ACE I,ARB
Vasodilator
Combination Therapy

Hormat Rahimzadeh

Assistant professor of Nephrology

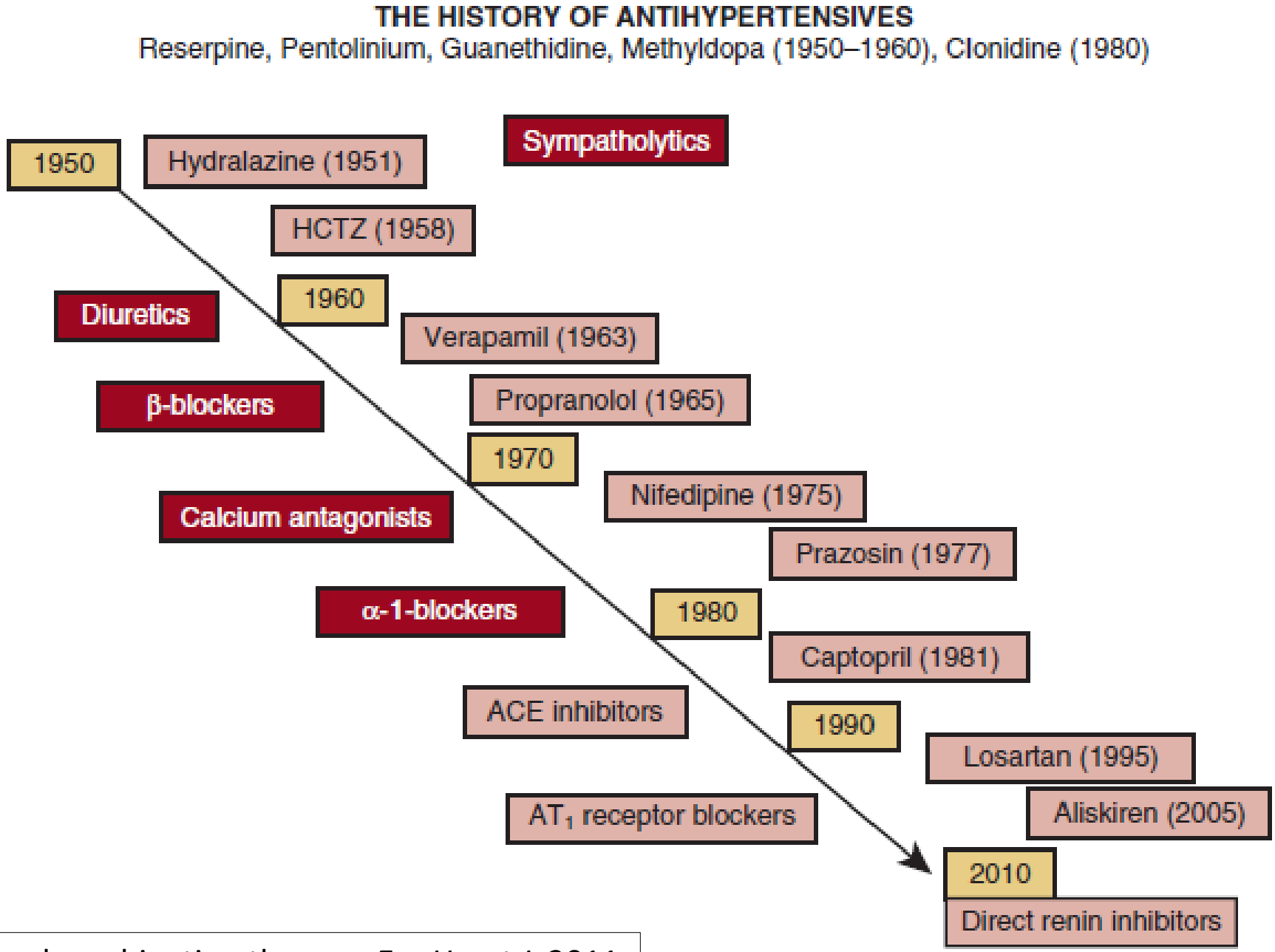
TUMS

Sina Hospital

- WHO recommends the use of drugs from any of the following three classes an initial treatment:

1. Thiazide and Thiazide-like agents
2. (ACEis) / (ARBs)
3. long-acting dihydropyridine (CCBs).

Strong recommendation, high-certainty evidence
Implementation remarks: ▪ Long-acting antihypertensives are preferred. ▪ Examples of indications to consider specific agents include diuretics or CCBs in patients over 65 years or those of African descent, beta-blockers in ischaemic heart disease, ACEis/ARBs in patients with severe proteinuria, diabetes mellitus, heart failure or kidney disease.

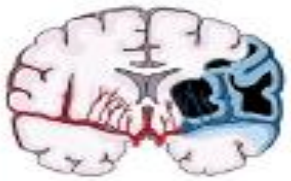


optimal combination therapy. *Eur Heart J.* 2011

PHARMACOLOGICAL CLASSES

MECHANISMS OF ACTION

Centrally acting agents
Betablockers



- ↘ sympathetic tone
  mol. targets: - alpha-2 adrenergic R. (clonidine)
  - imidazoline R. (rilmenidine)

Betablockers
CCBs (Verapamil, dilatiazem)

- bradycardia
  mol. targets: - beta1-adrenergic R (Betablockers)
  - L-type Ca^{2+} channels (non DHP- CCBs)
- ↘ cardiac output

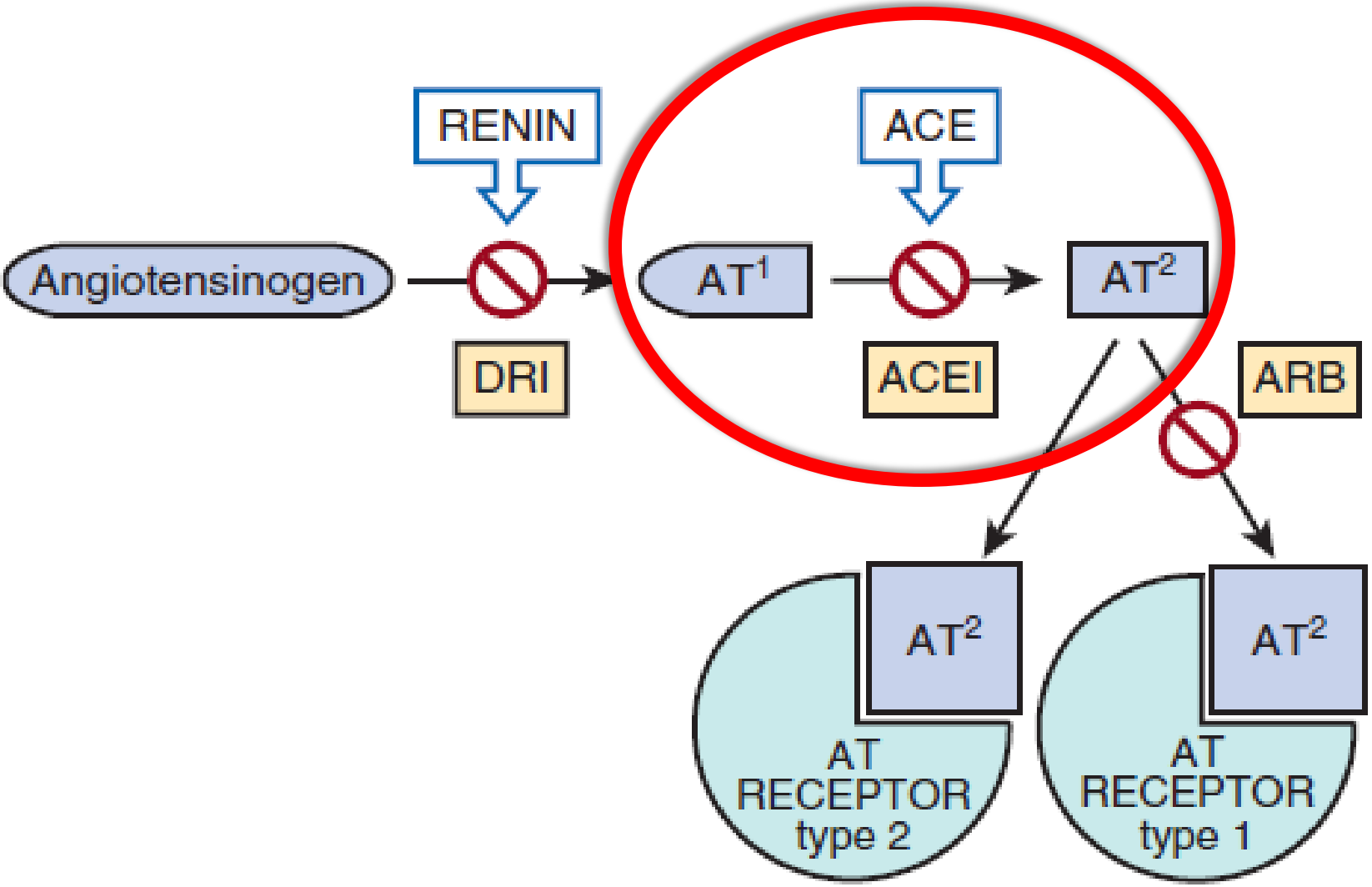
CCBs (Dihydropyridines)
ACE Inhibitors
ARBs
Renin inhibitors
Alpha-1 adrenergic R. antagonists
Direct vasodilators

- vasodilatation and large artery destiffening
  mol. targets: - Ang II-R vasoconstriction (ACEIs, ARBs, RI)
  - L-type Ca^{2+} channels vasoconstriction (DHP-CCBs)
  - alpha1-adrenergic R. (alpha 1-R. antagonists)
  - $SARCK_{ATP}$ (minoxidil, hydralazine)
- ↘ extra-cellular fluid volume (diuretics)

Diuretics
ACE Inhibitors
ARBs
Renin inhibitors
Betablockers

- ↗ Na^+ excretion
  mol. targets: - NKCC cotransport (loop diuretics)
  - Na+/2Cl- cotransport (thiazides diuretics)
  - ENaC (potassium-sparing diuretics)
- ↗ diuresis
- ↘ renin secretion (beta-blockers)

1. ACE Inhibitors
2. Ang II receptor blockers (ARBs)
3. Vasodilators
4. Combination Therapy


RENIN
ACE
Angiotensinogen
AT1
AT2
DRI
ACEI
ARB
AT2
AT2
AT
RECEPTOR
type 2
AT
RECEPTOR
type 1

Mechanism of action

- ACE inhibitors inhibit activity of ACE.
- ACE is located in endothelial cells of large and small vessels, capillaries and venules, and in pulmonary endothelial cells.

- ACE inhibitors directly reduce the circulating and tissue levels of Ang II

- ACEIs fail to suppress production of angiotensin II by alternative enzymatic pathways, such as chymase and other tissue-based protease ,particularly in the vasculature and the myocardium

- blockade of angio II:
  - ✓ vasodilation of small resistance arteries
  - ✓ reduction in total peripheral resistance
  - ✓ BP lowering.
  - ✓ …

- Cardiac output increases and heart rate remains unchanged
- There is no postural hypotension, likely because ACEIs reset baroreceptor function.

BP lowering effect of ACEIs

- is maintained for months and years.
- other mechanisms have been suggested:
  - ✓ increase in bradykinin (a vasodilatory peptide) in response to the inhibition of kininase II(degradation of bradykinin).
  - ✓ ACE is responsible for degradation of angiotensin(1–7).
  - ✓ ACEIs increase plasma concentration of angiotensin (1–7) is formed in the endothelial layer of blood vessels, and acts as vasodilator and antiproliferative agent.

BP lowering effect of ACEIs

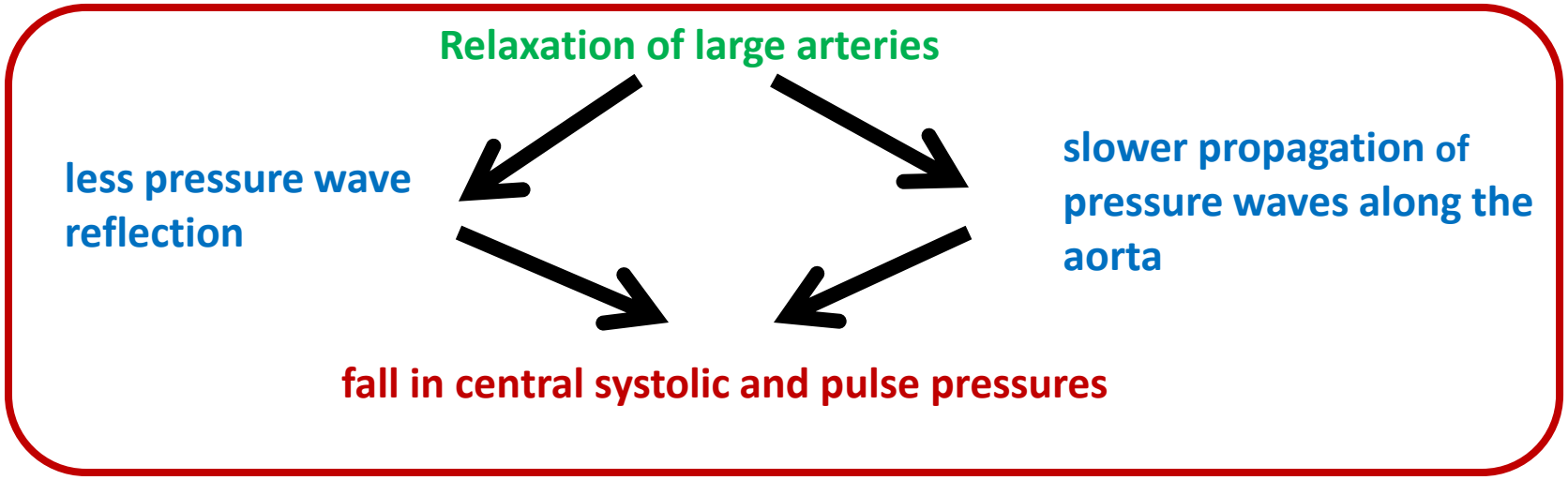
- long-term administration of ACEIs is associated :

  reduction of (LVH)

  improvement of endothelial function

  destiffening of large arteries

  remodeling of large and small arteries



Renal effect of ACEI

- Restore pressure-natriuresis relationship to normal.
- Inhibit tubule sodium resorption.
- Increase in the activity of 11β-HSD 2 enzyme
- Decrease proteinuria.
- Improve altered lipid profiles.
- Decrease filtration fraction.
- Decrease renal vascular resistance.
- Reduce scarring and fibrosis.
- Attenuate oxidative stress and reduce free radicals.
- …

ACEI

sulfhydryl	carboxyl	phosphinyl
• **Captopril**	• **Enalapril** • **Lisinopril** • **Ramipril** • **Benazepril** • **Cilazapril** • **Imidapril** • **Moexipril** • **Perindopril** • **Quinapril** • **Trandolapril**	• **Fosinopril**

Characteristics of ACEIs

Drug	Zinc Ligand	Prodrug	Rate of Elimination	Duration of Action (h)	Dose Range (mg/d)
Benazepril	Carboxyl	Yes	Renal	24	10–40
Captopril	Sulfhydryl	No	Renal	6–12	25–150
Cilazapril	Carboxyl	Yes	Renal	24+	2.5–5.0
Enalapril	Carboxyl	Yes	Renal	18–24	20–40
Fosinopril	Phosphoryl	Yes	Renal–hepatic	24	10–40
Lisinopril	Carboxyl	No	Renal	24	20–40
Moexipril	Carboxyl	Yes	Renal	12–18	15–30
Perindopril	Carboxyl	Yes	Renal	24	4–16
Quinapril	Carboxyl	Yes	Renal	24	20–80
Ramipril	Carboxyl	Yes	Renal	24	5–20
Spirapril	Carboxyl	Yes	Hepatic	24	12.5–50
Trandolapril	Carboxyl	Yes	Renal	24+	4–8

Side effects

- cough (10–20%) (increased in bradykinin & substance P)
- angioedema (0.55% of white & 1.62% of black)
- anemia
- Hyperkalemia
- Hypoglycemia
- Functional renal insufficiency

- ACEIs are contraindicated: in pregnancy
  bilateral renal artery stenosis

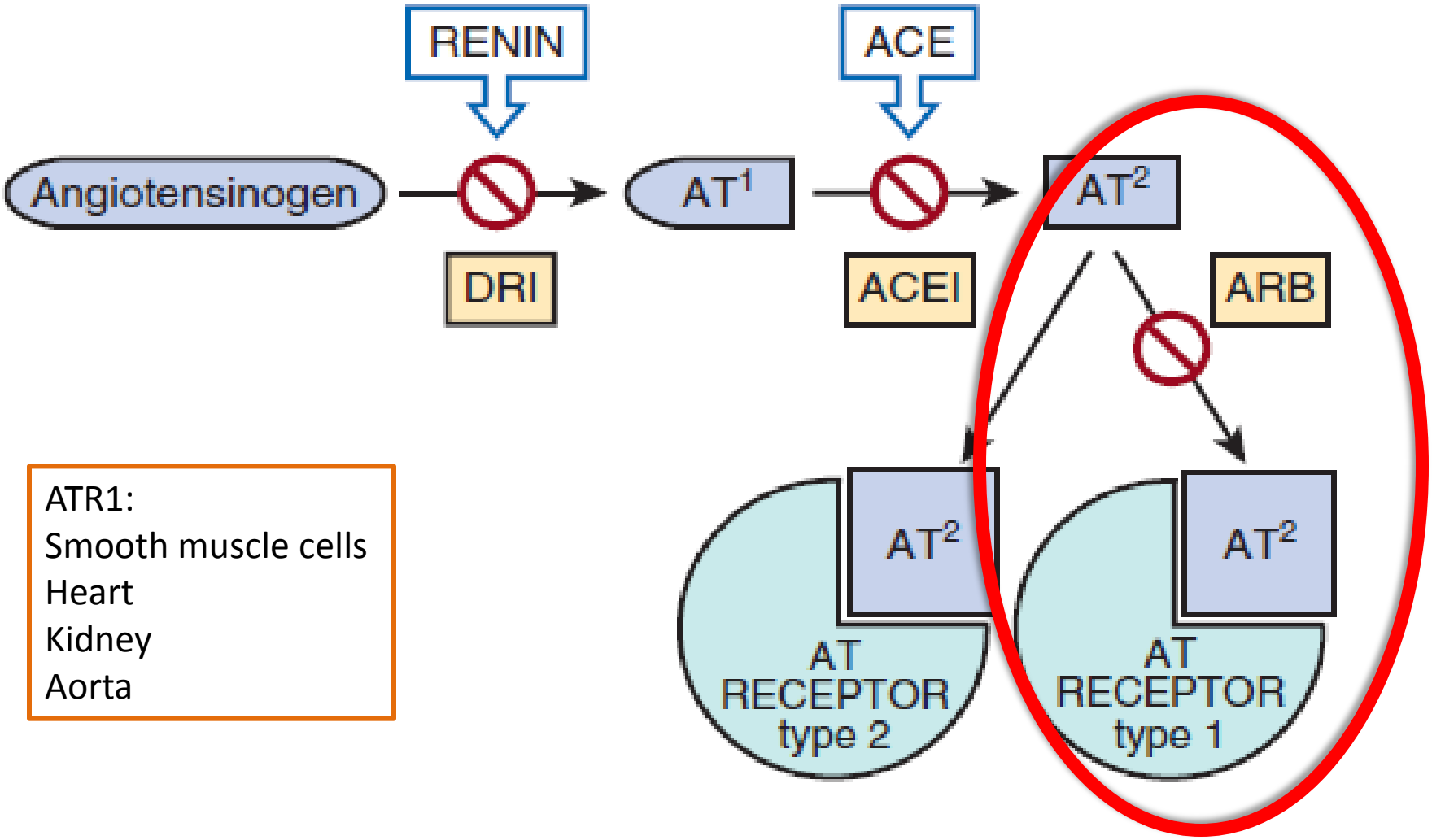
Functional renal insufficiency

- acute increases of creatinine of up to 30% that stabilize within the first 2 months of ACEI therapy are associated with *better* long-term renoprotection
- such rises need not lead to withdrawal of ACEI.

CHF patients:

- An increase in creatinine up to 50% baseline: acceptable
- ACEi should be stopped: creatinine increases by more than 100 % above baseline

1. ACE Inhibitors
2. **Ang II receptor blockers (ARBs)**
3. Vasodilators
4. Combination Therapy



ATR1:
Smooth muscle cells
Heart
Kidney
Aorta

Mechanism of action

- The hemodynamic effects of ARBs are similar to those of ACEIs.
- vasodilation of small resistance arteries, reduction in total peripheral resistance and BP lowering.
- CO increases & HR remains unchanged.
- No postural hypotension
- Reduction of (LVH)
- …

ARBs ⟹ SARTANS

biphenyl tetrazoles	nonbiphenyl tetrazoles	nonheterocyclic
• **Losartan** • **Eprosartan** • **Irbesartan** • **Candesartan** • **Azilsartan** • **Olmesartan**	• **Telmisartan**	• **Valsartan**

Angiotensin II Receptor Blockers

Drug	Trade Name	Half-Life (h)	Active Metabolite	Daily Dosage (mg)
Azilsartan	Edarbi (Tekeda)	11	Yes	40–80 in 1 dose
Candesartan	Atacand (Astra)	3–11	Yes	8–32 in 1 dose
Eprosartan	Tevetan (Smith Kline)	5–7	No	400–800 in 1–2 doses
Irbesartan	Avapro (BMS, Sanofi)	11–15	No	150–300 in 1 dose
Losarían	Cozaar (Merck)	2 (6–9)	Yes	50–100 in 1–2 doses
Olmesartan	Benicar (Sankyo)	13	Yes	20–40 in 1 dose
Telmisartan	Micardis (BI)	24	No	40–80 in 1 dose
Valsarían	Diovan (Novartis)	9	No	80–320 in 1 dose

Side effects

- ARBs are generally well-tolerated drugs. By contrast to ACEIs, cough and angioedema are much less common with ARs.
- Functional renal insufficiency is as common as with ACEIs.
- No association with cancer has been documented

PLOS ONE

RESEARCH ARTICLE

Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: Meta-regression analysis of randomized trials

Ilke Sipahi *

Department of Cardiology, Acibadem University Medical School, Istanbul, Turkey

- 15 RCT was included
- cumulative exposure to ARBs and risk of all cancers/lung?
- highly significant correlation between the degree of cumulative exposure to ARBs and risk of all cancers combined ([95% CI 0.03 to 0.11], $p<0.001$), and also lung cancer ([95% CI 0.05 to 0.27], $p = 0.003$).
- cumulative exposure was greater than 3 years of exposure to daily high dose.
- Limitation: a trial-level analysis

doi.org/10.1371/journal.pone.0263461 March 2, 2022

Journal of Personalized Medicine

MDPI

Commentary

Angiotensin Receptor Blocker Associated with a Decreased Risk of Lung Cancer: An Updated Meta-Analysis

Zexu Wang [1], Lingyun Wei [2], Cheng Yin [3], Wang Li [1] and Bing Wan [1,*]

- 10 RCTs, 18 retrospective cohort ,3 case-control studies
- Results of 10 retrospective studies revealed a decreased lung cancer incidence in patients treated with ARBs, especially in patients using Valsartan.
- No significant decrease in lung cancer occurrence was found in RCTs
- Conclusion: Compared with ACEIs and CCBs, ARBs significantly reduce the risk of lung cancer, especially in Asian and Mongolian populations. (Valsartan)
- No access to raw data of patients

J. Pers. Med. 2023, 13, 243

Angiotensin receptor neprilysin inhibitor (ARNI)

- Sacubitril/valsartan is the first agent
- CHF with reduced ejection fraction (HFrEF) with NYHA class II, III, or IV.
- elevated BNP & NT-pro BNP seen in CHF exacerbations.
- Natriuretic peptides are broken down by an enzyme called neprilysin.
- neprilysin breaks down angiotensin II.
- neprilysin breaks down bradykinin. (36 h washout period)

Angiotensin receptor neprilysin inhibitor (ARNI)

- Sacubitril/valsartan is available as an oral tablet:

  1- sacubitril (24 mg, 49 mg, or 97 mg)

  2- and valsartan (26 mg, 51 mg, or 103 mg)

- valsartan in brand-name combination are equivalent to valsartan 40 mg, 80 mg, and 160 mg
- Sacubitril/valsartan is to be taken twice a day

ARBs are more effective than ACEIs ?

- reducing proteinuria in diabetic nephropathy: ✗
- ARB (telmisartan) versus ACEI (enalapril) in patients with type 2 diabetes : ✗
- ONTARGET study: eGFR declined significantly least with ramipril vs telmisartan, whereas increase in albuminuria was less with telmisartan than with ramipril
- ACEIs protected diabetics against cardiovascular diseases

ACEI /ARB and COVID-19

- RAS blockade is capable of increasing ACE2 expression in different tissues(heart, vasculature, and lungs)
- Circulating ACE2 activity is increased in patients on dialysis who are treated with ARBs
- Coronaviruses use ACE2 as a receptor to enter type II pneumocytes.

Result:

- history of ACEi or ARB use was not associated with increased severity of COVID-19 illness.
- discontinuation of ACEis or ARBs may yield worse outcomes than continuation in patients COVID-19.

1. ACE Inhibitors
2. Ang II receptor blockers (ARBs)
3. **Vasodilators**
4. Combination Therapy

Vasodilators

- Several different vasodilators:
  1. Direct-acting vasodilators (hydralazine, minoxidil, nitrates, nitroprusside)
  2. Calcium channel blockers
  3. Antagonist of the RAAS
  4. Beta-2 receptor agonist
  5. Alpha-1 receptor antagonist (prazosin, phenoxybenzamine, phentolamine)
  6. Centrally acting alpha-2 receptor agonist (clonidine, α-methyldopa)
  7. Endothelin receptor antagonist (bosentan, ambrisentan)
  8. Phosphodiesterase inhibitors (sildenafil, tadalafil)

Vasodilators

Clinical indication:

- ✓Systemic hypertension
- ✓MI(both ST elevation and non-ST elevation), angina,
- ✓Heart failure,
- ✓Stroke,
- ✓CKD
- ✓Preeclampsia
- ✓Hypertensive emergency

Direct-acting vasodilators

Minoxidil, Hydralazine:

- **Minoxidil:** Open sarcolemnal ATP-dependent k channels (SARCKATP) on vascular smooth muscle cells (VSMCs), leading to arterial relaxation
- **Hydralazine:** inhibit release of Ca from SMC sarcoplasmic reticulum and inhibits myosin phosphorylation within the arterial smooth muscle
- Both large and small arteries are relaxed.
- act predominantly on the arterial site of the blood vessels, without venodilation.
- HR, SV and CO rise, reflecting a baroreceptor-mediated reflex increase in sympathetic discharge

- **Hydralazine**
- usually be started at 25 mg two times per day. The maximal dose should be limited to 200 mg/day
- Hydralazine is approved for use during pregnancy
- **Minoxidil**
- More potent than hydralazine, in the therapy of severe hypertension associated with renal insufficiency
- It can be given once daily in a range of 2.5 to 80 mg.

Side effects

- counter-regulatory and neurohumoral changes include activation of SNS and RAAS leading to tachycardia and fluid retention.

- Hydralazine: Hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome have also been reported.

- Minoxidil: hypertrichosis may require discontinuation of minoxidil, but usually disappears within a few weeks. Pericardial effusions (3% of patients)

1. ACE Inhibitors
2. Ang II receptor blockers (ARBs)
3. Vasodilators
4. **Combination Therapy**

When to initiate combination therapy?

- baseline BP is ≥20/10 mmHg higher than the target blood pressure.
- Stage 2 hypertension
- patients whose systolic pressure is ≥150 mmHg and/or diastolic pressure ≥90 mmHg.

Studies showed:

- Combination therapy lowers blood pressure more than monotherapy
- increases the likelihood that target blood pressure will be achieved in a reasonable time period
- attainment of goal blood pressure with lower doses of each medication, and this reduces the risk of dose-related side effects

Single-pill combination vs free equivalents

- Some experts initiate therapy with a SPC containing low doses of each drug.
- Single-pill combinations lead to greater blood pressure reduction, increased attainment of blood pressure goal, and better medication adherence as compared with free equivalents
- other experts initiate free equivalents and then, after titrating the dose of each drug, convert to a SPC
- in patients with a history of multiple drug allergies or intolerances, identify the culprit drug if a side effect occurs.

Take home message

- ACEi and ARB are 2 first class antihypertensive for patients with DM,CKD,LVH,HF and proteinuria,…
- ARB and risk of cancer: data is conflicting.
- vasodilators: potent drugs in special settnig
- Single-pill combination therapy improves medication-taking adherence and persistence and BP control.

Thank you