ACE Inhibitors, ARBs, & Renin Inhibitors

Drug Class Review

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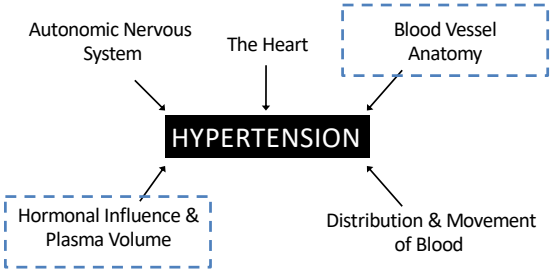
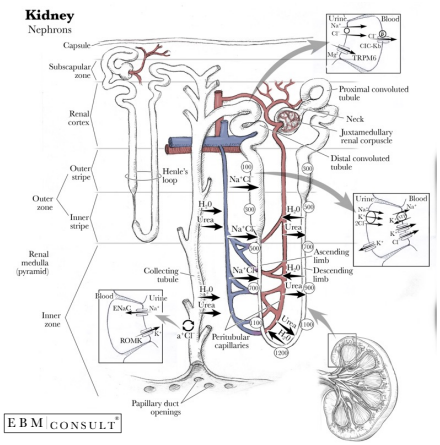
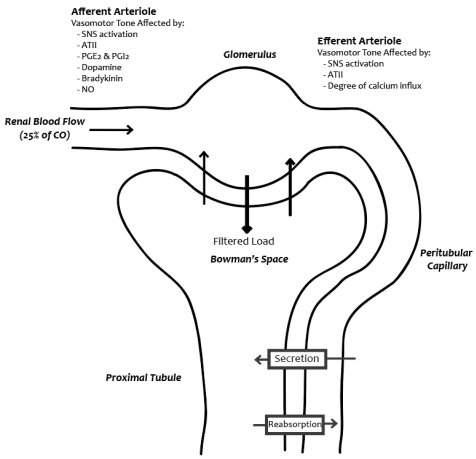
Outline

- Mechanism of Actions
- Drug Class Review
- Clinical Considerations

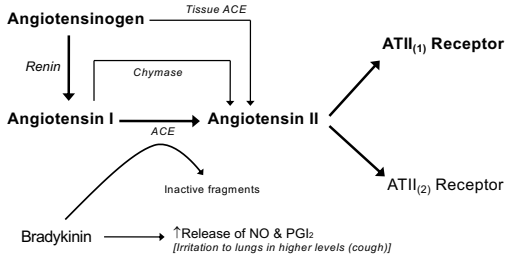
Contributors of Blood Pressure







Renin-Angiotensin-Aldosterone System



Mechanism of Action

$ATII_1$ Receptor → **Arteries**

↓

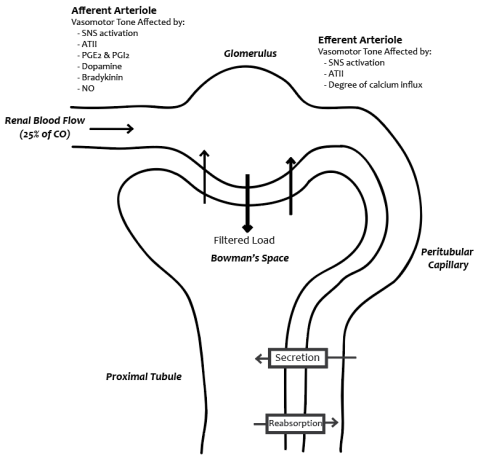
Vasoconstriction

↓

Increased SVR or Afterload

↓

Increased BP



Mechanism of Action

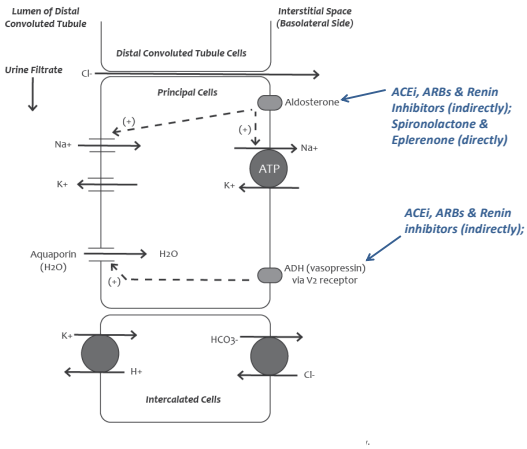
$ATII_1$ Receptor → Adrenal Gland

↓

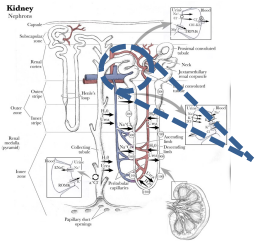
Release of Aldosterone

↓

Na/H2O Reabsorption at the DCT



Renin-Angiotensin-Aldosterone System



$ATII_{(1)}$ Receptor

Adrenal Gland	**Arteries**
↓	↓
Release of Aldosterone	Vasoconstriction
↓	↓
Na/H2O Reabsorption at the DCT	Increased SVR or Afterload
↓	
Increase Plasma Volume	

Increase BP

Mechanism of Action

$ATII_1$ Receptor → Adrenal Gland

↓

Release of Aldosterone

↓

Na/H2O Reabsorption at the DCT

↓

Increase Plasma Volume

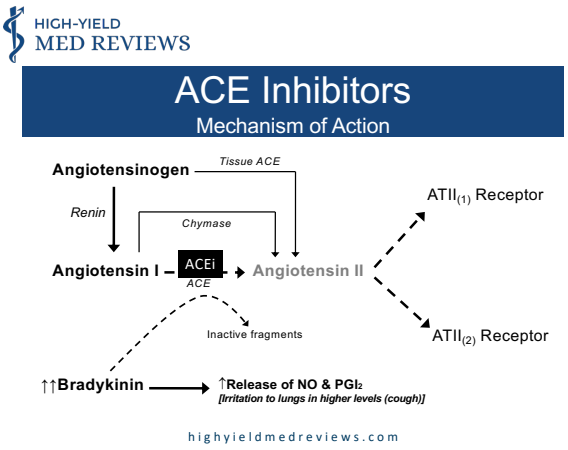
↓

Increase BP

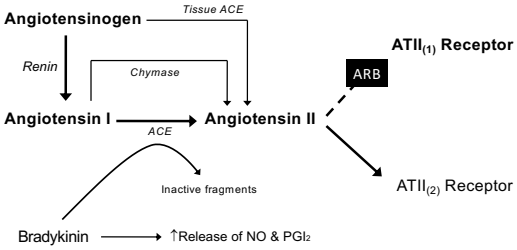
Renin Angiotensin Aldosterone System

- Angiotensin II (ATII) mediates most of its effects in HTN via $ATII_1$ receptor
- $ATII_1$ mediated effects:
  - Increases aldosterone release resulting in ↑ Na^+ reabsorption & K^+ excretion in distal renal tubule
  - Increases thirst and water consumption
  - Increases TPR by acting as a vasoconstrictor
  - Participates in vascular remodeling
- $ATII_2$ receptor mediated effects:
  - Opposite of $ATII_1$ receptor which is reason for selective AT_1 inhibition

Lets Pull it Together



ARBs Mechanism of Action



ACEi / ARBs/RI: Preload

MAP = CO x SVR

Heart Rate | Stroke Volume

Stroke Volume: ***Preload***, Inotropy, Afterload

Medication Impact on Preload	
DECREASE	**INCREASE**
▪ ***ACE Inhibitors*** – Lisinopril ▪ Aldosterone Antagonist – Spironolactone ▪ ***ARBs*** – ***Losartan*** ▪ Diuretics (Loop) – Furosemide ▪ Diuretics (Thiazide) – HCTZ ▪ Nitroglycerin ▪ Nitroprusside ▪ Milrinone ▪ Morphine	▪ Fluids

ACEi / ARBs: Afterload

MAP = CO x SVR

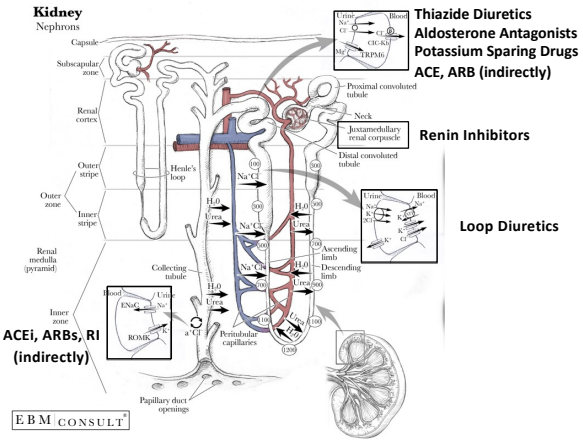
Heart Rate | Stroke Volume

Stroke Volume: Preload, Inotropy, ***Afterload***

Medication Impact on Afterload	
DECREASE	**INCREASE**
▪ α1-Blockers ▪ α2-Agonists ▪ ***ACE Inhibitors*** ▪ Aliskiren ▪ ***ARBs*** ▪ Carvedilol ▪ DHP-CCB ▪ Dobutamine +/- ▪ Fenoldopam ▪ Labetalol ▪ Metyrosine ▪ Milrinone ▪ Nitroglycerine ▪ Nitroprusside ▪ Phentolamine ▪ Propofol ▪ Reserpine	▪ Desvenlafaxine ▪ Dobutamine +/- ▪ Dopamine (higher doses) ▪ Epinephrine ▪ Ketamine ▪ Norepinephrine ▪ Stimulants for ADHD ▪ TCAs ▪ Vasopressin ▪ Venlafaxine

ACE Inhibitors & ARBs

- Net Effect:
  - Afterload is reduced
  - Preload is reduced
  - Acts mainly as functional vasodilators of both resistance and capacitance vessels
  - Reduce CV remodeling



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ACE Inhibitors

Drug	Indication	Dosing	Half-life (hrs)	Trough:Peak Ratio
Benazepril (Lotensin) + HCTZ (Lotensin HCT)	HTN	10-80 mg; QD-BID (max 80 mg/d)	10-11	40%
Captopril (Capoten) + HCTZ (Capozide)	HTN, HF, LVSD, Diabetic Neuropathy	25-450 mg; in 2-3 divided doses (max 450 mg/d)	1.9	25%
Enalapril (Vasotec) + HCTZ (Vaseretic)	HTN, HF, LVD	2.5-40 mg; QD-BID (max 40 mg/d)	2 (11)	40-79%
Fosinopril (Monopril) + HCTZ (Monopril HCT)	HTN, HF (as adjunct)	10-80 mg; QD-BID (max 80 mg/d);	12	64%
Lisinopril (Prinivil; Zestril) + HCTZ (Prinzide); + felodipine (Lexxel)	HTN, HF, AMI	10-80 mg; QD-BID (max 80 mg/d)	11-12	30-70%

Zannad F et al. Am J Hypertens 1996;9:633-43.
Piepho RW. Am J Health-Syst Pharm 2000;57:S3-7.

ACE Inhibitors

Drug	Indication	Dosing	Half-life (hrs)	Trough:Peak Ratio
Moexipril (Univasc) + HCTZ (Uniretic)	HTN	7.5-30 mg; QD-BID (max 30 mg/d)	1 (2-10)	0-9%
Perindopril (Aceon)	HTN, Stable CAD	2-16 mg QD-BID (max 16 mg/d)	0.8-1	75-100%
Quinapril (Accupril) + HCTZ (Accuretic)	HTN, HF	10-80 mg; QD-BID (max 80 mg/d)	0.8 (2)	10-40%
Ramipril (Altace)	HTN, HF s/p MI, Reduction in CV Events	2.5 – 20 mg; QD-BID (max dose is 20 mg). Gets metabolized to ramiprilat (more potent)	9-18	> 50%
Trandolapril (Mavik) + Verapamil (Tarka)	HTN, HF s/p MI	1-8 mg; QD-BID (max 8 mg/d)	6 (10)	50-100%

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Piepho RW. Am J Health-Syst Pharm 2000;57:S3-7.

Angiotensin Receptor Blockers (ARB)

Drug	Indication	Dosing	Half-life (hrs)	Trough:Peak Ratio
Azilsartan (Edarbi) + Chlorthalidone (Edarbyclor)	HTN	80 mg QD	11	95%
Candesartan (Atacand) + HCTZ (Atacand HCT)	HTN (down to 1 year of age), NYHA Class II-IV HF	2-32 mg; QD	9	80%
Eprosartan (Teveten) + HCTZ (Teveten HCT)	HTN	400-800 mg; QD-BID (max 800 mg/d)	5-9	67%
Irbesartan (Avapro) + HCTZ (Avalide)	HTN, Nephropathy in DM2	75-300 mg; QD (max 300 mg/d)	11-15	>60%

Song JC et al. Pharmacotherapy 2000;20:130-9.

Angiotensin Receptor Blockers (ARB)

Drug	Indication	Dosing	Half-life (hrs)	Trough:Peak Ratio
Losartan (Cozaar) + HCTZ (Hyzaar)	HTN, HTN + LVH, Nephropathy in DM2	25-100 mg QD-BID (max 100 mg/d)	1.5-2 (6-9)	58-78%
Olmesartan (Benicar) + HCTZ (Benicar HCT)	HTN (including to 6 yrs of age)	20-40 mg QD (max 40 mg/d)	13	60-80%
Telmisartan (Micardis) + HCTZ (Micardis HCT); + amlodipine (Twynsta)	HTN, CV Risk Reduction	20-80 mg QD (max 80 mg/d)	24	> 97%
Valsartan (Diovan) + HCTZ (Diovan HCT) + Nebivolol (Byvalson)	HTN, NYHA Class II-IV, Post-MI	80-320 mg QD (max 320 mg/d)	6	69-76%
Valsartan + Sacubitril (Entresto)	Heart Failure	51/24 mg BID; double q2-4 wks to 103/97 mg BID	9.9; 1.4 (11.5)	N/A

Renin Inhibitors

Drug	Indication	Dosing	Half-life (hrs)	Trough:Peak Ratio
Aliskiren (Tekturna)	HTN	150-300 mg QD; Sub: CYP3A4; PgP; No renal dosing	24	150 mg = 64% 300 mg = 98%
Aliskiren + HCTZ (Tekturna HCT)	Ad-On or Replacement Therapy for HTN	Titrate up to max of 300 mg/25 mg QD	-	-
Aliskiren + amlodipine (Tekamlo); + HCTZ (Amturnide)	HTN	150/5 mg QD and after 2-4 weeks can increase to 300/10 mg QD; 150-300/5-10/12.5-25 mg QD	-	-

ARB + Neprilysin Inhibitor

- Valsartan + Sacubitril (Entresto)
- Indication:
  - Heart failure (mainly newly diagnosed NYHA class II to III HF currently on maximum doses of current standard treatment)
- Mechanism of Action:
  - Valsartan = Inhibition of ATII receptor
  - Sacubitril = A pro-drug that inhibits neprilysin (a neutral endopeptidase [NEP] via its metabolite (LBQ657) leading to the rise in natriuretic peptides (e.g., BNP). Increase BNP can lead to vasodilation, natriuresis, renin & aldosterone suppression, and antifibrotic effects.
- PARADIGM-HF trial: Compared to enalapril, showed a 20% reduction in CV death and first hospitalization from HF.

ARB + Neprilysin Inhibitor

- Notes:
  - Dosing based on use of ACE or ARB at time of initiation:
    - If on < 10 mg of enalapril or < 160 mg/d of valsartan equivalent then start at 24 mg sacubitril and 26 mg valsartan
  - Side Effects:
    - Up to 16% of patients can see an increases serum Cr of > 50%
    - Hypotension (18%), hyperkalemia (4-16%), dizziness (6%), angioedema
  - Limit dose when CrCl < 30 mL/min to 24 mg sacubitril and 26 mg valsartan

Side Effects

Side Effect	ACEi	ARB	Note
Angioedema	✓✓	✓	▪ ACEi >> ARB
Cough (Dry; Non-Productive)	✓		▪ ACEi only
Hyperkalemia	✓	✓	▪ Especially if used with aldosterone antagonist or salt substitutes
Acute Renal Failure	✓	✓	▪ Mainly in BILATERAL renal artery stenosis
Hypotension	✓	✓	▪ Especially if dehydrated or low plasma volume
Agranulocytosis & Neutropenia	✓	✓	▪ Especially if on other drugs with BMS

Outline

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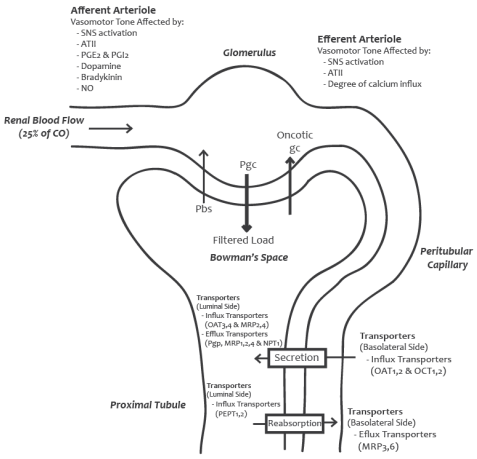
Clinical Considerations

- Clinical Pearls:
  - Very useful as monotherapy since they do not cause "pseudo" tolerance as with other vasodilator medications. Why?
  - As ***monotherapy***, ACE inhibitors may be less effective in African Americans due to lower renin release
  - Confer "renal protective effects" in diabetics by decreasing glomerular filtration pressures

High-Yield
CLINICAL INTEGRATION

How Do ACEi & ARBs Confer Renal Protective Benefits in Diabetics?



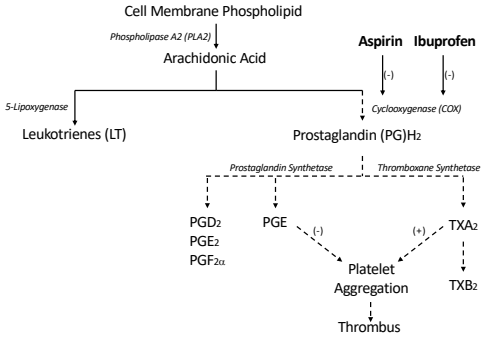
ACE Inhibitors & ARBs

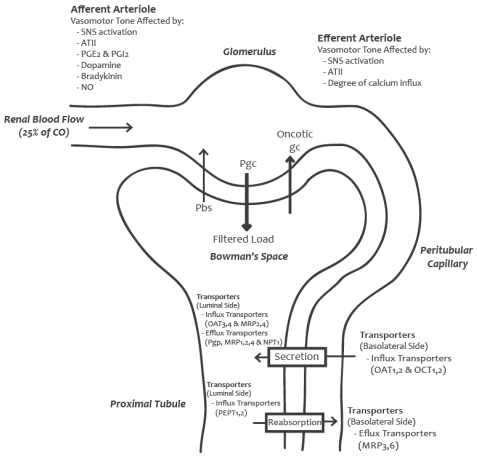
- Pregnancy:
  - Category D
  - Increased infant mortality has been associated with use in all trimesters and birth defects if used in the first 9 weeks of gestation.
- Drug Interactions:
  - Hyperkalemia is increased if used with a potassium sparing diuretic, aldosterone antagonist, salt-substitutes
  - Allopurinol, digoxin, lithium, methotrexate medications have ↓ renal excretion (note: digoxin & lithium are narrow therapeutic index drugs)
  - NSAIDs will ↓ effectiveness of ACEi

High-Yield
CLINICAL INTEGRATION

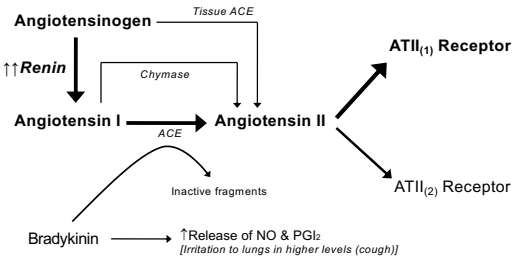
How Do NSAIDs Decrease the Effectiveness of ACEi & ARBs?

Mechanism of Action: NSAIDs





Renin-Angiotensin-Aldosterone System



High-Yield
CORE CONCEPTS

- ACE inhibitors as class are cost effective
- All ACEi & ARBs are considered equally efficacious
- ACEi, ARBs, & RI reduce preload, afterload, and remodeling
- ACEi & ARBs:
  - Increase serum K+
  - Can cause acute renal failure in bilateral renal artery stenosis
  - Reduce CV remodeling
  - Associated with angioedema (ACE >> ARB)
  - Contraindicated in pregnancy

High-Yield
FAST FACTS

- Captopril has shortest half-life of all ACEi
- ACEi, ARBs, & Renin Inhibitors can ALL cause HYPERkalemia
- ALL ACEi, ARBs are contraindicated in BILATERAL renal artery stenosis
- ALL ACEi, ARBs, and RI are contraindicated in pregnancy

HIGH-YIELD
MED REVIEWS