**Cardiovascular Drugs Throughout the Continuum of Care**

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**Drugs that keep blood from clotting:**  
ASA  
Plavix  
Reopro, Integrilin, Aggrastat  
Cynamide, Heparins

**Drugs that increase contractility:**  
Dobutamine  
Dopamine  
Milrinone  
Digitalis

**Drugs that dilate veins (preload reducers):**  
Nitrates (NTG, etc.)  
ACEI  
ARBs  
Aldosterone blockers  
Neseritide

**Drugs that reduce blood volume:**  
Diuretics  
ACEI  
ARBs  
Aldosterone blockers

**Drugs to treat angina:**  
Nitrates (NTG, etc.)  
Beta blockers  
Calcium blockers

**Drugs that cause vasoconstriction and support BP:**  
Neseritide  
Levophed  
High dose dopamine  
Epinephrine  
Vasopressor

**CO = HR x SV**

**Physiological Basis Of Cardiovascular Drug Therapy**

**Determinants of Cardiac Output**

- Preload
- Afterload
- Contractility

- Venous tone
- Body Position
- Intrathoracic pressure
- Intrapericardial pressure
- Blood Volume
- Distribution of blood volume
- Atrial Kick
- LV Function

- Preload is ventricular fiber length  
- Volume determines fiber length  
- CVP is the clinical indicator of RV preload  
- JVD is physical assessment parameter that reflects RV preload  
- PWP is the clinical indicator of LV preload  
- Lung sounds are physical assessment parameter that reflect LV preload

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Sympathetic NS & Circulating vasodilator or vasoconstrictor mediators

Arteriolar Tone

SVR

Aortic Pressure & Compliance

Aortic Stenosis

HOCM

AFTERLOAD

SVR

Aortic Pressure

Aortic Pressure

Aortic Pressure

Aortic Pressure

Aortic Stenosis

Aortic Stenosis

Aortic Stenosis

Aortic Stenosis

HOCM

HOCM

HOCM

HOCM

Circulating vasodilator or vasoconstrictor mediators

Afterload is the work done by a ventricle to eject its volume

PVR is clinical indicator of RV afterload

SVR is clinical indicator of LV afterload

Diastolic BP is a reflection of LV afterload

SNS Adrenals

H

CO

2

O

2

Ventricular Catecholamines

Metabolic Drugs

Muscle Mass State

CONTRACTILITY

Contractility is how efficiently the fibers shorten regardless of how long they are

No good direct measure of contractility

LVSWI sometimes used as clinical indicator

CO  =  HR  x  SV

Preload

Afterload

Contractility

CO  =  HR  x  SV

Atropine

Pacing

Beta Blockers

Calcium Channel Blockers

Digoxin

Adenosine

Antiarrhythmics

CO  =  HR  x  SV

Preload

Fluids

Blood Products

Volume Expanders

Diuretics

Venous Dilators (NTG)

ACE Inhibitors

ARBS

Nesiritide (Natrecor)

Morphine

Aldosterone Blockers

CO  =  HR  x  SV

Afterload

Arterial Dilators

Nitroprusside (Nipride)

Mltrinone (Prinmis)

Ca++ blockers

Antihypertensives

ACEI, ARBs

Nesiritide

Vasopressors

Norepinephrine (Levophed)

Dopamine (high dose)

Epinephrine

Phenylephrine (Neoaphrine)

Vasopressin

Other drugs that increase HR:

dopamine, dobutamine, epinephrine, norepinephrine

Hypoxemia

Ischemia
\[
\text{CO} = \text{HR} \times \text{SV} \\
\]

### Inotropes
- Dobutamine
- Dopamine
- Milrinone
- Digoxin

### Beta Blockers
- Calcium Channel Blockers
- Others: Antiarrhythmics, Anesthetics, Propofol, Chemo

### Balancing \( O_2 \) Supply & Demand

<table>
<thead>
<tr>
<th>( \downarrow \text{Demand} )</th>
<th>( \uparrow \text{Supply} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preload</td>
<td>Afterload</td>
</tr>
<tr>
<td>Diuretics</td>
<td>ACEI, ARBs, SARKs, Nortricor, Mophine</td>
</tr>
<tr>
<td>( \downarrow \text{SVR} )</td>
<td>( \uparrow \text{CO} )</td>
</tr>
<tr>
<td>Contractility</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>NTG, Ca++ blockers, ASA, Platelet inhibitors, Anticoagulants, Angioplasty, PDE inhibitors, Calcium Channel Blockers, Centrally Acting Agents</td>
<td></td>
</tr>
</tbody>
</table>

### Drug Therapy to Increase BP

\[ \uparrow \text{BP} = \uparrow \text{CO} \times \uparrow \text{SVR} \]

#### Drugs to \( \uparrow \text{CO} \)
- Volume
  - Dobutamine
  - Dopamine
  - Milrinone
  - Epinephrine

#### Drugs to \( \uparrow \text{SVR} \)
- Vasopressors
  - Norepinephrine
  - Phenylephrine
  - Vasopressin
  - Epinephrine
  - Dopamine

### Drug Therapy to Decrease BP

\[ \downarrow \text{BP} = \downarrow \text{CO} \times \downarrow \text{SVR} \]

#### Drugs to \( \downarrow \text{CO} \)
- Diuretics
- Beta Blockers ("betalol"
- Calcium Channel Blockers

#### Drugs to \( \downarrow \text{SVR} \)
- Peripheral Alpha Blockers (prazosin, terazosin, regimine etc)
- Direct Arterial Dilators (hydralazine, minoxidil)
- ACEI ("prils"), ARBs ("sartans"
- PDE inhibitors (milrinone)
- Calcium Channel Blockers ("pines": amlodipine, felodipine, etc)
- Nitric oxide in vascular tissue (nitroprusside, nitrates)
- Centrally Acting Agents (clonidine, guanabenz, guanfacine)

### Open arteries
- Heart Rate
- CO
- Preload
- \( \text{paO}_2 \)
- Afterload
- \( \text{Hb, Hct} \)

### Heart Rate
- Slower is better in CAD

### Low BP could be due to:
- Low CO
- HR too slow or too fast
- Preload too low or too high
- Contractility low
- Low SVR
- Vasodilation due to sepsis, drugs, anaphylaxis

### BP = CO \times SVR

- BP value does not tell you WHY the BP is low – must evaluate determinants of BP and treat the cause
Role of Kidney in HF

Renin-Angiotensin System

- Renal blood flow (↓BP, ↓Na\(^+\), diuresis)
- Renin release
- Angiotensinogen → Angiotensin I → Angiotensin II
- Vasoconstriction → Aldosterone release
- ↑Na\(^+\) & H\(_2\)O retention
- ↓BP & Organ perfusion

Mechanism of Action

- Angiotensin I
- (converting enzyme) ACEI
- Angiotensin II
- ARBs

- ↓Vasoconstriction
- ↓Aldosterone release
- Na\(^+\) & H\(_2\)O retention

Venous dilation = ↓preload
Arterial dilation = ↓afterload

Drugs That Block The RAAS

- ACE Inhibitors
- ARBs
- Aldosterone Blockers
- Renin Blockers

More pressure
More volume
Negative Effects of Angiotensin II in Heart Failure

- Promotes sodium and water reabsorption
- Causes systemic arteriolar vasoconstriction
- Promotes endothelial dysfunction
- Stimulates the sympathetic nervous system

Cardiac effects:
- Stimulates hypertrophy of cardiac myocytes.
- Appears to contribute to remodeling that occurs in patients with left ventricular dysfunction.
- Promotes the development and severity of atherosclerosis

ACE INHIBITORS

Block conversion of Angiotensin I to Angiotensin II

- ↓ Preload
- ↓ Afterload
- ↑ Levels of Bradykinin
- ↑ Prostaglandin Production
- ↓ Ventricular Remodeling

Clinical Uses of ACE Inhibitors

Hypertension
- Heart Failure (all stages) - ↑ survival, ↑ exercise capacity, ↓ symptoms, ↓ hospitalization
- Post-MI to limit remodeling - improved survival
- Acute Coronary Syndromes
- Slow the progression of diabetic and nondiabetic chronic renal failure (↓ intraglomerular pressures)
- May decrease incidence of new onset Type II diabetes in patients with and without HTN

Side Effects of ACE Inhibitors

- Cough (5-20%) - due to increased bradykinin level
- Hypotension - due to arterial and venous dilation
- Hyperkalemia (3%) - due to decreased aldosterone (which increases K+ reabsorption)
- Decreased glomerular filtration in some patients with renal disease or heart failure - due to dilation of efferent arteriole which reduces glomerular perfusion pressure
- Angioedema (0.1-0.7%) - due to vasodilation and increased vascular permeability resulting from increased bradykinin level

Contraindications for ACE Inhibitors

- Bilateral renal artery stenosis
- Renal artery stenosis of single kidney
- Severe aortic stenosis or HOCM
- Severe renal failure (creatinine > 2.5)
- Pregnancy
**Patient Teaching Issues**

- Report swelling of face, eyes, lips, tongue; difficulty breathing or swallowing (angioedema)
- Report lightheadedness (may indicate ↓BP)
- Report to MD if nausea or vomiting
  - Vomiting, diarrhea, or excessive sweating can cause hypovolemia and result in hypotension
- Get up slowly, move ankles & feet prior to standing to prevent postural hypotension
- Do not take K⁺ containing salt substitutes (risk of ↑K⁺)
- Report signs of infection: sore throat, fever

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**ACE Inhibitors**

- Benazapril (Lotensin)
- Captopril (Capoten)
  - Not a prodrug
- Enalapril (Vasotec)
- Enalaprilat (IV form)
- Fosinopril (Monopril)
  - Water soluble
  - Not a prodrug
- Moexipril (Univasc)
- Perindopril (Aceon)
- Ramipril (Altace)
- Quinapril (Accupril)
- Trandolapril (Mavik)

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**Angiotensin Receptor Blockers (ARBS)**

- Block effects of Angiotensin II at receptor sites
- Block Angiotensin II formed via all pathways
- Result in vasodilation (afterload reduction) and decreased volume (preload reduction)
- No effect on bradykinin
- Slow the progression of proteinuric diabetic and nondiabetic chronic renal failure
- May decrease incidence of new onset Type II diabetes in patients with and without HTN

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**Angiotensin II Receptor Blockers**

- Losartan (Cozaar)
  - 25-100 mg once or twice a day
- Irbesartan (Avapro)
  - 150-300 mg once a day
- Candesartan (Atacand)
  - 8 – 32 mg once or twice a day
- Eprosartan (Teveten)
  - 400 – 800 mg/day (once or twice daily)
- Telmisartan (Micardis)
  - 20-80 mg once a day
- Valsartan (Diovan)
  - 80-320 mg once a day
- Olmesartan (Benecar)
  - 20 -40 mg once a day
  - Possible increased risk of death from MI or stroke?

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**ARBs and Cancer Risk**

- In June 2010, a published meta-analysis of 5 clinical trials reported a statistically significant increased risk of developing cancer in patients who received treatment with ARBs compared to those who did not.
- The FDA has completed a meta-analysis of 31 trials to further investigate the association between ARB use and cancer risk.
  - The results of the FDA meta-analysis, along with other available data, have found no evidence for an increased risk of cancer with ARB use.
Aldosterone Blockers

- Renal blood flow
- Renin release
- Angiotensinogen → Angiotensin I → Angiotensin II → Vasodilatation → Na+ & H2O retention
- BP & Organ perfusion

Aldosterone contributes to the pathophysiology of heart failure:
- Promotes retention of Na+
- Loss of Mg++ and K+
- Activation of SNS
- Inhibition of parasympathetic NS
- Myocardial and vascular fibrosis
- Dysfunction of endothelium (formation of endothelin – powerful vasoconstrictor)

Aldosterone Blockers in HF

- ↓ morbidity and mortality in patients with LV dysfunction post MI, LV dysfunction in diabetics, and in chronic systolic HF
- ↓ hospitalizations for HF
- Class I Recommendations:
  - NYHA class II HF and LVEF ≤ 30%
  - NYHA class III or IV HF and LVEF < 35%
  - Creatinine should be ≤ 2.5 mg/dL in men and ≤ 2.0 mg/dL in women
  - Potassium should be less than 5.0
  - Patients must be carefully monitored for serum potassium and renal function

Spironolactone (non-selective)

- 29% reduction in mortality over 3 years compared to placebo
- Vasodilator properties
- Decreases cardiac norepinephrine release
- Blocks aldosterone and androgen, stimulates progesterone
- Major side effects: gynecomastia, breast pain, sexual dysfunction and menstrual problems
- Causes K+ reabsorption

Eplerenone (Inspra)

- Selective Aldosterone Receptor Antagonist
- Indicated for treatment of hypertension and heart failure
- ↓ mortality and hospitalizations in HF patients
- 1000 fold less binding to androgen receptor
- 100 fold less binding to progesterone receptor
- Results in blockade of aldosterone receptors without side effects associated with spironolactone

Renin Blockers

- Renal blood flow
- Renin release
- Angiotensinogen → Angiotensin I → Angiotensin II → Vasodilatation → Na+ & H2O retention
- BP & Organ perfusion
**Renin Blocker**

- **Aliskiren (Tekturna)**
  - **Action:** direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I
  - **Indicated for treatment of hypertension**
  - **Dose:** 150 mg qd, can increase to 300 mg qd
  - **Side effects:** angioedema, hypotension, ↑ K⁺
  - **Contraindicated in severe renal failure and pregnancy**
  - **Maximum antihypertensive effect within 2 weeks**

**FDA Warning**

- **ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints) study.**
  - Worldwide study of 8606 patients with type 2 diabetes and renal impairment intended to evaluate if aliskiren-containing products, when given in addition to ACEI or ARBs could reduce the risk of cardiovascular and renal events.
  - Study was terminated early based on findings that use of aliskiren was of unlikely benefit and that concomitant use with ACE inhibitors or ARBs was associated with an increased risk of nonfatal stroke, hyperkalemia, hypotension, and renal complications.
- **FDA warning issued in April 2012**
  - Diabetic patients and patients with moderate to severe renal impairment who mix the drugs are at risk of renal impairment, hypotension, and hyperkalemia.

**Beta Blockers**

<table>
<thead>
<tr>
<th>Alpha Receptors (Arteries &amp; Veins)</th>
<th>Beta Receptors (Heart)</th>
</tr>
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<tbody>
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<td>Vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>↓ Heart rate</td>
<td></td>
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<tr>
<td>↓ Renin release (kidney)</td>
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**Cardiovascular Effects of SNS**

- **Alpha Receptors** (Arteries & Veins)
  - Vasoconstriction
  - ↓ Heart rate
  - ↓ Contractility
  - ↓ Automaticity
  - ↓ Conduction velocity
  - ↓ Renin release (kidney)

**Beta Blockers**

- **Beta Receptors**
  - Beta₁ (Heart)
  - Beta₂ (Arteries, Veins, Lungs)

**Effects of Beta Blockers**

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<td>Beta₁ (Heart)</td>
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<td>(Arteries, Veins, Lungs)</td>
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<td>↓ Heart rate</td>
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<td>↓ Renin release (kidney)</td>
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**Side Effects of Beta Blockers**

- **Cardiac**
  - Bradycardia, AV block
  - Heart Failure
  - Hypotension

- **Pulmonary**
  - Bronchoconstriction
  - Pulmonary edema

- **Peripheral Vascular**
  - Vasoconstriction
Side Effects of Beta Blockers

- **Metabolic**
  - Mask signs of hypoglycemia
  - Augment hypoglycemic actions of insulin
  - Increase serum triglycerides
- **Other**
  - Fatigue, sleep disturbances
  - Depression
  - Sexual dysfunction
  - Weight gain

<table>
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<tr>
<th>Use</th>
<th>Mechanism of Action</th>
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</table>
| **Hypertension** | Heart rate = \( \frac{\text{CO} \times \text{SVR}}{\text{BP}} \)  
  BP = CO x SVR  
  Heart rate = \( \frac{\text{CO} \times \text{SVR}}{\text{BP}} \)  
  BP = CO x SVR  
  renin release in kidney = \( \text{angiotensin II formation} \)  |
| **Classic Angina** | \( \text{O}_2 \) demand by \( \text{HR}, \text{contractility}, \text{BP} \)  
  \( \text{CO} \) supply by \( \text{HR} \) which \( \text{diastolic filling time} \) and \( \text{coronary perfusion time} \)  |
| **Acute Coronary Syndromes** | automatically in ventricle so \( \text{risk of VF} \) early in MI  
  Preserves ischemic myocardium by \( \text{O}_2 \) demands  
  \( \text{mortality rates} \)  |
| **Heart Failure** | Upregulation of beta receptors, decrease circulating vasoconstrictors,  
  LR remodeling, improve \( \text{O}_2 \) supply & demand, \( \text{SCD} \) and A Fib  |
| **Arrhythmias** | \( \text{automaticity so} \) VT and VF  
  \( \text{AV conduction to slow ventricular rate in A Fib or flutter, may terminate SVTs} \)  |
| **Hypertrophic Cardiomyopathy** | automatically so \( \text{VT and VF} \)  
  \( \text{AV conduction to slow ventricular rate in A Fib or flutter, may terminate SVTs} \)  |

Beta Blockers in ACS

- Should be given to all patients without contraindications (STEMI & NSTEMI)
  - Contraindications: PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease
- Oral within 24 hours
- IV if ongoing chest pain, hypertension, or tachycardia not caused by heart failure
- Metoprolol or atenolol preferred
- Continue indefinitely for secondary prevention

- Decrease LV end-systolic and end-diastolic volume (reverse remodeling)
- May reduce production of some of the inflammatory cytokines that occurs during HF
- May improve function in regions of hibernating myocardium (dysfunctional but viable tissue) by reducing myocardial \( \text{O}_2 \) consumption and increasing diastolic perfusion
- Decrease the frequency of PVCs and the incidence of SCD, especially after MI
- May decrease incidence of atrial fibrillation in HF patients

Why Do We Use Beta Blockers in HF?

- Chronic SNS stimulation is cardiotoxic and contributes to the progression of HF
  - Beta blockers increase survival and decrease mortality and progression of HF
- Chronic beta stimulation \( \rightarrow \) downregulation of beta receptors \( \rightarrow \) decreased responsiveness of beta receptors to SNS stimulation
  - Beta blockade upregulates beta receptor density and restores inotropic and chronotropic responsiveness to improve contractility
- Beta blockers reduce circulating levels of vasoconstrictors (norepinephrine, endothelin, renin)

Beta Blockers in Heart Failure

- Shown to slow progression of HF, improve survival, decrease hospitalizations for HF and improve symptoms and exercise capacity
- Carvedilol, metoprolol, or bisoprolol are preferred (proven benefit in studies)
- Initiated after the patient is stable on ACE inhibitors
- Begin with low doses and titrate to maximum tolerated dose
- Symptoms may increase for 2-3 months before improvement is noted
Beta Blockers

- **Nonselective:** Block both Beta \(_1\) & Beta \(_2\)
  - Propranolol
  - Timolol
  - Penbutolol (ISA)
  - Pindolol (ISA)
  - Nadolol
  - Sotalol
  - Oxprenolol
  - Pindolol

- **Cardioselective:** Block Beta \(_1\)
  - Acebutolol (ISA)
  - Atenolol
  - Metoprolol
  - Esmolol
  - Bisoprolol

- **Combined Alpha & Beta Blocking:**
  - Labetalol - nonselective
  - Carvedilol - nonselective

Calcium Channel Blockers

**Effects of Ca\(^{++}\) on Heart & Blood Vessels**

- Depolarization of SA node and AV node cells ("slow current" calcium dependent cells)
- Facilitates contraction of heart and smooth muscle layer of blood vessels
  - Facilitates actin-myosin interaction in muscle

[Diagram of heart and blood vessels]

**Effects of Ca\(^{++}\) Channel Blockers**

- **Heart:**
  - ↓ heart rate (except Nifedipine-like agents)
  - ↓ AV conduction velocity
  - ↓ contractility (especially Verapamil)

- **Blood Vessels:**
  - Coronary vasodilation (prevent vasospasm)
  - Peripheral vasodilation (afterload reduction)
  - Dihydropyridines have most peripheral vascular effect

**Side Effects of Ca\(^{++}\) Channel Blockers**

- Bradycardia (Diltiazem, Verapamil)
- AV Block (Diltiazem, Verapamil)
- Hypotension (especially Nifedipine)
- HF (especially Verapamil)
- Flushing, headaches
- Peripheral edema
- Constipation (especially Verapamil)

**Clinical Uses of Ca\(^{++}\) Channel Blockers**

<table>
<thead>
<tr>
<th>Use</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina: Coronary Spasm Classic Angina</td>
<td>Prevents vasoconstriction by decreasing amount of Ca(^{++}) available for contraction. Coronary vasodilation increases collateral blood flow. ↓ MVO(_2) by ↓ HR, ↓ contractility, ↓ afterload</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↓ BP = ↓ CO (\times) SVR by vasodilation</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>↓ contractility lessens outflow tract obstruction. ↓ HR allows longer diastolic filling time, more blood in ventricle keeps outflow tract open</td>
</tr>
</tbody>
</table>
**Ca++ Channel Blockers**

- **Heart Rate Lowering:**
  - Verapamil – most depression of contractility
  - Diltiazem

- **Dihydropyridines** (potent vasodilators, little or no depression of contractility):
  - Clevidipine – ultra-short acting (IV only)
  - Nifedipine – short acting, comes in sustained release form for longer action
  - Felodipine
  - Isradipine
  - Nisoldipine
  - Amlodipine – long acting, no cardiac depression, safest one in HF

**Antiplatelet Drugs**

**Drug Site of Action**

- **Thrombin**
- **Epinephrine**
- **Collagen**

**Plaque Rupture:**
- Spontaneous
- Induced by PCI

**Platelet Activation**

**Platelet Aggregation**

**Pathogenesis of ACS**

**IIb-IIIa Inhibitors**

- Reopro
- Eptifibatide
- Tirofiban

**Clopidogrel**

Irreversibly interferes with platelet activation and aggregation by inhibiting binding of ADP to receptors; inhibition lasts lifetime of platelet (10 days)

- **Loading dose:** 300-600 mg – maximal platelet inhibition in 2 hours
- **Maintenance dose:** 75 mg daily for up to 12 months following stent placement; at least 1 month and preferably up to 1 year for medically treated UA/NSTEMI.
- **Discontinue at least 5 days prior to CABG whenever possible**
**Indications for Clopidogrel**

Reduce rate of MI, stroke, and vascular deaths in patients with ACS, ischemic stroke, or peripheral arterial disease; decreases stent thrombosis

Used in patients with unstable angina, NSTEMI, STEMI managed medically or with PCI (with or without stent), or CABG

In place of ASA in ASA-intolerant patients

**Prasugrel**

Irreversibly interferes with platelet activation and aggregation by inhibiting binding of ADP to receptors; inhibition lasts lifetime of platelet (10 days)

More potent platelet inhibition than clopidogrel, but higher rate of bleeding

Indications: reduce rate of thrombotic CV events, including stent thrombosis, in patients with unstable angina, NSTEMI, or STEMI managed with PCI.

- Not used with fibrinolytic therapy or patients treated medically without PCI.
- Not used in patients with history of TIA or stroke.

**Ticagrelor**

- Binds reversibly to the ADP receptor and has faster onset of action than clopidogrel
- Indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS, and reduces the rate of stent thrombosis
- Initial dose 180 mg orally
- Maintenance dose 90 mg bid
- Most common adverse reactions: bleeding, dyspnea

**Anticoagulants**

- Contraindicated with HX of intracranial bleeding, active bleeding, severe hepatic impairment
- Drug interactions:
  - ASA in dose > 100mg decreases efficacy
  - After initiating ASA with 325mg, use 81mg daily dose
  - Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects
  - Monitor digoxin levels with initiation and change of dose
- DC 5 days prior to surgery whenever possible
Extrinsic Pathway

Plaque rupture

**Extrinsic Pathway**

Plaque rupture

VII

VIIa

Prothrombin

Fibrinogen

Prothrombin Activator

Ca++

Thrombin

Thrombus

Factors formed in liver and inhibited by warfarin

Indirect Xa inhibitor: fondaparinux

Direct Xa inhibitor: rivaroxaban

Heparin

LMWH: enoxaparin, dalteparin

Heparin Direct thrombin inhibitors:

- argatroban
- bivalirudin
- lepirudin
- dabigatran

**Vasoactive Drugs**

**Inotropes:**

- increase contractility

**Vasodilators:**

- preload &/or afterload reduction

**Vasoconstrictors:**

- blood pressure support

**Receptor Physiology**

- **Alpha-1 receptors**
  - Located in blood vessels
  - Stimulation causes vasoconstriction
  - Respond strongly to norepinephrine and weakly to epinephrine

- **Beta-1 receptors**
  - Located in heart and kidney
  - Stimulation causes increase HR, contractility, conduction velocity, renin release in kidney
  - Respond equally to norepinephrine and epinephrine

- **Beta-2 receptors**
  - Located in blood vessels
  - Stimulation causes vasodilation
  - More sensitive to epinephrine than norepinephrine

- **Dopaminergic receptors**
  - Located in renal, mesenteric, and coronary blood vessels and in the CNS
  - Stimulation causes vasodilation

**General Considerations with Vasoactive Drugs**

- **B₁ effect** increases HR & contractility so can cause myocardial ischemia (use with caution post MI)

- **B₁ effect** increases AV conduction velocity so may cause increased ventricular rate in atrial fibrillation

- Beta blocker therapy may diminish **B₁** effects

- Correct hypovolemia before initiating vasoactive drugs

- Drugs that increase contractility are contraindicated in aortic stenosis or obstructive cardiomyopathy

- Tachyphylaxis can occur – decreased response to drug requiring increasing doses

**General Considerations with Vasoactive Drugs**

- Alpha effect causes local vasoconstriction if the drug infiltrates

- Central line preferred to prevent infiltration and more rapid distribution of drug to the heart

- Subcutaneous drugs (heparin, insulin) may not be absorbed as well when vasoconstrictors are used

- Hyperglycemia may occur due to the inhibition of insulin secretion (more pronounced with norepinephrine and epinephrine than dopamine)

- Monitor BP, HR, urine output, hemodynamics when possible (CO, PWP, CVP, SVR)

**Half Life of a Drug**

- Time needed for ½ of the drug to be eliminated

- Generally takes about 5 half-lives to eliminate most drugs

- The shorter the half life of the drug, the slower it should be titrated off
  - Most vasoactive drugs have a 2-3 minute half life

- Drugs with long half lives can be turned off and the body will eliminate them slowly
### Sympathomimetic Drugs

**Alpha Receptors** (Arteries & Veins)
- Phenylephrine
- Vasoconstriction
- Dopamine
- Epinephrine
- Norepinephrine

**Beta Receptors**
- Beta₁ (Heart)
- Beta₂ (Arteries, veins)
- Dobutamine
- heart rate
- contractility
- automaticity
- conduction velocity
- Bronchodilation
- Renin release

### Adrenergic Effects of Sympathomimetic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alpha-1 (vasoconstriction)</th>
<th>Beta-1 (cardiac stimulation)</th>
<th>Beta-2 (vasodilation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>++ (&gt;0.2 mcg/kg/min)</td>
<td>+++</td>
<td>+++ (+0.01 mcg/kg/min)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Dopamine</td>
<td>++ (&gt;10 mcg/kg/min)</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0/+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>++++++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

### Vasodilators

- Nitroprusside – arterial & venous
- Nitroglycerin - mostly venous
- Nesiritide – arterial & venous
- Ca++ Channel Blockers (“pines”)
- Milrinone – PDE inhibitor
- ACE Inhibitors (“prils”)
- ARBs (“sartans”)
- Hydralazine
- Fenoldapam

### Inotropes

- Dobutamine
- Milrinone
- Dopamine
- Epinephrine
- Levophed
- Digoxin

### Vasopressors

- Norepinephrine
- Dopamine (high dose)
- Phenylephrine
- Epinephrine
- Vasopressin

- Vasopressors are indicated for a decrease in systolic BP of >30 mmHg from baseline, or a mean arterial pressure <60 mmHg when either condition results in end-organ dysfunction due to hypoperfusion.
- Vasopressors are contraindicated when SVR is > 1200 dynes

Correct hypovolemia before using a vasopressor for BP support
### Hemodynamic Effects of Vasoactive Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>CO/CI</th>
<th>HR</th>
<th>PWP</th>
<th>SVR</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>↑↑↑</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levophed</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>↔</td>
<td>↔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>↑↑↑</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>↔</td>
<td>↔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>↑↑↑↑</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesiritide</td>
<td>↑</td>
<td>↔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Antiarrhythmics

### Class I: Na Channel Blockers
- **Examples**: Quinidine, Procainamide, Disopyramide

### Class IV: Ca²⁺ Blockers
- **Examples**: Diltiazem, Verapamil

### Cardiac Action Potential

In the resting cell, Na⁺ enters and Ca²⁺ leaves, maintaining the inner negative membrane potential. During depolarization, Na⁺ enters, Ca²⁺ leaves, and K⁺ leaves, leading to repolarization.

### Antiarrhythmic Drug Sites of Action

- **Class IA**: Quinidine, Procainamide
- **Class IB**: Lidocaine, Mexilitine
- **Class IC**: Propafenone, Flecaïnide
- **Class III**: Amiodarone, Dronedarone, Sotalol, Dobutilidé
- **Class IV**: Calcium channel blockers: Verapamil, Diltiazem
Class | Action | ECG Effect
--- | --- | ---
I A | Sodium channel blockade | \( \uparrow \) QRS
| Prolong repolarization time | \( \uparrow \) QT
| Slow conduction velocity | Suppress automatically
I B | Sodium channel blockade | \( \downarrow \) QT
| Accelerate repolarization |
I C | Sodium channel blockade | \( \uparrow \) QRS
| Marked slowing of conduction | No effect on repolarization
| II | Beta blockade | \( \downarrow \) HR \( \uparrow \) PR
| III | Potassium channel blockade | \( \uparrow \) QT
| Prolong repolarization time |
| IV | Calcium channel blockade | \( \downarrow \) HR \( \uparrow \) PR

### Recommended Drugs for Management of Ventricular Arrhythmias

- Beta blockers
  - Ischemia induced VT, VF
  - Torsades
  - Sustained or repetitive monomorphic VT
- Amiodarone
  - VF, all VT except Torsades
- Procainamide
  - All VT except Torsades
- Lidocaine
  - Ischemia induced VT, VF
  - Torsades
- Sotalol
  - Repetitive monomorphic VT (can \( \uparrow \) QT interval)

### Recommended Drugs for Management of Atrial Fibrillation (or Flutter)

- **Rate Control**
  - Beta blockers
  - Ca++ blockers (Verapamil, Diltiazem)
  - Digoxin in heart failure patients
  - Amiodarone (if other drugs don’t work)
- **Cardioversion of A Fib/Flutter**
  - Flecainide, dofetilide, propafenone, or ibutilide
  - Amiodarone
  - Dronedarone (only for paroxysmal AF, not permanent AF)

### Recommended Drugs for Management of SVT

- Adenosine (most effective drug for termination)
- Beta blockers
- Ca++ channel blockers (Verapamil, Diltiazem)
- Pre-excited SVT (WPW)
  - Flecainide
  - Ibutilide
  - Procainamide
  - Amiodarone

### Treatment of Specific Conditions

- Shock
- Hypotension
- Bradycardia
- Tachycardia
- Conduction abnormalities
- Arrhythmias
- Beta blockers
- Ca++ blockers
- Amiodarone
- Sotalol
- Magnesium
### Shock States
- **Hypovolemic Shock** (volume problem)
  - Fluids
- **Cardiogenic Shock** (pump problem)
  - Inotropes: dopamine, norepinephrine, dobutamine (if no significant hypotension)
  - Vasopressors: norepinephrine
- **Vasodilated Shock** (vessel problem)
  - Vasopressors: phenylephrine, norepinephrine, vasopressin

### Drug Therapy for Hypertension
- **Thiazide diuretics** (chlorthalidone, HCTZ)
- **ACE Inhibitors / ARBs**
- **Calcium blockers**
- **Beta blockers**

The amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk, not the choice of antihypertensive drug.

### Hypertensive Emergencies
(Severe hypertension associated with acute end-organ damage)
- **Nitroprusside** - most effective drug, arterial and venous dilation
- Nitroglycerine – mostly venous dilation
- Ca**+**channel blockers – clevidipine, nicardipine
- Esmolol – short acting beta blocker
- Labetalol – combined alpha & beta blocker
- Fenoldopam – dopamine receptor agonist
- Hydralazine – direct arterial vasodilator
- Enalaprilat – IV ACEI

### Drug Therapy in Heart Failure
- **Diuretics**
  - Loops preferred
  - Thiazides
  - K+ sparing
- **Inotropes**
  - Dobutamine
  - Dopamine
  - Milrinone
  - Digoxin
- **Venous Dilators**
  - NTG
  - ACEI
  - ARBs
  - Nesiritide
  - Morphine
- **Arterial Dilators**
  - Nitroprusside
  - Milrinone
  - ACEI, ARBs
  - Hydralazine
  - Nesiritide
- **Beta Blockers**
  - Carvedilol
  - Metoprolol
  - Bisoprolol