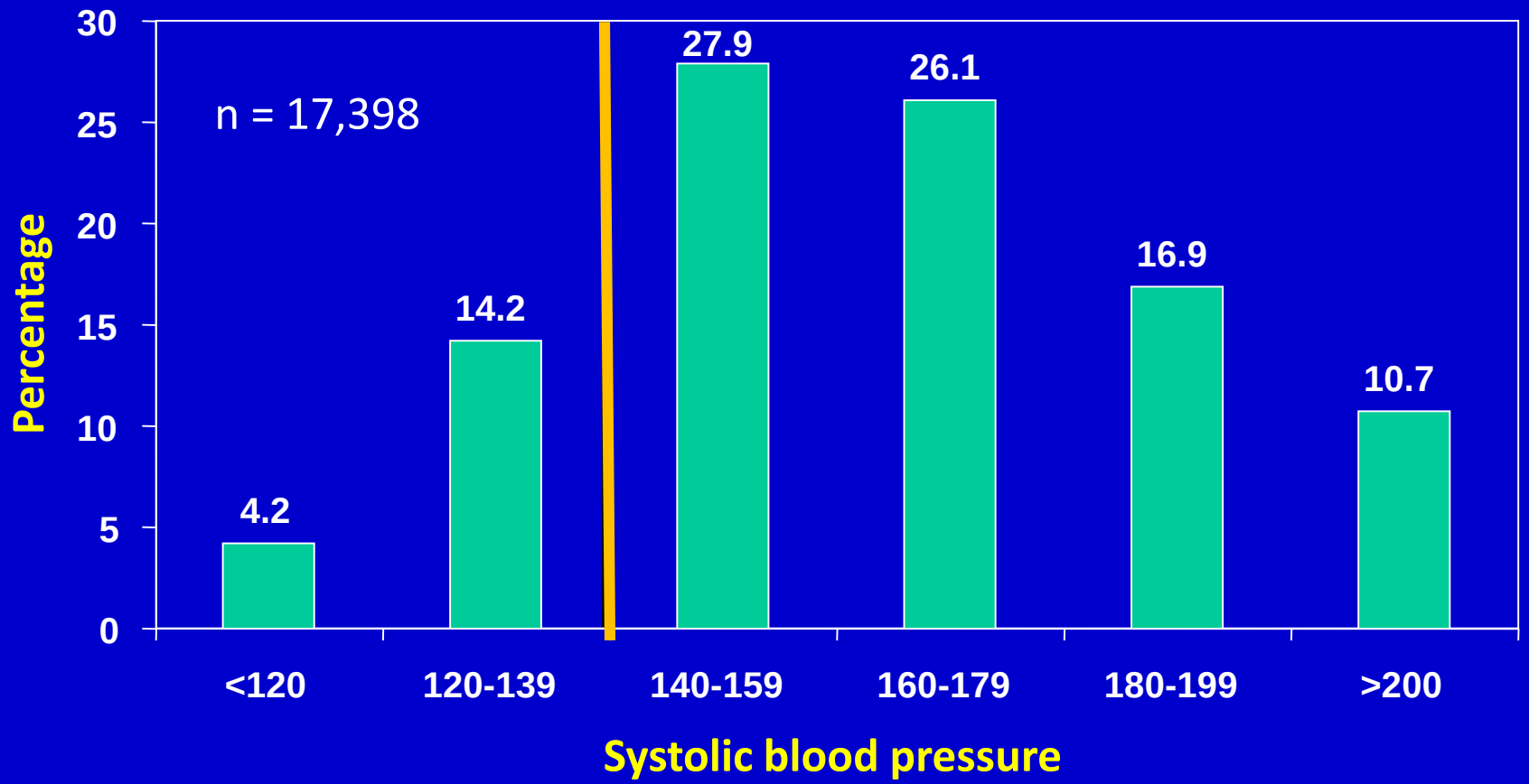


MacMahon S. *J Hypertens*. 1990;8(suppl):239-244.

High systolic BP is associated with similar risk

SBP in acute ischaemic stroke: IST

Hypertension is very common in acute ischaemic stroke affecting ~80% of patients



Leonardi-Bee et al. *Stroke* 2002;33:1315-20

High blood pressure

- Hypertension – one of the most important preventable causes of mortality/morbidity
- Primary / essential hypertension – no cure
- ? Secondary – especially in your hypertensives
- Sri Lanka – 18.8% prevalence
- Generally poorly managed with high CVD morbidity
  - poor compliance
  - monotherapy

Treatment of hypertension

- Non-pharmacological (lifestyle changes)
- Pharmacological

Recent meta analyses have shown …

- Benefits of BP lowering – due to degree of BP control as well as the class of drug used
- Selection of drug – tailored to suit each patient
- Long acting CCBs – **first line therapy**

  Are safe in patients with DM & hypertension

  Free of metabolic adverse reactions

  No need for investigations related to drug effects

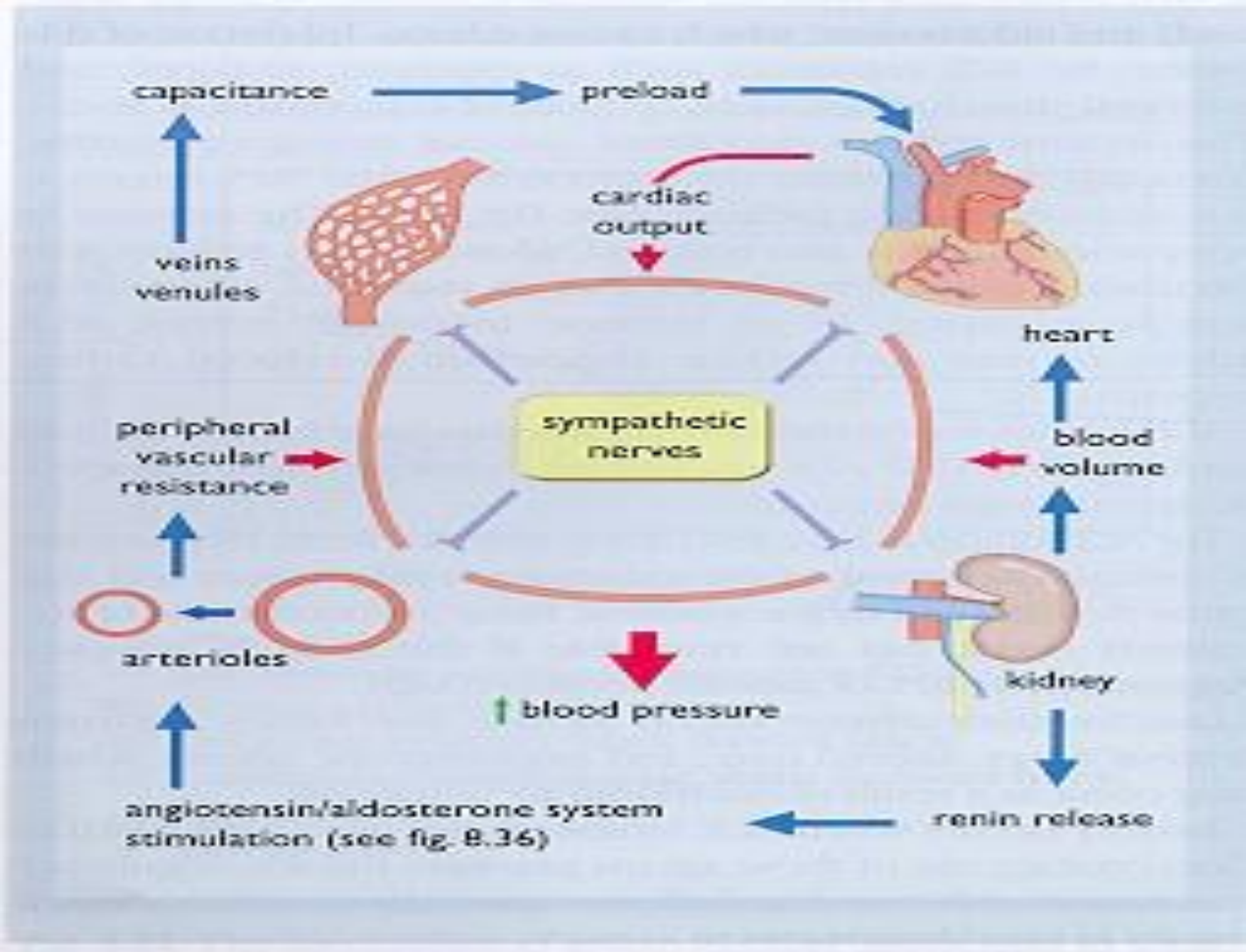
- In the US, only 30-50% hypertensives have adequate BP control
- Many effective drugs are available
- Knowledge of their MoA & sites of action – allows accurate prediction of efficacy & safety
- Rational use of these drugs alone or in combination at the correct doses – lowers BP with minimal risk of serious toxicity

Goals of treatment

- **60 years or older:** <150 / 90 mmHg
- **30-59 years:** DBP <90 mmHg; ? Systolic goal
- **Younger than 30:** ? diastolic goal
- **For these groups:** <140 90 mmHg
- **Hypertensives with DM, non-diabetic CKD:** same goals and thresholds as above

Joint National Committee (JNC) 8; 2014

Regulation of BP

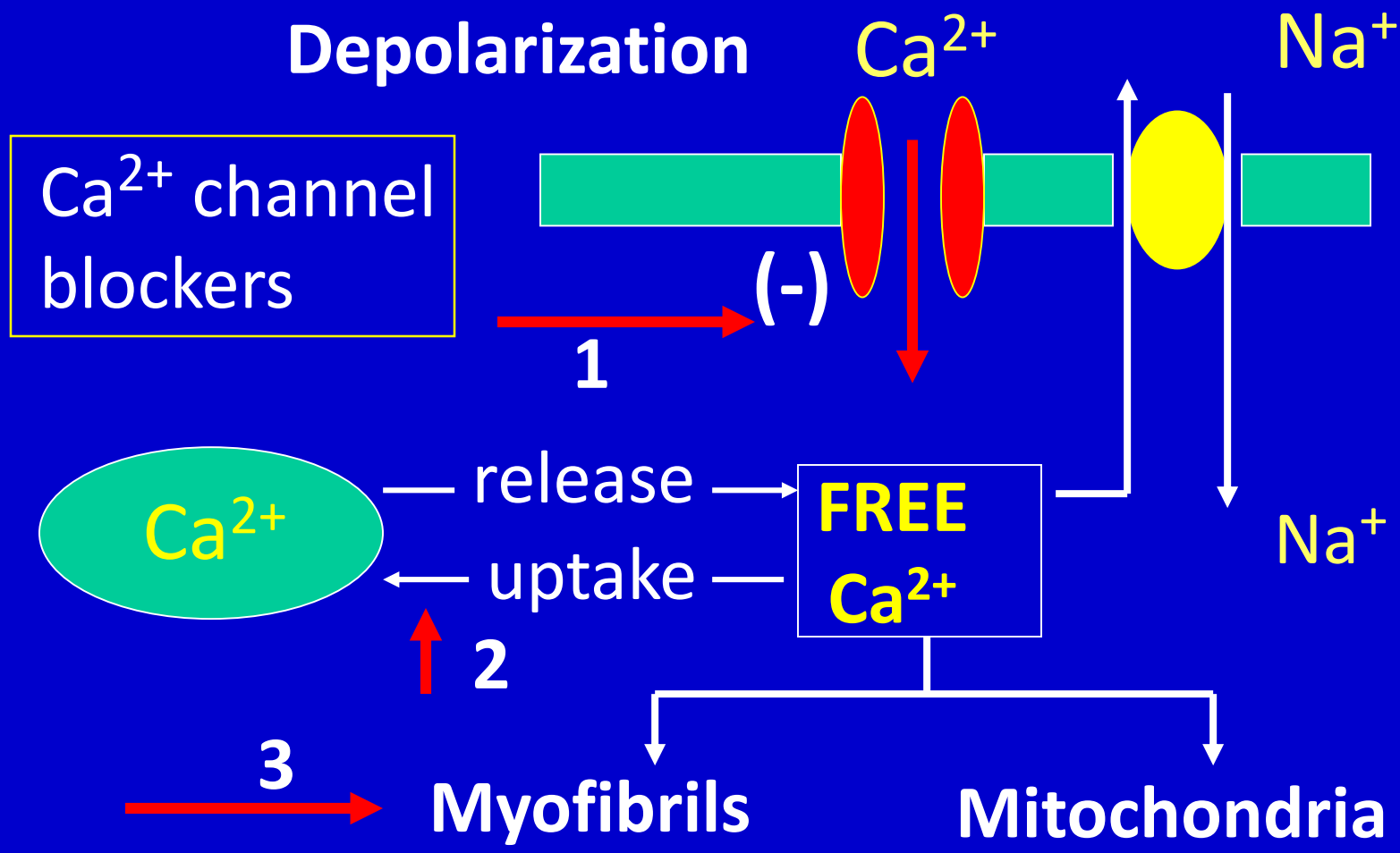


Drug therapy – classes of drugs

- Calcium channel blockers (long-acting)*
- Thiazide diuretics*
- ACE inhibitors*
- AT-II receptor blockers*
- Beta-blockers
- Alpha receptor blockers

* Recommended as first-line by JNC 8; 2014

Ca^{2+} channel blockers - CCB



Ca^{2+} channel blockers

- Mainly affect heart & vascular smooth muscle
- Therefore, in addition to antianginal & antiarrhythmic effects CCBs also reduce peripheral resistance & BP
- Block voltage-depend. L-type Ca^{2+} channels
- Most smooth muscle cells – depend on Ca^{2+} influx for resting tone & contractile response – these cells are relaxed by CCBs
- Given orally as well as parenterally
- Three groups - Verapamil, Diltiazem, Dihyropyridines
- Selectivity between heart & smooth muscle varies

Dihydropyridines

- Acts mainly on vascular smooth muscle - vasodilatation
- Vasodilator effect - mainly arterioles, not veins
- Those with longer half-lives (amlopidine, felodipine) or sustained release preparations (long acting nifedipine) – first line therapy
- Short acting preparations – not recommended
- Reflex tachycardia maintains / increased CO
- Common A/E: flushing, headache, ankle swelling
- Nimodipine – particularly selective for cerebral vessels

Ca^{2+} channel blockers

Clinical uses

- Hypertension
- Angina (variant angina)
- Supraventricular tachyarrythmias
- Migraine prophylaxis

Thiazide Diuretics

- Widely used in uncomplicated hypertension
  - HCT, bendrofluazide, (metolazone)
- Mechanism of action – unknown

  Initially diuresis - reduced blood volume & CO

  Reduced vascular resist 2^{ry} to removal of NaCl

  Opening of K_{ATP} channels - resistant arteries
- Usually given once a day (activity for 12-24 h)

Thiazide diuretics

Adverse effects - ↓K / Na, DM, Gout, impotence, ↑LDL, ↓HDL, ↑renin

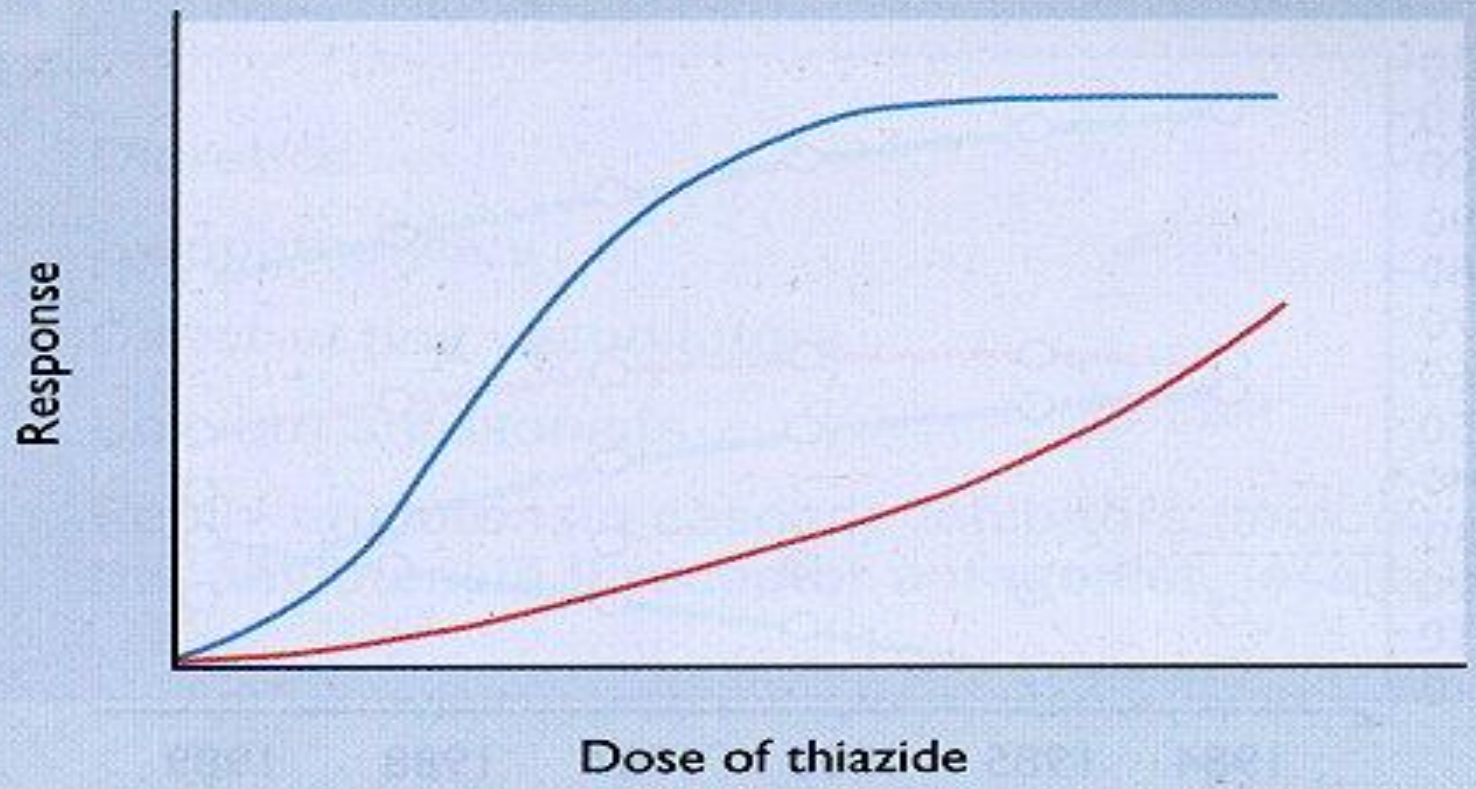
Thiazides - given orally at lowest possible dose

(e.g. HCT 12.5 mg o.d. in the morning)

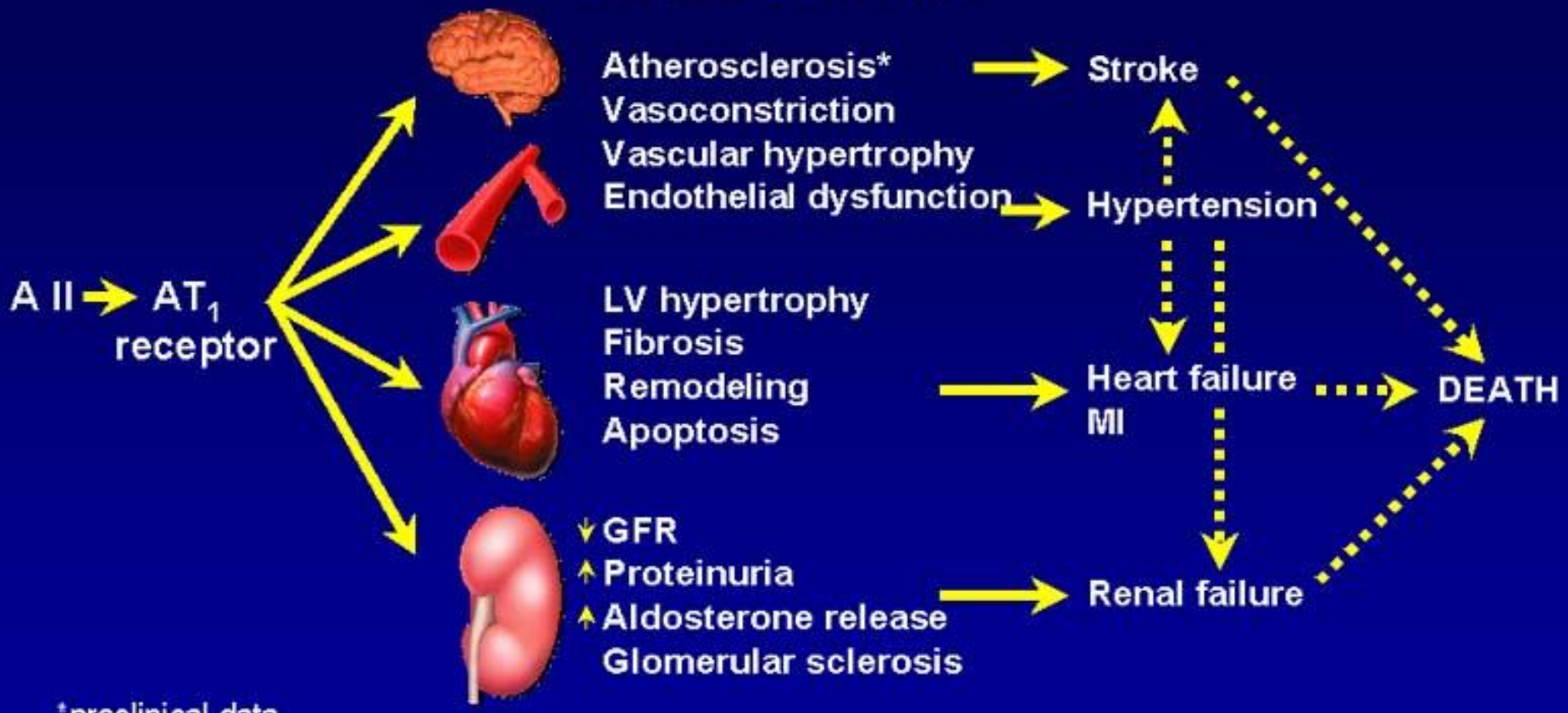
Higher doses don't ↓BP, but ↑adverse effects

If a diuretic not chosen as 1st line - usually indicated as add-on therapy

In severe hypertension – thiazides combined with vasodilators to reduce Na retention


Response
Dose of thiazide
Antihypertensive action
Kaliuretic action

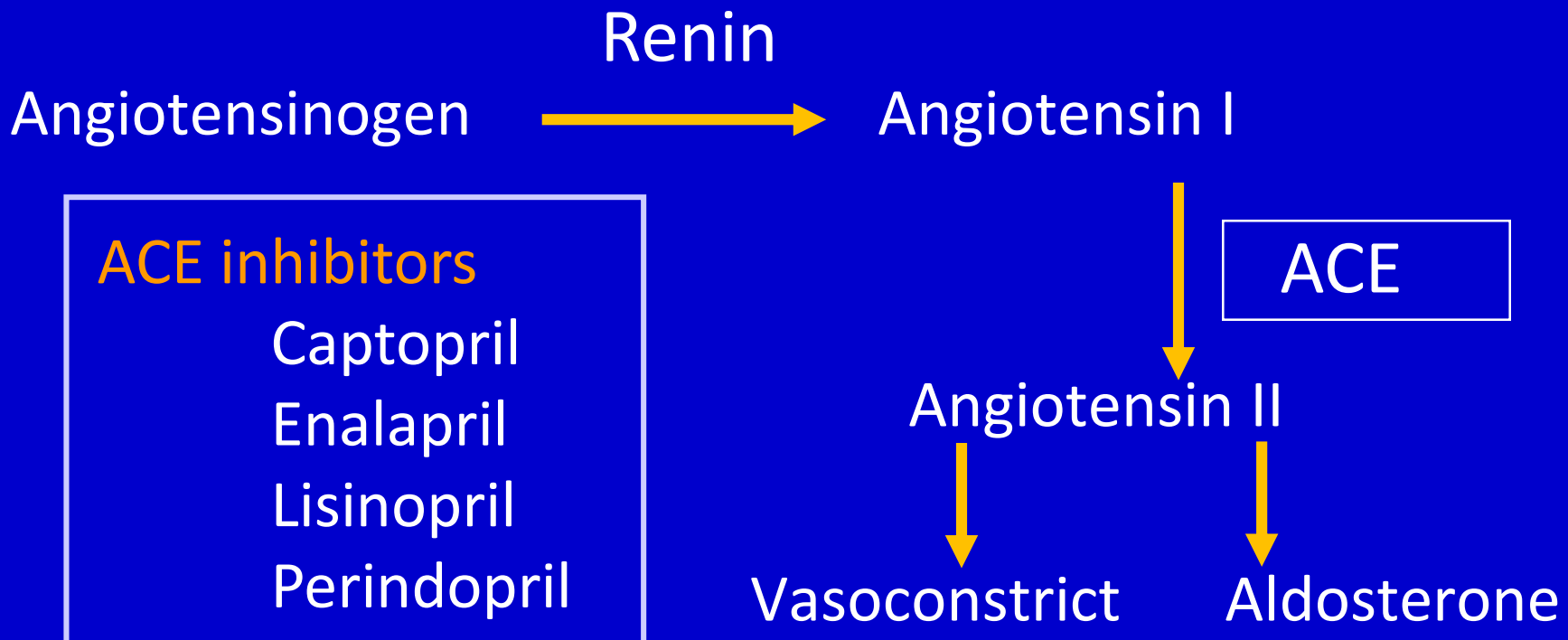
Angiotensin II Plays a Central Role in Organ Damage



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

Adapted from Willenheimer R et al *Eur Heart J* 1999; 20(14): 997–1008, Dahlöf B *J Hum Hypertens* 1995; 9(suppl 5): S37–S44, Daugherty A et al *J Clin Invest* 2000; 105(11): 1605–1612, Fyhrquist F et al *J Hum Hypertens* 1995; 9(suppl 5): S19–S24, Booz GW, Baker KM *Heart Fail Rev* 1998; 3: 125–130, Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories 1999: 1682–1704, Anderson S *Exp Nephrol* 1996; 4(suppl 1): 34–40, Fogo AB *Am J Kidney Dis* 2000; 35(2):179–188

Drugs acting on R-A system



ACE inhibitors
- Captopril
- Enalapril
- Lisinopril
- Perindopril

Angiotensin RB
- Losartan
- Valsartan
- Candesartan
- Telmisartan

ACE inhibitors

- Dilate capacitance & resistance vessels
  - reduce cardiac load & BP
- Clinically used in
  - Hypertension
  - Cardiac failure (AT II causes LVH)
  - MI (especially when HF is present)
  - Diabetic nephropathy (types I & II)

ACE inhibitors & BP

- Small fall in BP of normal people
- Large fall in hypertensives (with increased renin)
- First-line – patients aged ≥18 years with CKD
- Act mainly on angiotensin-sensitive vascular beds
  - kidney, heart & brain
- Selectivity useful - perfusion to vital organs
- Renal artery stenosis is an exception to this

Adverse effects

- Dry cough (? due to bradykinin)
- Hyperkalaemia, proteinuria – investigations done at initiation of drug therpay
- Hypotension - especially with first dose

Contraindications

- Renovascular disease (renal artery stenosis)
- Pregnancy
- Hypersensitivity
- Aortic stenosis

Effects of A II at AT_1 and AT_2 Receptors

AT_1

Sensitive to blockade by ARBs

- Vasoconstriction
- Aldosterone release
- Oxidative stress
- Vasopressin release
- SNS activation
- Inhibits renin release
- Renal Na^+ & H_2O reabsorption
- Cell growth & proliferation

AT_2

- Vasodilation
- Antiproliferation
- Apoptosis
- Antidiuresis/antinatriuresis
- Bradykinin production
- NO release

Siragy H. *Am J Cardiol.* 1999;84:3S-8S.

Angio II (AT 1) receptor blockers

Losartan / Valsartan / Candesartan

- Theoretically more effective than ACEIs – more complete inhibtion of AT II
- Similar efficy to ACE inhibitors in patients with HF and chronic kidney disease
- Less adverse effects - useful in those who develop cough with ACEIs
- Usually given orally once daily

Beta-receptor antagonists

- Not widely recommended as first-line treatment
- Reduces BP gradually in hypertensives
- Mechanism of action - complex
  - reduction in cardiac output:
  - reduction in renin release
  - reduced central sympathetic activity
  - block pre-synaptic beta receptors – reduce release of NA

Beta blockers

Propranolol, atenolol, metoprolol, carvedilol

- More cardio-selective drugs preferred
- Atenolol (b_1 selective) preferred to propranolol
  - less effect on airway beta receptors
  - convenient once daily dosing
  - water soluble; less CNS related adverse effects
- Trend to use lower doses - less adverse effects
- Recent studies – metoprolol more effective in preventing complications of hypertension

Beta-blockers (adverse effects)

- Bronchoconstriction - mainly in asthmatics
- Fatigue
- Cardiac failure
- Bradycardia - life threatening heart block
- Hypoglycaemia - avoid in uncontrolled DM
- Cold extremities (less with beta-1 selective)
- Withdrawal syndrome – not discontinued abruptly

Beta-blockers: clinical uses

- Hypertension, Angina
- Following MI / heart failure – Carvedilol
- Cardiac arrhythmias
- Thyrotoxicosis (e.g. before surgery)
- Migraine prophylaxis
- Anxiety, Benign essential tremor
- Glaucoma - Timolol as eye drops

alpha$_1$-receptor antagonists (Prazosin)

- Vasodilatation - block NA at postsynaptic a_1-receptors
- May be used with other anti-hypertensives
- Potentially useful in hypertensives with CHF & prostate hyperplasia
- ↓ LDL, VLDL, total TGs & ↑ HDL - beneficial effects in coronary artery disease
- Doxazosin / terazosin - require only o.d. dosing
- Main adverse effects - postural hypotension, dizziness, fatigue, ejaculation failure, priapism

Other anti-hypertensive drugs

- Methyldopa - pregnancy related hypertension
- K channel activators - diazoxide, minoxidil, pinacidil, cromakalim
- Nitroprusside - for hypertensive emergencies & for controlled hypotension in surgery

  - Very short half life: given as an i.v. infusion
- Hydralazine - acts mainly on arteries/arterioles SLE-like syndrome limits its use

Hypertensive emergencies

- BP has to be lowered urgently
- Hospitalized if:
  - Hypertensive encephalopathy
  - Acute LVF (due to hypertension)
  - Aortic dissection
  - Pregnancy induced - eclampsia
- Nitroprusside, hydralazine (pregnancy), GTN infusion, CCB i.v. (nicardipine , clevidipine)

Guidelines for therapy

- Lifelong therapy
- Quality of life
- Economic considerations
- Frequent assessment for end-organ damage
- Concomitant diseases
- Drug interactions - e.g. NSAIDs
- Use recommended / appropriate drugs alone or in combination