# Cardiac Medications

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# Objectives

- Understand various mechanisms of cardiac medications
- Examine the pharmacology of multiple classes of cardiac medications
- Look at the physiology of Myocardial Infraction (MI) and its complications
- Understand the concept of heart failure and its pharmacological management
- Anti-arrhythmics
- Look at selected ICU cardiac medications

# Important Definitions

- Inotrope – Agent that effects the force of myocardial contractions
- Cardiac Output – Measure of blood flow through the heart to the systemic circulation (L / min)
- Vasopressor – Constricts blood vessels resulting in a rise in blood pressure

# Hypertension

## Blood Pressure Categories

American Heart Association | American Stroke Association

| BLOOD PRESSURE CATEGORY | SYSTOLIC mm Hg (upper number) | | DIASTOLIC mm Hg (lower number) |
|---|---|---|---|
| NORMAL | LESS THAN 120 | and | LESS THAN 80 |
| ELEVATED | 120 – 129 | and | LESS THAN 80 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1 | 130 – 139 | or | 80 – 89 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2 | 140 OR HIGHER | or | 90 OR HIGHER |
| HYPERTENSIVE CRISIS (consult your doctor immediately) | HIGHER THAN 180 | and/or | HIGHER THAN 120 |

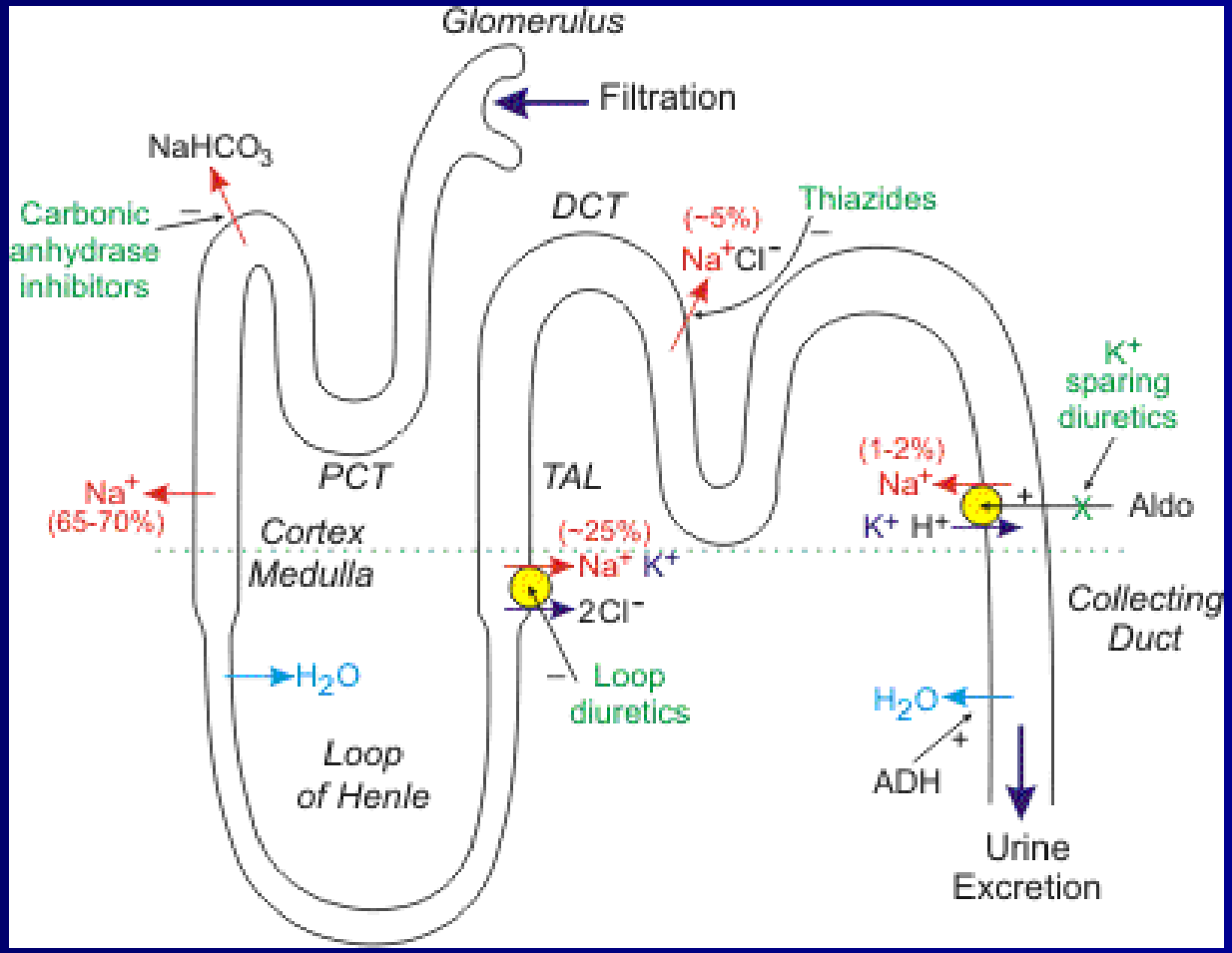
# When to Treat Hypertension

- Stage 1
  - If high risk individual
  - CCB, ACE-I or ARB
- Stage 2
  - Combination of above classes

# Medications to Treat Hypertension

- Thiazide diuretics
  - HCTZ
  - Chlorthalidone
  - Indapamide
  - Metolazone
- Potassium-sparing diuretics
  - Amiloride
  - Triamterene
- ACE- inhibitors / ARBs
  - -PRIL's / -SARTANs
- Direct Renin Inhibitor
  - Aliskiren
- Beta-Blockers
  - Metoprolol
  - Bisoprolol
  - Carvedilol
  - Atenolol
- Calcium Channel Blockers
  - Amlodipine
  - Nifedipine
  - Diltiazem
  - Verapamil
- Alpha-1 blockers
  - Prazosin
  - Terazosin
  - Doxazosin

# Site of Action of Diuretics



# Thiazide Diuretics

- Inhibit sodium chloride reabsorption in tubules of the kidney
- Allows the flow of Na+ through the nephrons
- Causes a decrease in intravascular volume

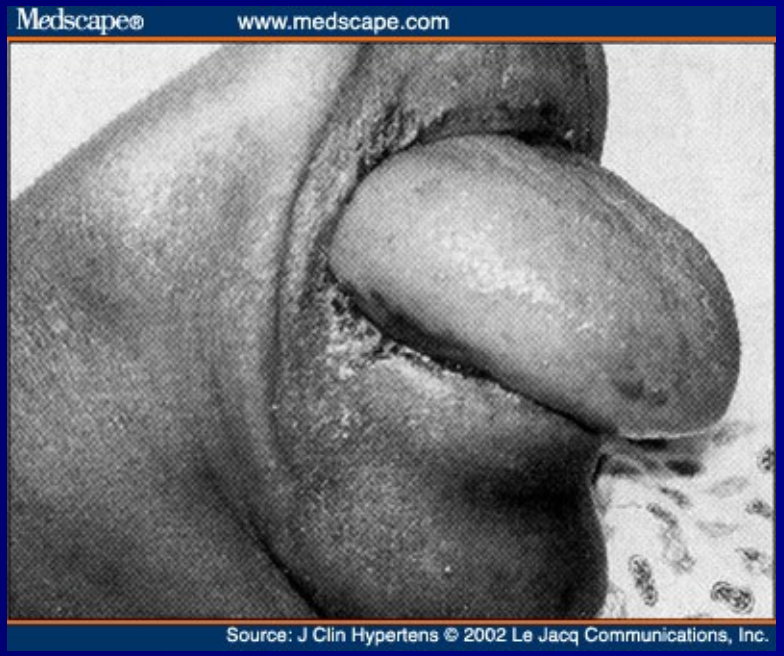
- Does NOT work well in renal patients (CrCl<30ml/min)
  - Except thiazide-like diuretics
- Potassium-sparing diuretics are not very effective as monotherapy
- ADRs: hypokalemia, hyponatremia, hypomagnesemia, photosensitivty, dyslipidemia, hypercalcemia

# ACE Inhibitors

- Suppresses cardiac remodeling
- Inhibits the conversion of Angiotensin I to Angiotensin II
  - Angiotensin II is a very potent vasoconstrictor
- Renally and cardio protective
  - Diabetics
  - Heart Failure

# ACE Inhibitors

- ADRs: hyperkalemia, cough, angioedema, acute renal failure, fetal abnormalities



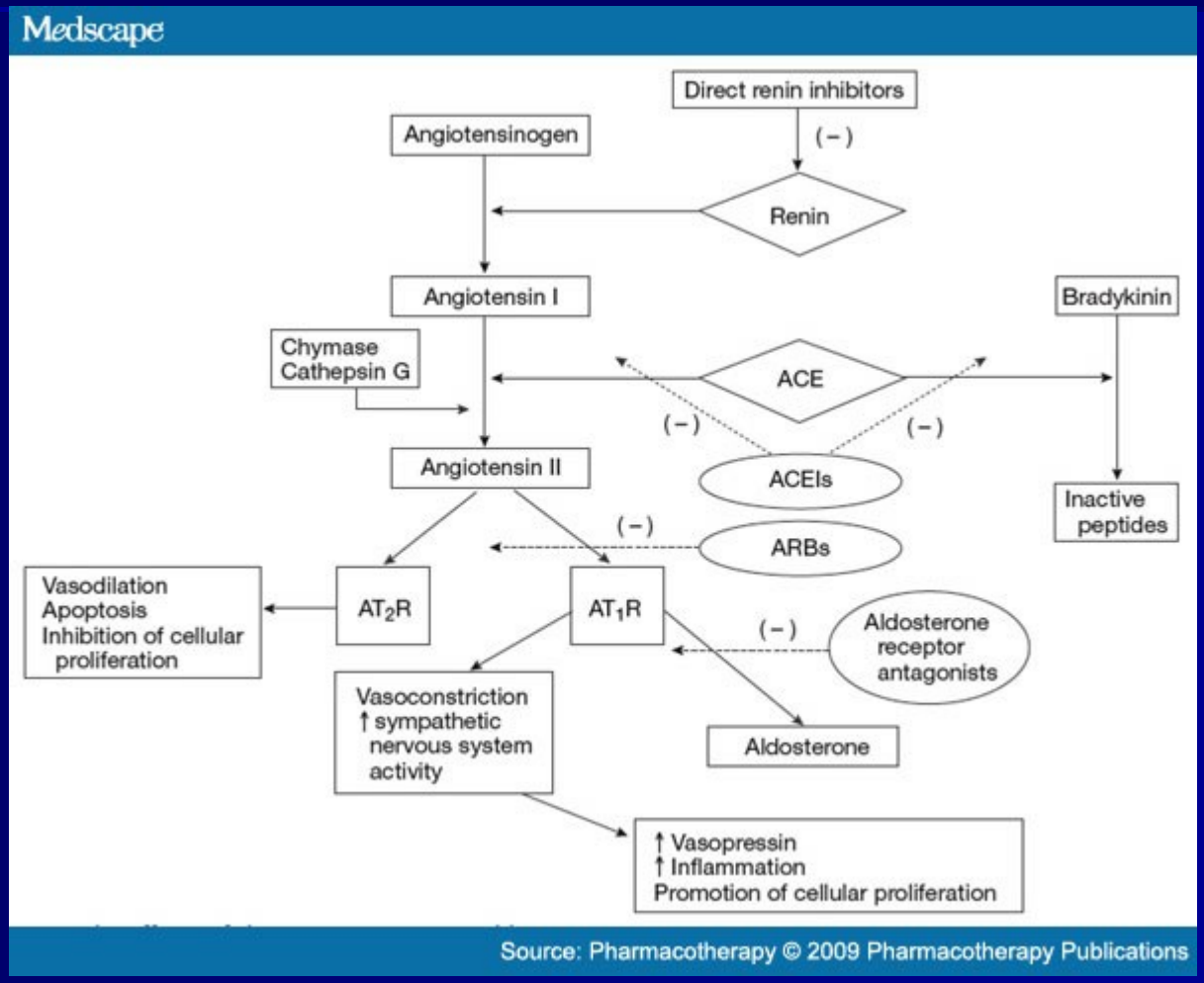
# Angiotensin Receptor Blockers

- Inhibits the attachment of active angiotensin to its enzymatic receptor
- Lower incidence of ACE inhibitor related side effects
- Same Indications as ACE Inhibitors
  - Combination therapy?  Answer is NO!
    - ONTARGET trial = lowers BP but outcomes the same

# Direct Renin Inhibitors

- Tekturna (Aliskieren)
- Blocks Renin which converts Angiotensin to Angiotensin I
- Takes 7 days to reach steady state
- Increased adverse events when used with ACEI or ARB
  - Hypotension
  - Renal impairment
  - Hyperkalemia

# ACE/ARB/DRI Pathways



# Beta - Blockers

- Selectivity for *B-1* receptor is ideal
  - The higher dose, the more chance to “unselect”
- Decreases catecholamine actions thereby leading to a decrease in blood pressure as well as a decrease in heart rate
- Prevents remodeling as well as decreasing $O_2$ demand
- Medications vary in receptor potency and site of action
  - Beta-1
  - Beta-2
  - Alpha
- ADRs: bradycardia, brochoconstriction (high-dose), lethargy, AV block, hyper-hypoglycemia, drowsiness, decreased libido

# Calcium Channel Blockers

- Dihydropyridines vs. nondihydropyridines
- Inhibits $Ca^{++}$ channels at various parts of the body leading to vasodilation
- Diltiazem and Verapamil are cardiac selective (non-dihydro)
  - Vasodilatory
  - Negative inotropic effect!
- Dihydropyridines peripheral acting agents with very little cardiac actions
- ADR's: Peripheral edema, flushing, nausea, constipation (Verapamil), gingival hyperplasia

# Alpha – 1 Blockers

- Generally used in situations with patients that have specific comorbidities
- Inhibits the Alpha –1 receptors located throughout the vascular system and other organs (bladder and prostate)
  - Peripheral vasodilation
- May increase insulin receptor sensitivity
- ADRs: First-dose syncope, dizziness, nasal congestion, postural hypotension

# Post MI Response

Pulmonary congestion

Peripheral Edema

↑ LV Preload

Myocardial Insult

↑ Afterload

↑ Blood Volume

↓ SV & CO


Arteriole Vasoconstriction

Renin

Angio II

Aldosterone

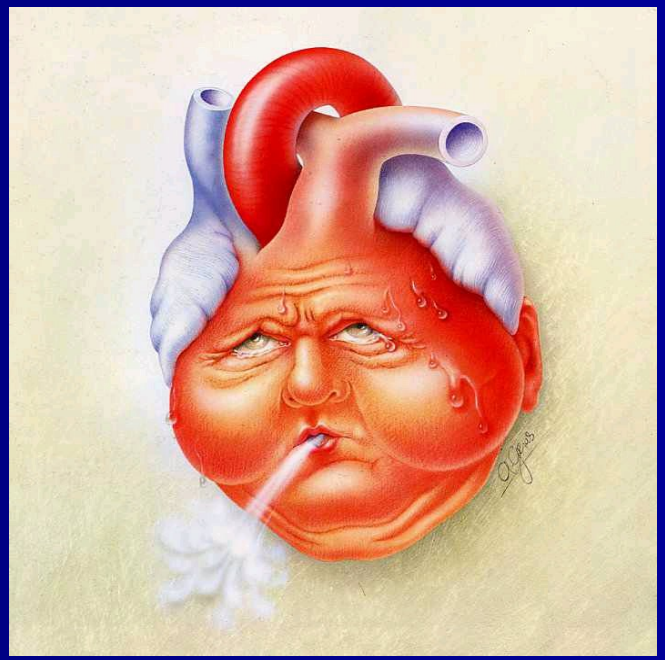
$Na^+/H_20$ Retension

# ACUTE MI

- Beta-blocker is essential
  - Decreased oxygen demand
- Nitroglycerin
  - Caution in RV involvement – Decrease preload = Hypotension
  - Seen in up to 60% of pts
- Oxygen
- ASA / Plavix / Heparin / LMWH / Statin
- ACE inhibitor after patient is stabilized
- Evaluate patient for PCI / CABG intervention

# Heart Failure

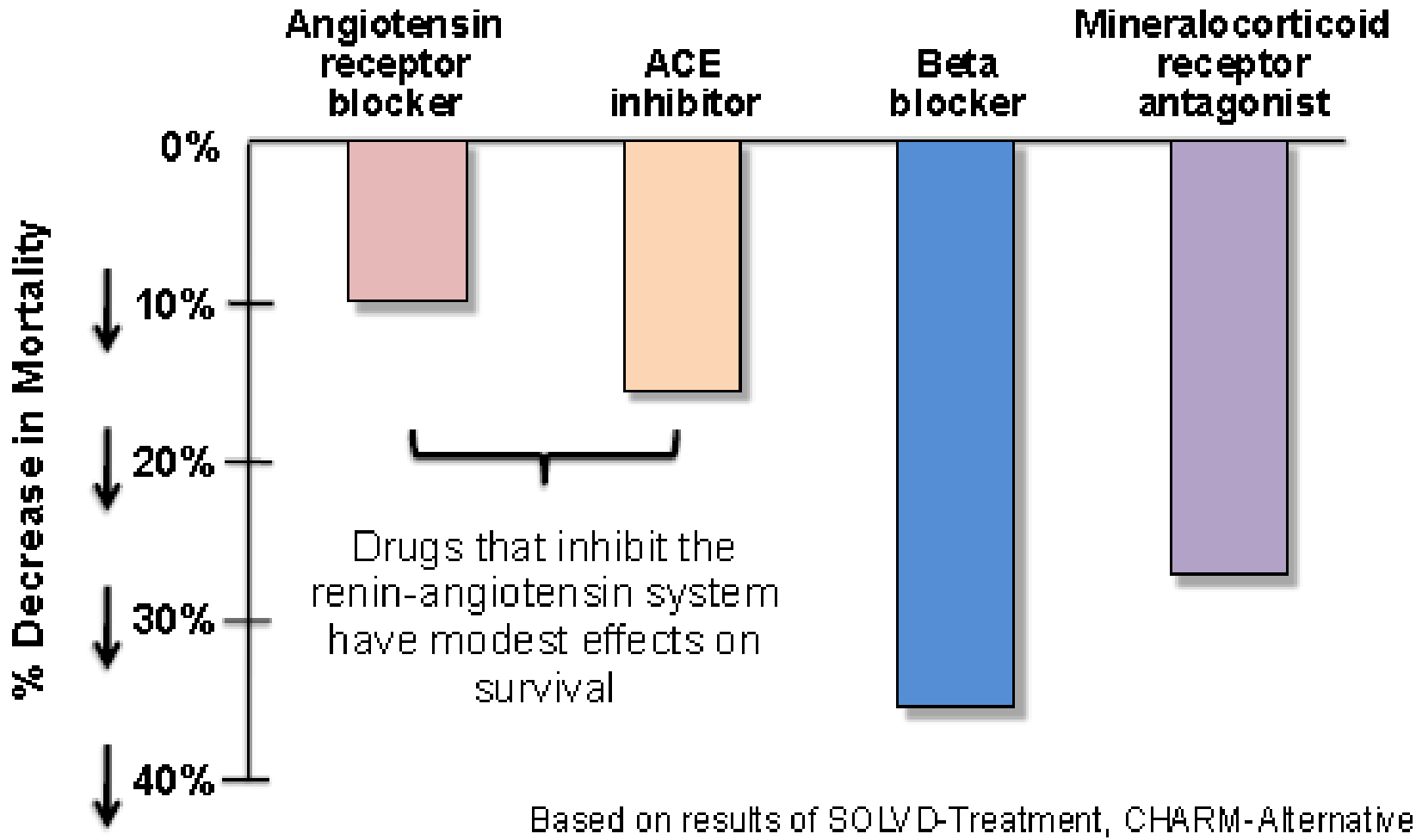
- Systolic vs. Diastolic failure (Left vs. Right)
  - Treatment is different for each
    - Beta-blockers
    - ACE inhibitors
    - Neprolysin Inhibitors
    - Mineralocortocoid Receptor Antagonists
    - SGLT2 inhibitors
    - Loop diuretics
    - Inotropes
    - Glycosides
    - Vasodilators



# Medications for Heart Failure

- ACE Inhibitors
  - Cardioprotective
  - Decreases hormonal remodeling
  - Decreases all-cause mortality
    - Enalapril
    - Captopril
    - Ramipril
    - Lisinopril
    - Benazepril
- Beta-Blockers
  - Decreases hormonal remodeling
    - Inhibits cardiac toxins
    - Anti-arrhythmic effects
  - Decreases all-cause mortality
    - Metoprolol Succinate (Toprol)
    - Bisoprolol
    - Carvedilol*
- Mineralocortocoid Receptor Blockers
  - Reduces hypokalemia
  - Blocks Aldosterone
    - Prevents structual changes to heart and progression to HF
    - Prevents arrhythmia

# Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

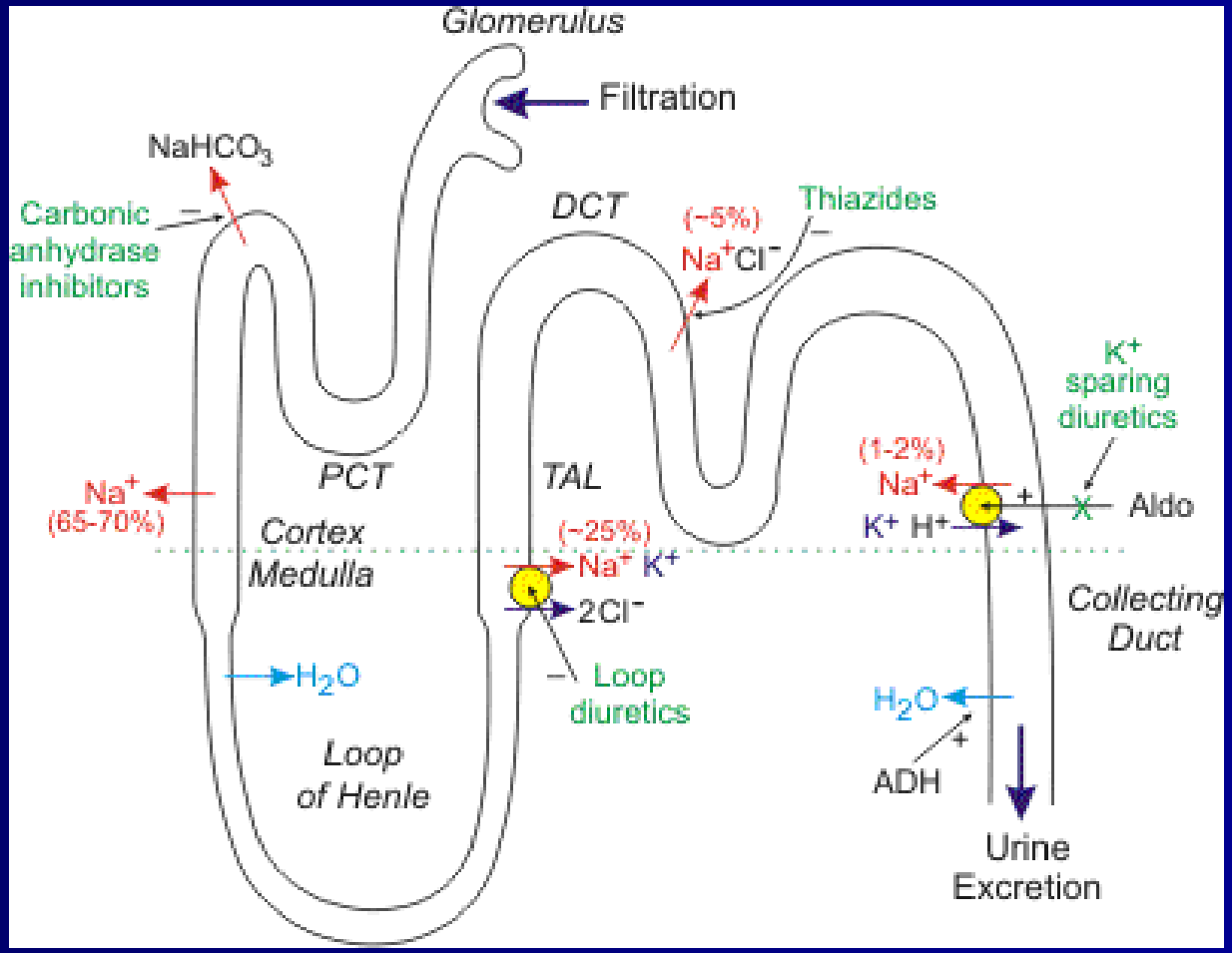



Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

# Loop Diuretics

- Disrupts Na-K-Cl transport in ascending loop of henle.
- Indicated for the symptomatic relief of HF
- Does NOT improve morbidity or mortality
- Furosemide < Torsemide < Bumetanide
  - HCTZ works at a different site and is *not* indicated for HF patients as monotherapy
    - May be used as adjunct
- Helps pull fluid out of pulmonary and interstitial spaces
- More pronounced hypokalemia

# Site of Action of Diuretics



# Inotropic Therapy

- Increased force of contraction:
  - Increased volume of blood ejected
  - End Systolic Volume Decreased
  - Decreased Tension on Heart Wall
  - Oxygenation Improved

# Inotropic Therapy

- Milrinone (Primacor®)
  - Onset in 5 – 15 minutes, $t_{1/2}$ of 2 – 4 hours
  - Needs to be renally adjusted (85% renally cleared)
  - Dose: 50 mcg / Kg IV load over 10 minutes, followed by maintence of 0.375 – 0.75 mcg / Kg / min
  - ADRs: hypotension, arrythmias, thrombocytopenia
  - Nursing pearls:
    - No furosemide in “Y” site
    - Watch renal function

# Inotropic Therapy

- Dobutamine
  - Onset 1 minute
  - Dose: 2.5-20 mcg/kg/min IV; titrate according to response
  - MAX dose, 40 mcg/kg/min IV
  - Nursing pearls:
    - Monitor BP, Heart Rate, Urine Flow

# Digoxin

- Indicated for Afib & Heart Failure (systolic dysfunction only!)
- Does NOT change mortality
- Increases calcium inside myocytes (stronger contraction)
- Does NOT convert patients to normal sinus rhythm
- Renally eliminated
  - Need to adjust accordingly
- Levels correlate with disease
  - HF : 0.5 – 0.9 ng/mL
  - Afib : 1.5 – 2.2 ng/mL
- Levels do ***NOT*** correlate with clinical efficacy or toxicity

# Digoxin Inspired Art

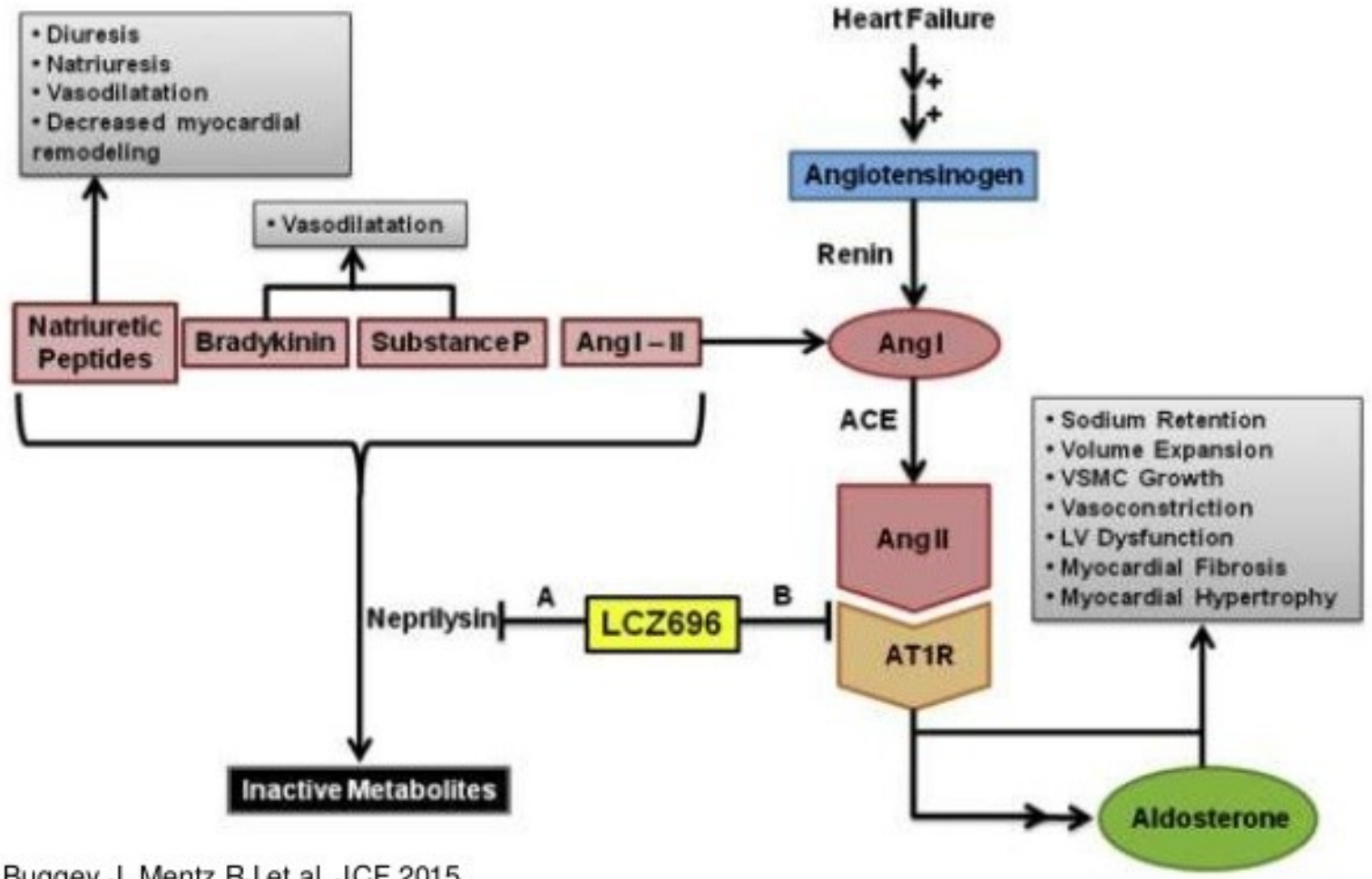
# Mineralocortocoid Receptor Antagonists

- Spironolactone (and Eplerenone) has been shown to add benefit to post-MI and heart failure patients
- Indicated for patients with reduced ejection fraction (EF $\leq$40%)
- Patient should have Scr < 2.5 mg/dL
- ADRs: Hyperkalemia, gynecomastia, alopecia

# New Kid On The Block

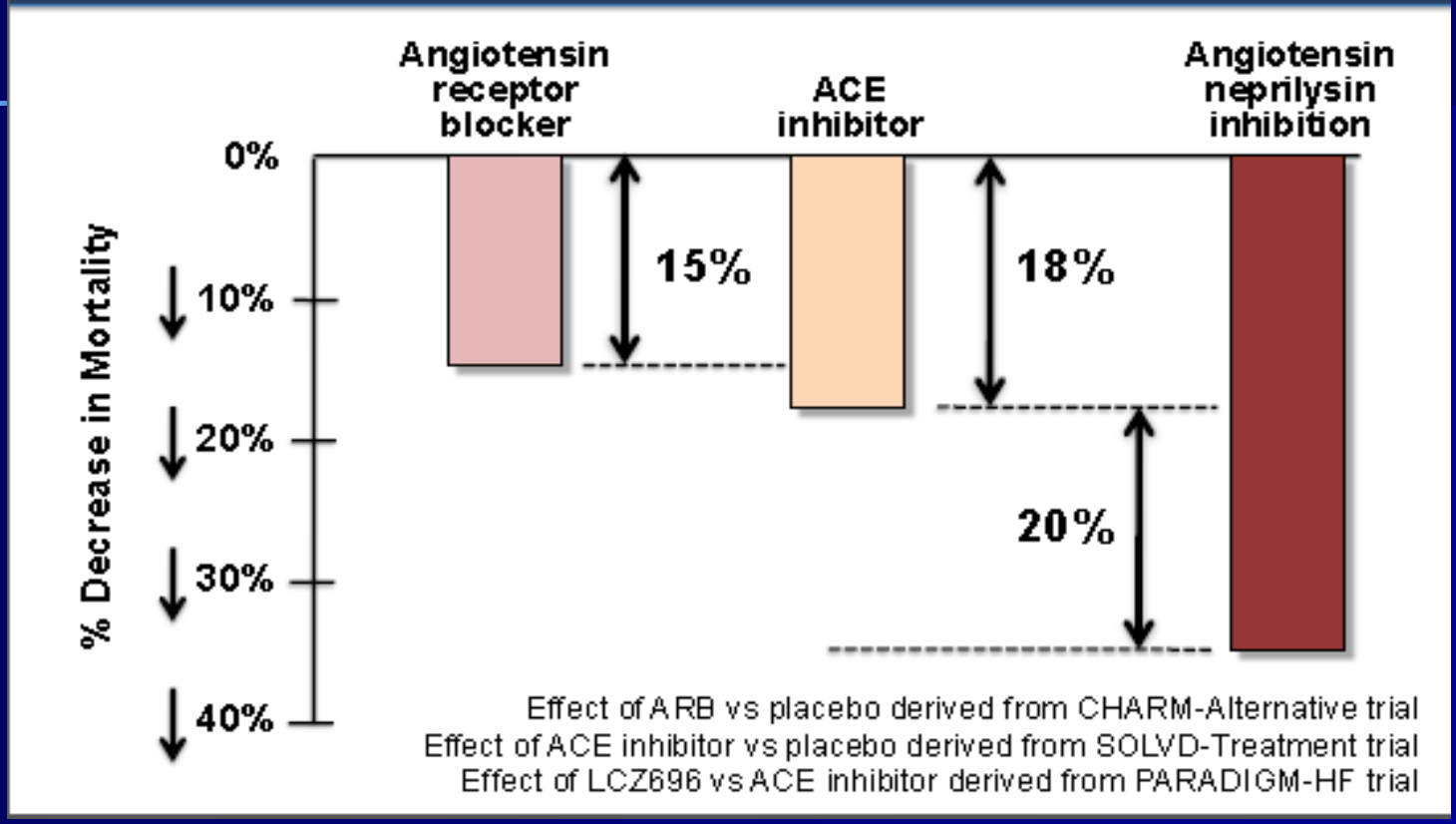
- Entresto (Sacubitril / Valsartan)
  - Neprilysin Inhibitor + ARB
    - Sacubitril inhibits breakdown of naturetic peptides, substance P, bradykinin, AND Angiotensin II (ARB needed)
    - Decreased neurohormonal activation, vascular tone, cardiac fibrosis / hypertrophy, and sodium retention
  - Adverse events
    - Same as seen with Valsartan
      - Hypotension, hyperkalemia, renal failure, etc.
    - Angioedema
      - Must have 36 hour washout with ACE-I use

# LCZ696 – sacubitril/valsartan - Entresto




Buggey J, Mentz RJ et al. JCF 2015

# Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System




- 21% Decrease in Hospitalizations vs. ACE-I/ARB
- 16% Decrease in All Cause Mortality vs. ACE-I
- 20% Decrease in Cardiovascular Death vs. ACE-I/ARB (NNT =32)

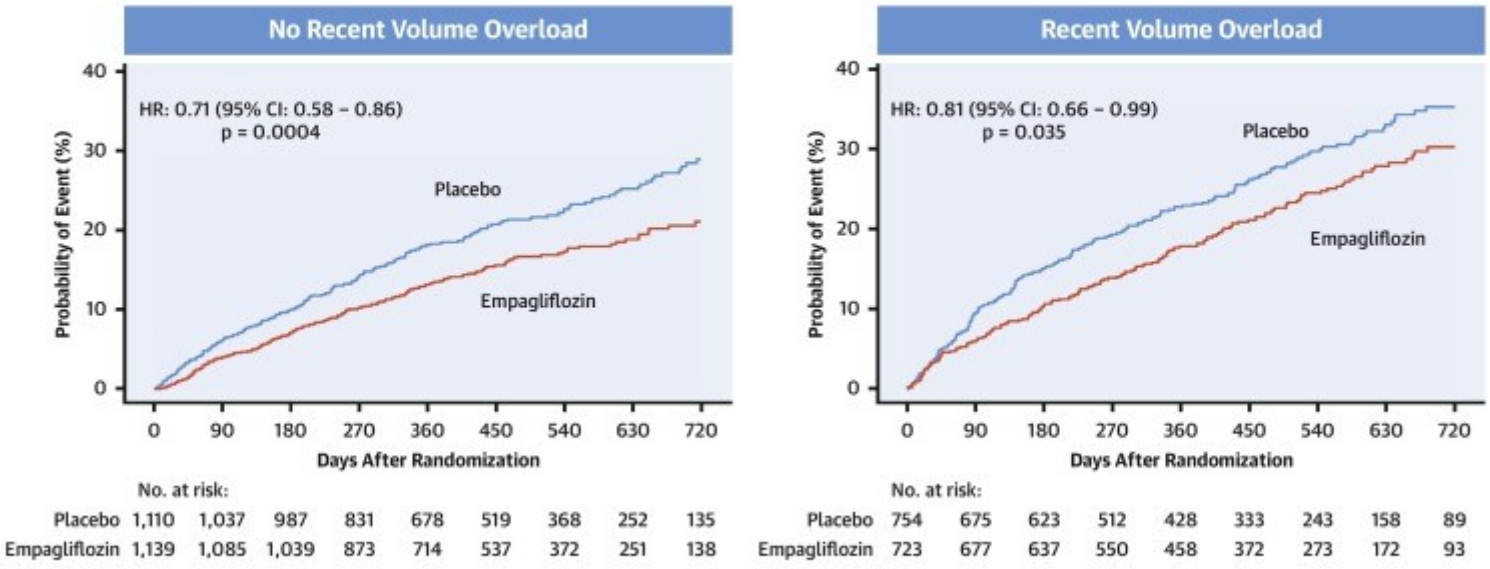
# Not Just for Diabetes!

- SGLT2 Inhibitors
  - Dapagliflozin
  - Empagliflozin (BHC formulary agent)
  - Canagliflozin
- Decreases sodium reabsorption and increases sodium delivery to the distal tubule,
  - cardiac preload/afterload, downregulate sympathetic activity, and decrease intraglomerular pressure
- Adverse Reactions:
  - >10%: Urinary tract infection females: 18% males: 4%
  - 1% to 10% Dyslipidemia (4%), increased thirst (2%), Nausea (2%), Increased urine output (3%), Increased hematocrit (3% to 4%), Genitourinary fungal infection (2% to 6% [placebo: ≤2%])

# What's The Big Deal?

- EMPEROR-Reduced Trial

**CENTRAL ILLUSTRATION: Effect of Empagliflozin on the Combined Risk of Cardiovascular Death or Hospitalization for Heart Failure in Patients With or Without Recent Volume Overload at Baseline**




Packer, M. et al. J Am Coll Cardiol. 2021;77(11):1381-92.

# What's The Big Deal?

Table 1: Summary of Heart Failure Outcomes in SGLT2 Inhibitor Clinical Studies

| Outcome | Meta-analysis of SGLT2 Inhibitors in T2D CVOTs (Empagliflozin, Canagliflozin and Dapagliflozin)[17] | | DAPA-HF (Dapagliflozin)[8] | EMPEROR-Reduced (Empagliflozin)[9] |
|---|---|---|---|---|
| | Overall Population (n=38,723) | History of HF (n=4,543) | HFrEF (n=4,744) | HFrEF (n=3,700) |
| **Relative risk reduction (%)** | | | | |
| HHF | 32 | 31 | 30 | 30 |
| HHF and CV death | 24 | 27 | 26 | 25 |
| **HR** | | | | |
| HHF | 0.68 (95% CI [0.60–0.76]; p<0.001) | 0.69 (95% CI [0.57–0.83]; p<0.001) | 0.70 (95% CI [0.59–0.83]; p<0.001) | 0.70 (95% CI [0.58–0.85]; p<0.001) |
| HHF and CV death | 0.76 (95% CI [0.63–0.84]; p<0.001) | 0.73 (95% CI [0.63–0.84]; p<0.001) | 0.74 (95% CI [0.65–0.85]; p<0.001) | 0.75 (95% CI [0.65–0.86]; p<0.001) |

*CV = cardiovascular; CVOT = cardiovascular outcomes trial; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalisation for heart failure; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes. Source: Arnott et al. 2020,[17] McMurray et al. 2019[8] and Packer et al. 2020.[9]*

Cardiac Failure Review 2020;6:e31. DOI: **https://doi.org/10.15420/cfr.2020.23**

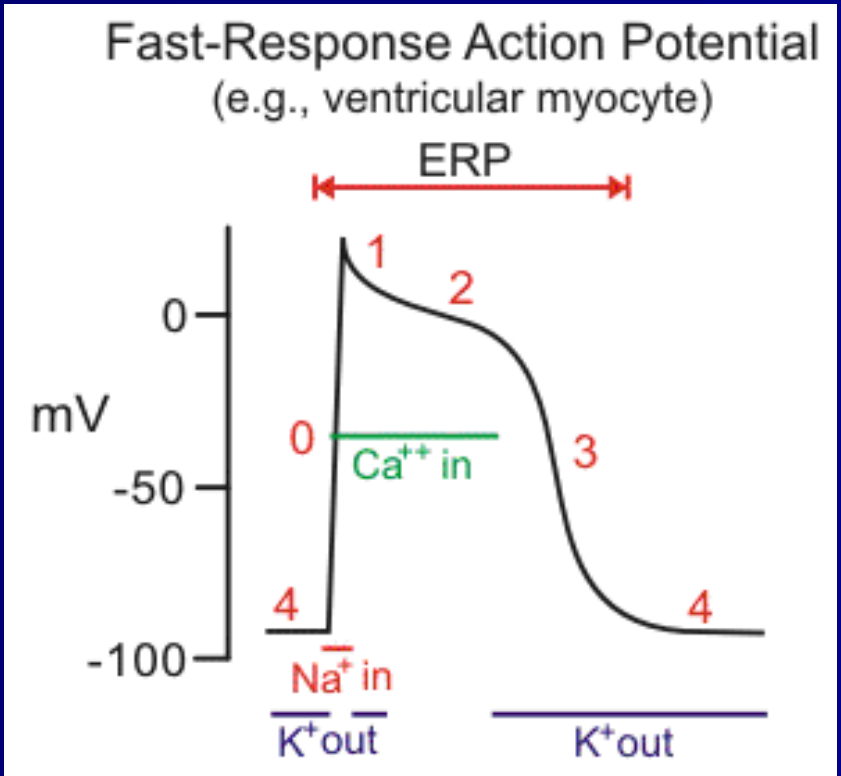
# Vasodilators

- Nitrates (NTG / NTP / Isosorbide)
  - Improves hemodynamics
  - Decreases $O_2$ demand
  - Increases venous system's capacity
  - Decreases congestion
  - Decreases myocardial work
  - Improves cardiac output
  - Leads to vascular and cardiac vessel relaxation
  - ADRs: Headache, hypotension, cyanide toxicity, lactic acidosis
- Hydralazine
  - Arterial vasodilator
  - Good for immediate treatment of hypertension (especially in renal patients)
  - Increases renal blood flow
  - ADRs: Lupus-like reaction, Reflex tachycardia

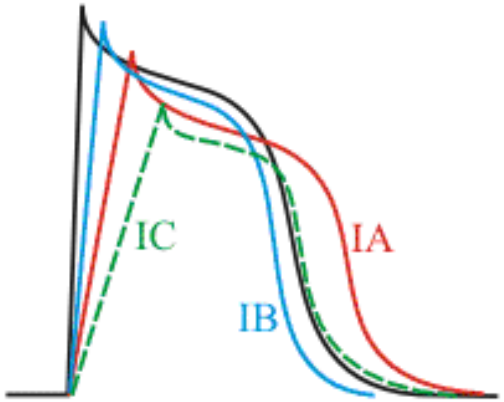
# Anti-arrhythmics

- Class Ia
  - Procainamide
  - Disopyramide
  - Quinidine
- Class Ib
  - Lidocaine
  - Toicanide
  - Mexelitine
- Class Ic
  - Flecainide
  - Propafenone
  - Moricizine
- Class II (beta-blockers)
  - Esmolol
  - Labetolol
  - Metoprolol
- Class III
  - **Amiodarone**
  - Sotalol
  - Dofetilide
  - Ibutilide
- Class IV (Calcium Channel Blockers)
  - Diltiazem
  - Verapamil

# Action Potential



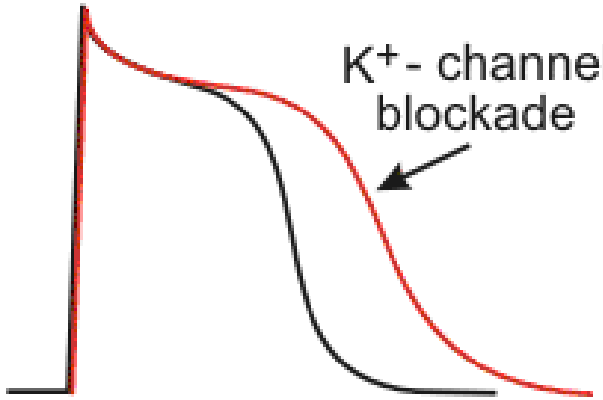
# Action Potential



Ventricular Action Potential

- Class IA: e.g., quinidine
  - Moderate $Na^+$-channel blockade
  - ↑ ERP
- Class IB: e.g., lidocaine
  - Weak $Na^+$-channel blockade
  - ↓ ERP
- Class IC: e.g., flecainide
  - Strong $Na^+$-channel blockade
  - → ERP

Delayed Repolarization by Potassium-Channel Blockade



Ventricular Action Potential

# Uses for Anti-arrythmics

| Condition | Drug | Comments |
|---|---|---|
| Sinus Tach | Class II, IV | Other underlying causes may need treatment |
| Afib/flutter | Class IA, IC, II, III, IV<br>digitalis; adenosine | Ventricular Rate Control |
| PSVT | Class IA, IC, II, III, IV<br>adenosine | |
| AV Block | atropine | Acute Reversal |
| V-Tach | Class I, II, III | |
| PVC | Class II, IV;<br>Mg++ salts | Usually not treated |
| Dig Toxicity | Class IB<br>Mg++ salts; KCl | |

# Amiodarone

- Most widely used agent indicated for almost every arrhythmia
- Class III anti-arrythmic
  - Acts on Na channels, Ca channels, K channels and adrenergic receptors
- Stability is major concern
  - Leeches onto PVC, therefore only glass or polyolefin for continuous infusions
    - 10 minute infusions may be administered through PVC bags
- Major *immediate* reactions include hypotension and arrhythmias

# Vasopressors

- Alpha 1
  - located in vascular walls; induces potent vasoconstriction
- Beta 1
  - located in heart; increases inotropy and chronotropy
- Beta 2
  - vasodilation
- Dopamine
  - mostly vasodilation, subtype induces vasoconstriction

# Selected ICU Medications

| | Alpha-1 | Beta-1 | Beta-2 | Da |
|---|---|---|---|---|
| Dopamine | ++++ | ++++ | ++ | ++ |
| Dobutamine | + | ++++ | ++ | 0 |
| Norepinephrine | ++++ | ++++ | 0 | 0 |
| Phenelephrine | ++++ | 0 | 0 | 0 |
| Epinephrine | ++++ | ++++ | ++ | ++ |
| Vasopressin | 0 | 0 | 0 | 0 |

# Norepinephrine (Levophed)

- Standard Concentration = 8 mg in 250 mL D5W
  - D5W protects from oxidation and extends stability
  - Independent studies show stability in NS
- Initial dosing
  - 0.1 mcg/kg/min or 8-12 mcg/min
- Max doses (BHC soft limits)
  - Doses up to 3 mcg/kg/min have been used rarely in sepsis
  - 0.5 mcg/kg/min or 30 mcg/min
- MAY BE INFUSED THROUGH PERIPHERAL LINE!!!
  - Get central access as soon as possible

# Norepinephrine (Levophed)

- Effects
  - Vasoconstriction (Alpha-1 activation)
  - Transient increase in heart rate (Beta-1 activation)
- Initial vasopressor in various shock
  - Septic, Cardiogenic, Hypovolemic
  - More potent than dopamine
  - Lower mortality and lower risk of arrhythmias vs. dopamine in septic shock
    - Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One 2015;10:e0129305.

Surviving Sepsis Campaign

# Vasoactive agents

- **We recommend norepinephrine as the first choice vasopressor**

(strong recommendation, moderate quality of evidence).

- **We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.**

(weak recommendation, low quality of evidence)

# Vasopressin

- Standard concentration 120 units in 250 mL
- Usual dosing
  - 0.01 to 0.04 units/min
  - 0.03 units/min
    - Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016
  - Usually non-titrating
  - Doses above 0.04 units/min may lead to cardiac arrest
    - den Ouden DT, Meinders AE. Vasopressin: physiology and clinical use in patients with vasodilatory shock: a review. Neth J Med. 2005 Jan;63(1):4-13.

# Vasopressin

- Effects
  - Smooth Muscle Contraction
    - Can decrease stroke volume and CO
    - Contracts gastrointestinal smooth muscle
    - Decreases splanchnic, renal, and cutaneous circulation
  - Non-catacholamine induced vasoconstriction
- Adjunct vasopressor
  - Septic shock
    - Vasopressin deficiency in septic shock

# Epinephrine

- Standard Concentration = 4 mg / 250 mL
- Usual dosing
  - 1 - 10 mcg/min
  - 0.1 – 0.5 mcg/kg/min
    - Titrate up by 0.2 mcg/kg/min every 5 minutes

# Epinephrine

- Effects
  - Most potent alpha agonist (vasoconstriction)
  - Direct cardiac stimulation through Beta-1 (heart rate)
- Primary in anaphylactic shock
- Adjunct in septic shock
  - May increase lactate levels

# Phenylephrine

- Standard Concentration = 25 mg / 250 mL
- Usual dosing
  - 100 – 180 mcg/min initially
  - Decrease rate to 40-60 mcg/min once BP stabilizes

# Phenylephrine

- Effects
  - Pure alpha agonist
    - Vasoconstriction
    - Heart rate neutral
- Place in therapy
  - Tachyarrythmias due to norepinephrine
  - Salvage therapy
  - High cardiac output with hypotension

# Dopamine

- Standard Concentration = 800 mg / 250 mL
- Usual dosing
  - 1 – 10 mcg/kg/min
    - Effects change as dose increases

| | Alpha-1 | Alpha-2 | Beta-1 | Beta-2 | Effect on SVR |
|---|---|---|---|---|---|
| 0.5-2 mcg/kg/min | NA | (+) | + | + | NA |
| 3-10 mcg/kg/min | + | (+) | ++ | ++ | up |
| > 10 mcg/kg/min | +(+)(+) | (+) | ++(+)(+) | +(+) | up |

# Dopamine

- Place in therapy
  - May be used in place of norepinephrine in selected patients
    - Low risk of tachyarrhythmias
    - Absolute or relative bradycardia