Calcium Channel Blockers

- MOA: smooth muscle relaxation (vasodilation)
- negative inotropic and chronotropic effects
- 3 classes:
  - benzothiazepines (diltiazem)
  - phenylalkylamines (verapamil)
  - dihydropyridines (nifedipine, amlodipine)
- all have similar antihypertensive effects
- Reflex neurohormonal or sympathetic activation

Calcium Channel Blockers

- Benzothiazepines and phenylalkylamines
  - (Diltiazem and Verapamil)
  - coronary and systemic vasodilation,
  - ↓ myocardial contractility, HR, and AV node conduction
- Dihidropyridines
  - (Amlodipine, felodipine, nifedipine, etc.)
  - coronary and systemic vasodilation,
  - 0 or ↓ myocardial contractility,
  - 0 or ↑ HR, no effect on AV node

Calcium Channel Blockers

- pharmacotherapy issues
  - increase in mortality (?)
    - possible ↑ risk of MI with short-acting CCB (primarily nifedipine)
  - Studies show decrease mortality in hypertension similar to conventional drugs
    - INSIGHT and NORDIL studies (Lancet 2000; 356:359-65;366-72.)

Calcium Channel Blockers

Advantages

- **>** response in elderly for systolic hypertension
- effective in CAD, reducing angina sx
- Once daily dosing
- additive BP-lowering effects with ACEI, BB
- neutral on lipids/glucose
- Reduction in CV mortality similar to conventional therapy

Calcium Channel Blockers

Disadvantages

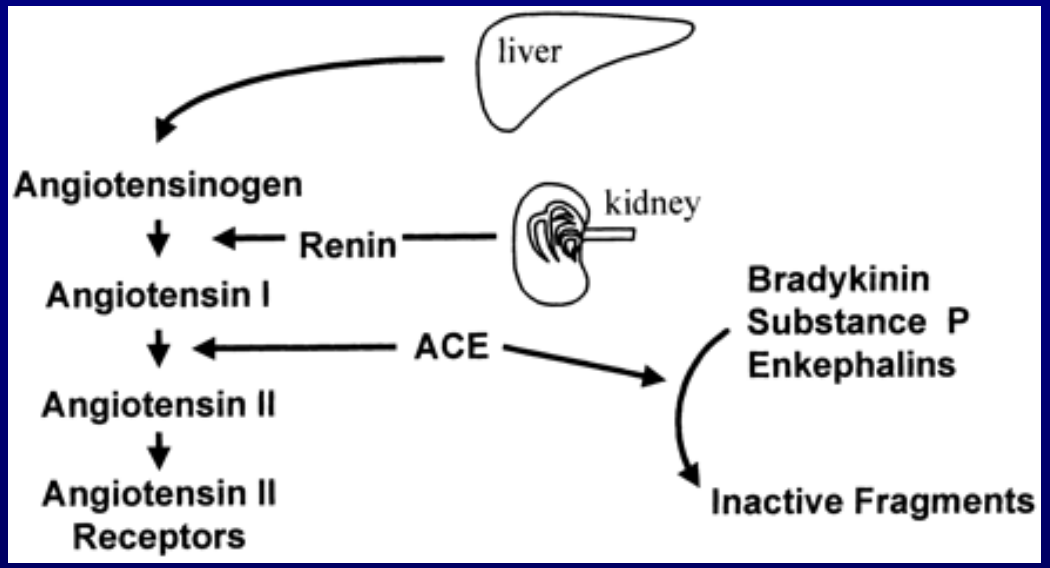
- Increase MI with short-acting agents - FDA warning
- Generally more expensive
- Caution in heart failure (only use amlodipine, felodipine)
- SE:
  - constipation,bradycardia, AV block, CHF (verapamil, diltiazem)
  - edema, dizziness, HA, tachycardia (especially dihydropyridines)
  - gingival hyperplasia (nifedipine)

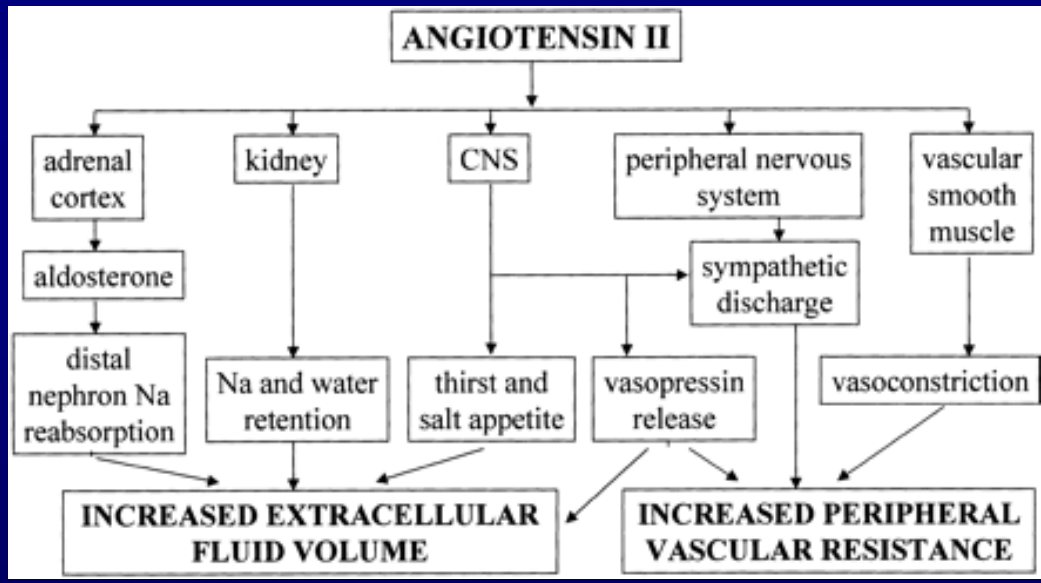
CCB Drug Interactions

- Diltiazem – CYP3A4 and PGP inhibitor
- Verapamil – CYP3A4 and PGP inhibitor
- Nifedipine – CYP3A4 substrate
- Amlodipine – CYP3A4 substrate
- Felodipine – CYP3A4 substrate

ACE Inhibitors

- MOA: inhibits conversion of Ag I to Ag II





e.g. ramipril, enalapril, lisinopril, benazepril, etc.

ACE Inhibitors

- promote regression of left ventricular hypertrophy
  - Improve systolic and diastolic function
- pharmacotherapy issues
  - Decrease mortality in CHF (symptomatic and asymptomatic)
  - Decrease progression of DM nephropathy
  - Decrease progression of CKD
  - Decrease mortality from CV causes, MI, stroke in high-risk patients

Drug Interactions - ACE Inhibitors

- Do not use salt substitutes with ACE-I (they contain potassium)
  - Instruct patients to use Mrs. Dash or herbs
- Careful using concomitantly with K^+ supplements, K^+ sparing diuretics, spironolactone

ACE Inhibitors

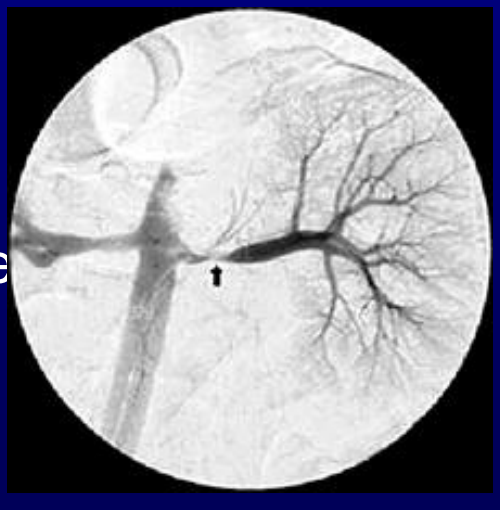
Advantages

- highly effective in whites and younger pts
  - ↑ response in African Americans with diuretic
- neutral on lipids
- DM nephropathy - renal protective
- improve survival in heart failure
- ↓ mortality in hypertension similar to conventional therapy (CAPP, ALLHAT, STOP-2 studies)

ACE Inhibitors

Disadvantages

- ↑ hypotensive response in renovascular HTN, CHF, hypovolemia, addition of diuretic
- cough (~10%)
  - consider switching to ARB
- contraindicated in:
- - pregnancy
- - bilateral renal arte
- stenosis (RAS)

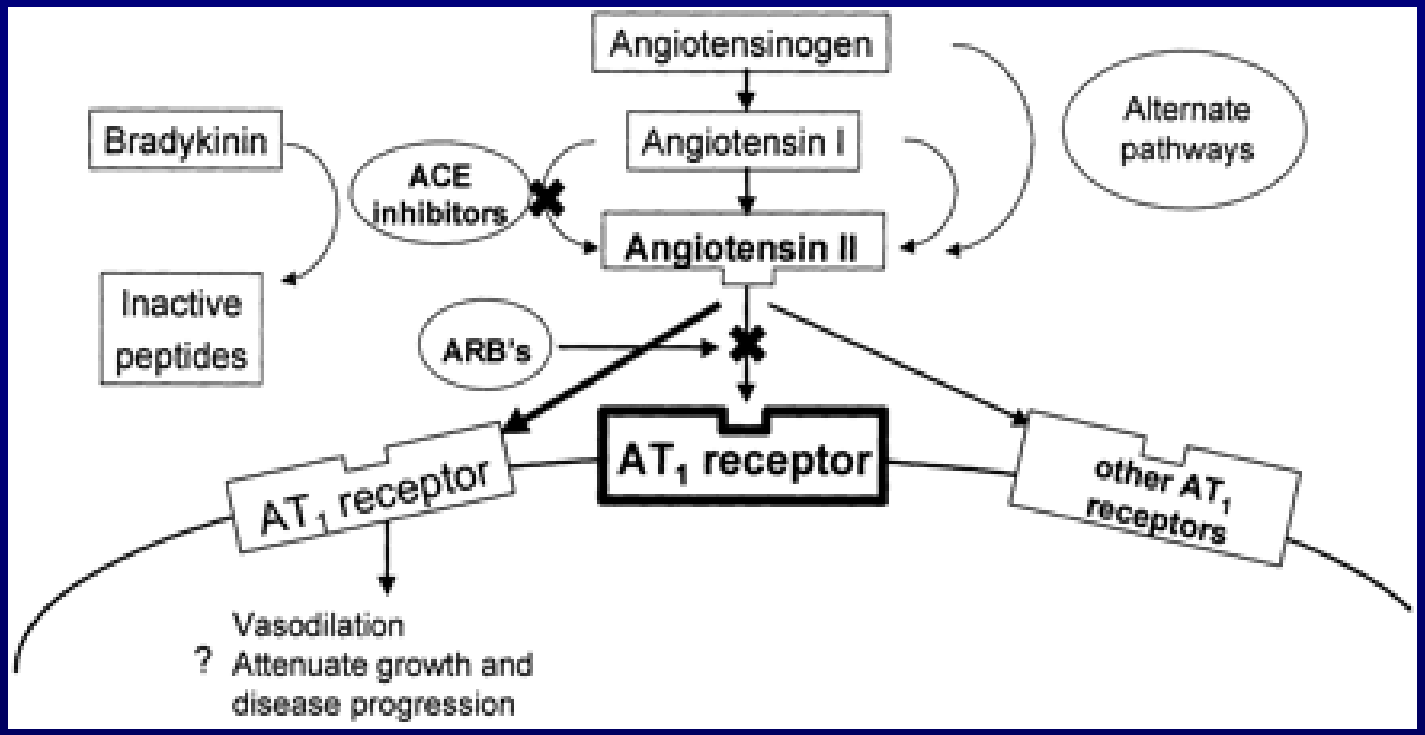


- SE:
  - rash,
  - angioedema,
  - hyperkalemia,
  - Acute kidney injury (if bilateral RAS present)
- Monitoring:
  - serum creatinine, K+
    - At baseline
    - After 2 weeks
    - Then periodically

Arch Dis Child 2003;88:938-939

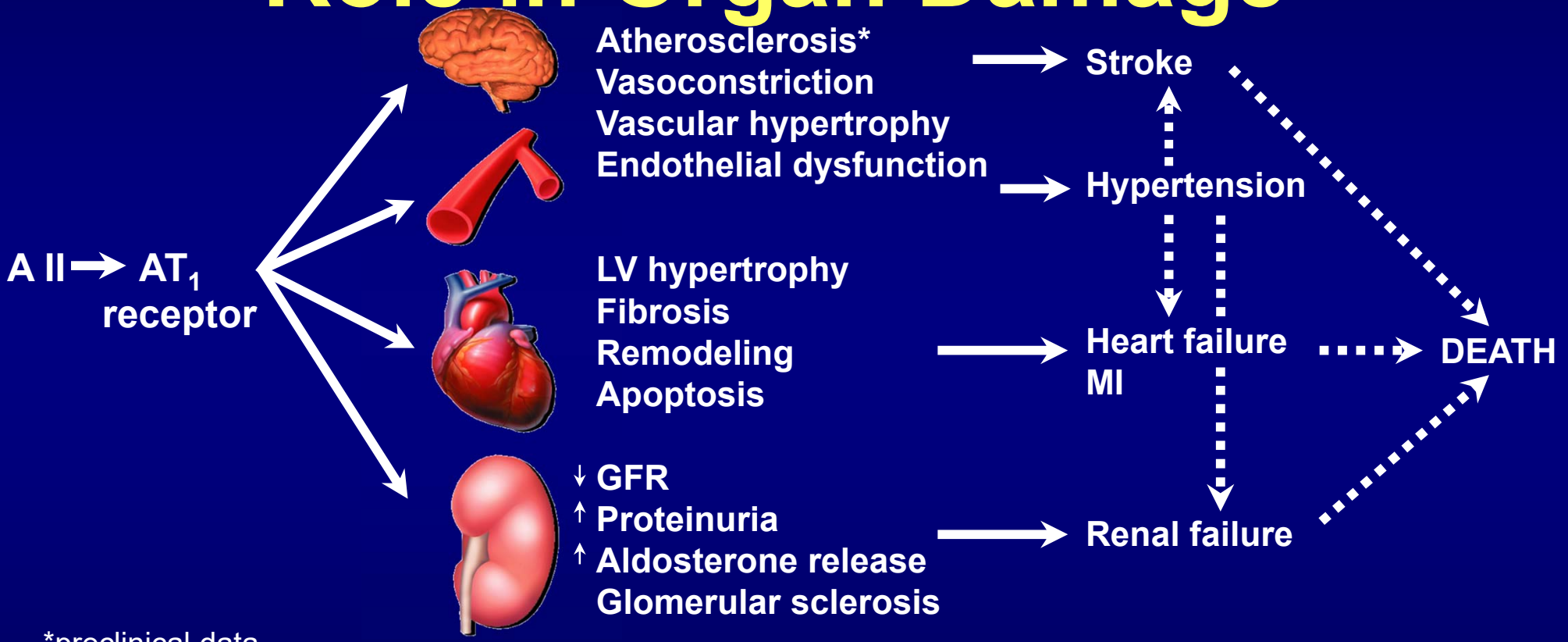
Angiotensin II Receptor Blockers (ARBs)

- Competitively inhibits Ang II at AT_1 receptor



e.g. losartan, valsartan, candesartan, etc.

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

Angiotensin II Receptor Blockers

Advantages:

- Similar beneficial effects as ACEI
  - CV, renal outcomes, DM
  - No lipid, glucose changes
- Useful in combination with other antihypertensives

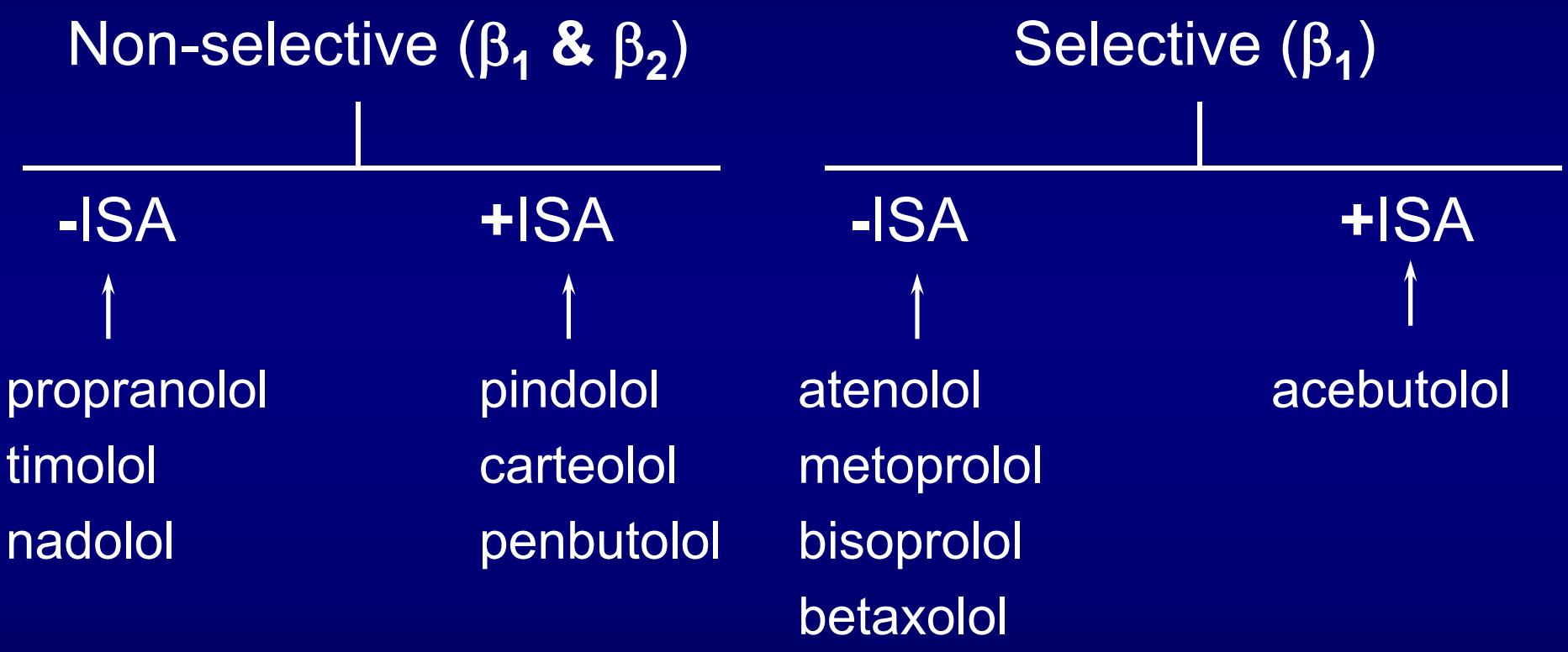
Disadvantages:

- More expensive
- Concerns about cancers and CV events
- Not free of ACEI-type side effects:
  - dizziness
  - cough (< than ACEI)
  - angioedema
  - hyperkalemia

Beta-Blockers

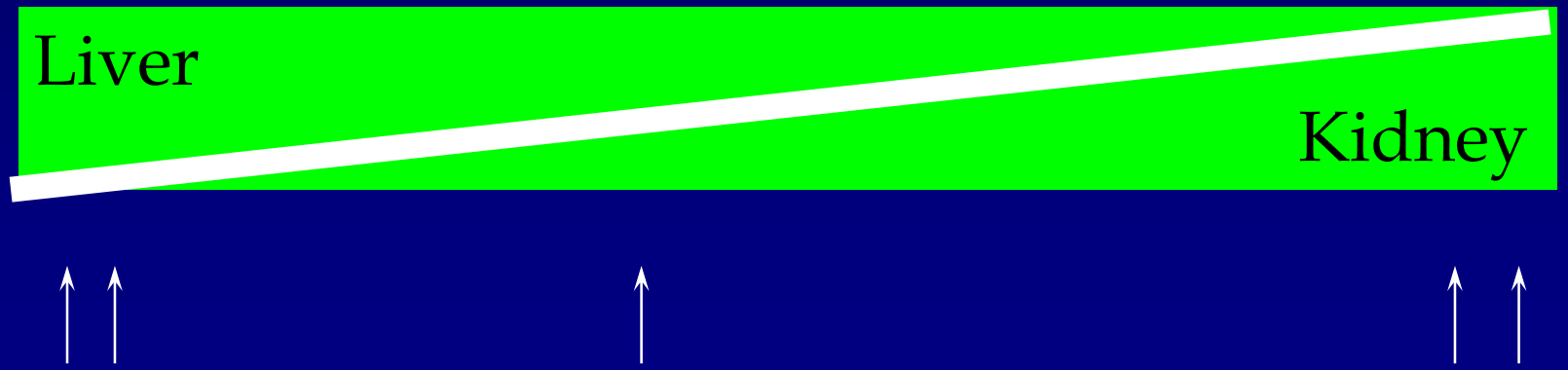
- Third-line therapy
- MOA = multi-factorial
  - ↓ CO by negative chronotropic and inotropic effects
  - ↓ renin release; ↓ PVR
- Differentiated by:
  - cardioselectivity (dose-dependent)
  - intrinsic sympathomimetic activity (ISA)
  - Metabolism
  - Alpha-beta blockade (carvedilol, labetalol)

Beta-Blockers



ISA = intrinsic sympathomimetic activity ~ mixed agonist/antagonist properties

Beta-Blockers



Propranolol

Metoprolol

Labetolol

Carvedilol

Acebutolol

Atenolol

Nadolol

Beta-Blockers

- Advantages
  - modest cost
  - once-twice daily dosing
  - decrease CAD mortality and progression
  - decrease mortality post-MI (avoid agents with ISA)
  - **>**effective in whites and younger pts.
  - ↓ M & M in CHF (metoprolol, bisoprolol, carvedilol)
  - No routine lab monitoring necessary

Beta-Blockers - Disadvantages

- Diabetes
  - glucose intolerance; mask hypoglycemia
    - Carvedilol vs Metoprolol
- May increase lipids
- asthma/COPD
- caution in CHF
- Questions about atenolol
  Lancet. 2004;364:1684-1689.

- angina with ISA agents
- sexual dysfunction
- ↓ exercise capacity
- withdrawal syndrome (rebound hypertension)
  - taper 1/2 dose q 2-3 days over 2 wk

- SE: bradycardia, tiredness, cold ext., CNS

Newest Beta-Blocker

- Nebivolol (Bystolic®)
  - Selective beta-1 antagonist
  - Causes vasodilation via nitric oxide release
  - Similar tolerance to carvedilol
  - Better side effect profile?
    - Not yet fully demonstrated
    - May have better effects on glucose in diabetics compared to other beta-blockers

Beta-blockers – Utility Questioned

- Beta blockers (especially atenolol) are:
  - Less effective than other antihypertensives in reducing stroke.
  - Beta blockers less effectively reduce central systolic BP
  - May be explained by once daily dosing of atenolol (better results obtained with twice daily dosing)
  - Authors argue: beta-blockers should not be first line antihypertensives or second drug added to diuretic.

Lindholm et al. Lancet 2005;366:1545-1553

Beta-blockers – Utility Questioned

Trials comparing beta-blockers with other antihypertensives

Outcome	Relative risk with beta blockers	95% CI
Stroke	1.16	1.04-1.30
MI	1.02	0.93-1.12
All-cause mortality	1.03	0.99-1.08

Atenolol vs other antihypertensives

Outcome	Relative risk with atenolol	95% CI
Stroke	1.26	1.15-1.38
MI	1.05	0.91-1.21
All-cause mortality	1.08	1.02-1.14

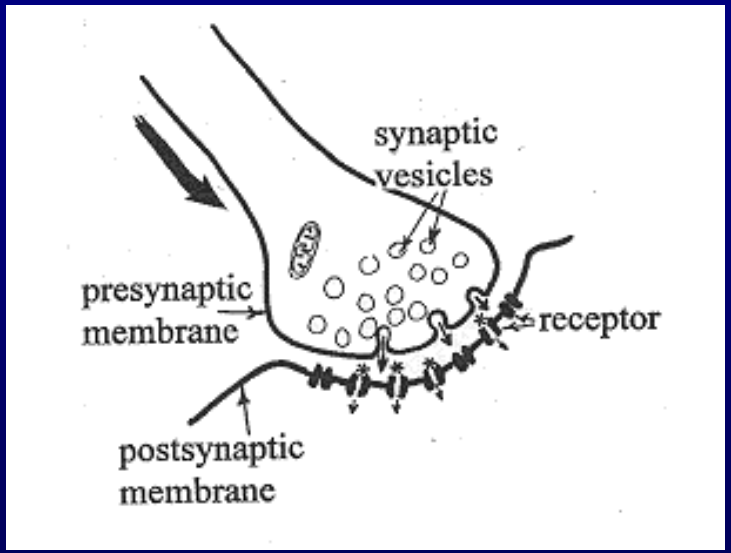
Lindholm et al. Lancet 2005;366:1545-1553

Beta-blockers
Drug Interactions

Medication	Interaction
Cimetidine	Decreased metabolism of metoprolol, labetalol, propranolol
Amiodarone	Hypotension, bradycardia
Ritonavir	Increased metoprolol concentrations
Digoxin	AV nodal block
CYP2D6 inhibitors -SSRIs	Increased metoprolol concentrations
St. John's Wort	Decreased effectiveness of beta-blockers
Diltiazem Verapamil	Increased bradycardia, hypotension, and AV conduction abnormalities

Alpha 1 Antagonists

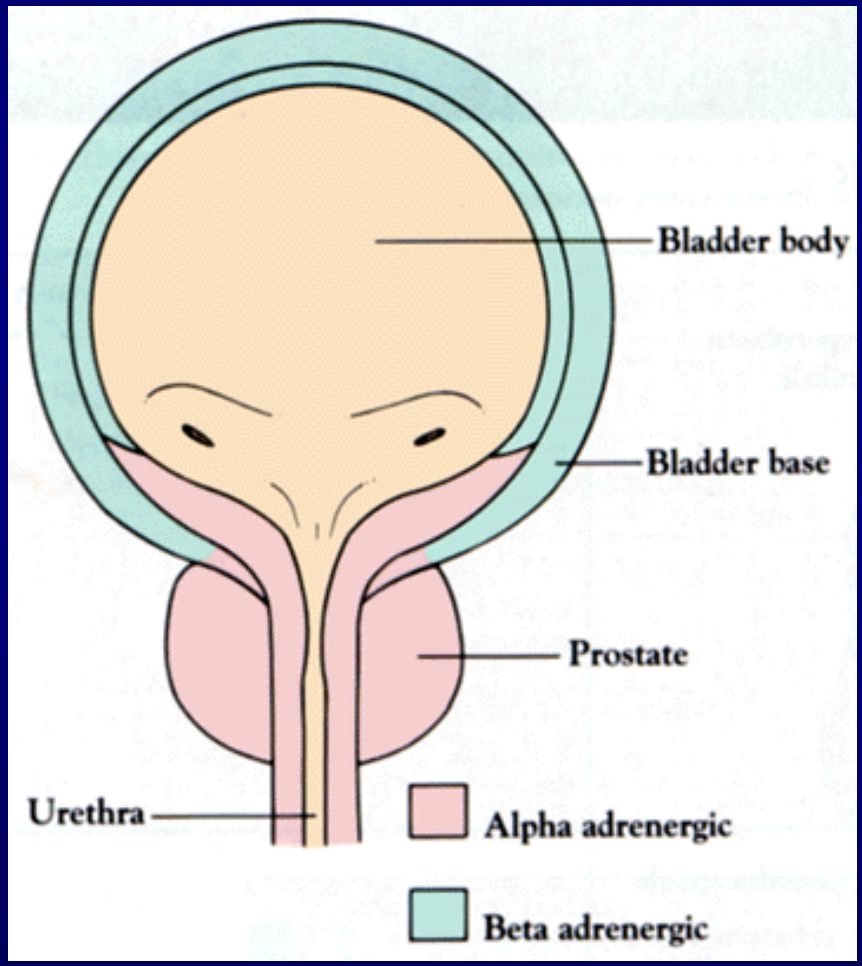
- MOA: inhibit efferent sympathetic activity
  - selective for α_1 - avoids reflex tachycardia associated with non-selective α blockers



e.g. doxazosin, prazosin

Alpha 1 Antagonists

- Monotherapy or alternative therapy
- Advantages
  - positive impact on lipids (↓ TC, LDL, TG, ↑ HDL)
  - improve BPH symptoms



Alpha $_1$ Antagonists

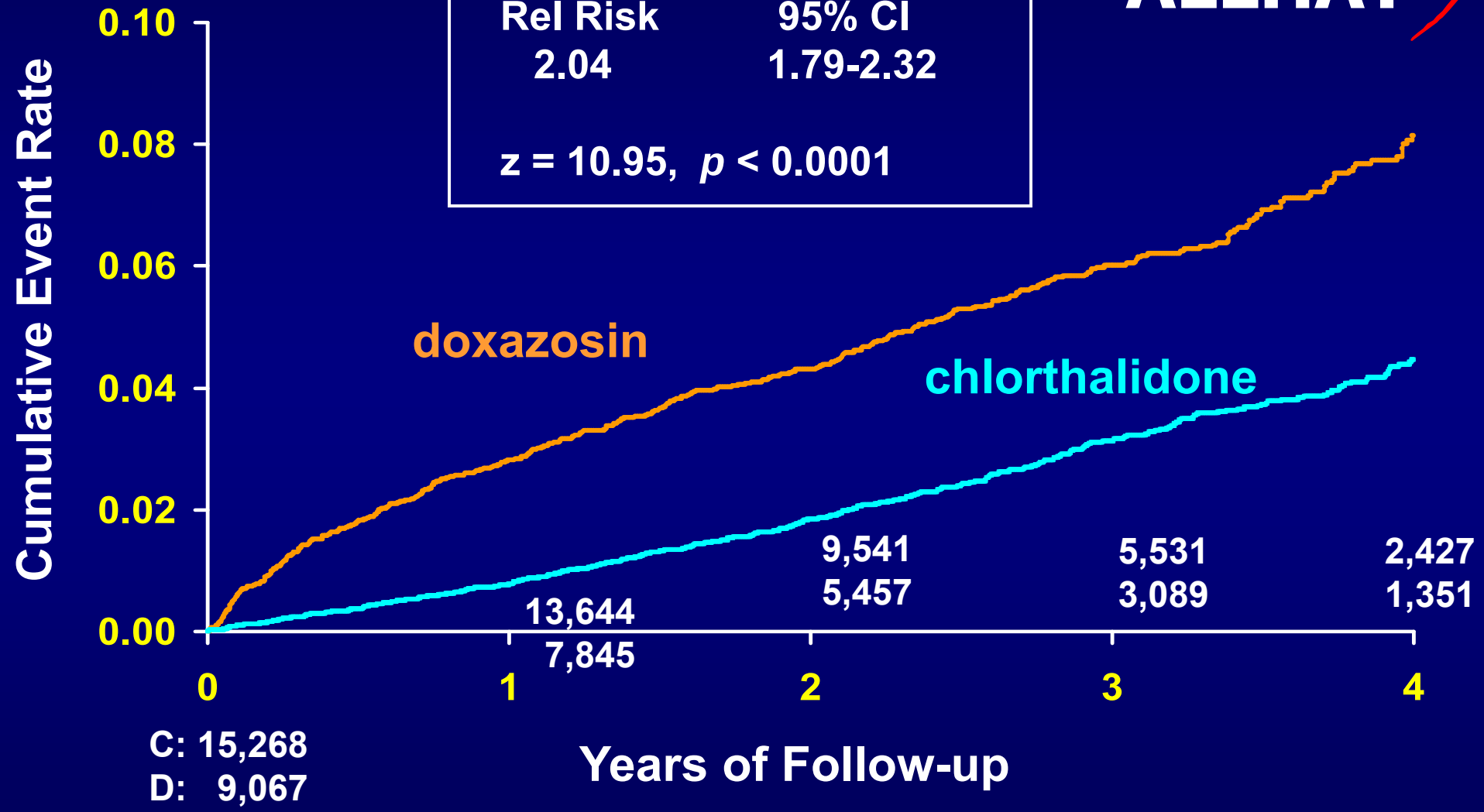
- Disadvantages
  - hypotension with 1st dose (“1st dose phenomenon)
    - transient dizziness or faintness; syncope
    - take first dose at HS
  - Not recommended as initial monotherapy for HTN (ALLHAT study)
  - SE: HA, fatigue, drowsiness, weakness, vivid dreams

Heart Failure

ALLHAT

Rel Risk	95% CI
2.04	1.79-2.32

z = 10.95, $p < 0.0001$



JAMA. 2000;283:1967-1975

Central Alpha $_2$ Agonists

- MOA: stimulate central alpha$_2$ receptors
  - inhibit sympathetic outflow, ↓ NE, ↓ HR, ↓ CO, ↓ PVR
- Advantages
  - cheap
  - neutral effects on lipids
  - clonidine patch
  - methyldopa safe in pregnancy

e.g. clonidine, methyldopa, guanfacine

Central Alpha $_2$ Agonists

- Disadvantages
  - withdrawal syndrome
    - rebound hypertension due to ↑ in NE
  - SE:
    - CNS - sedation, ↓ alertness, depression
    - dry mouth, bradycardia, sodium and fluid retention (methyldopa)