Secondary Prevention Therapies for Acute/Chronic Coronary Syndromes Part II

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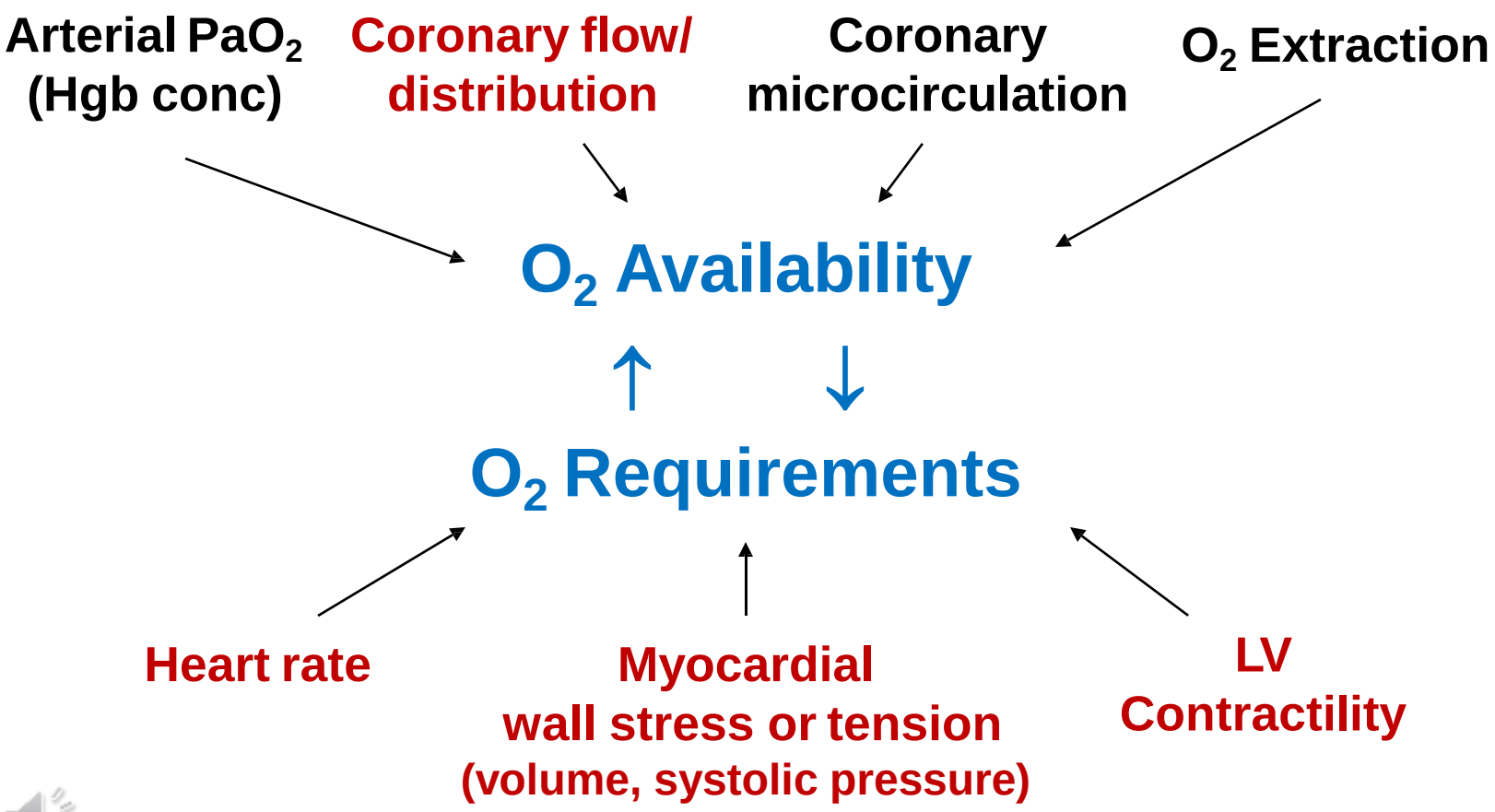
A is for:

"I'm going to take you off the nitroglycerin pills."

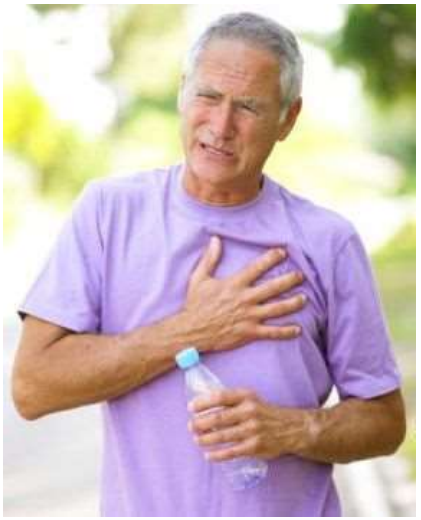
- Anti-platelet agents
- Anti-anginals
- ACE inhibitors (RAAS blockers)

O_2 Economics: Regulation of Oxygen Supply and Demand



A: Anti-Anginals

- ACC/AHA recommends for relief of symptoms:
  - BB should be prescribed as initial therapy for prevention of angina in patients with CHD
  - Various Agents:
    1. Beta-blockers (AHA)
    2. Calcium channel blockers (ESC)
    3. Long-acting nitrates
    4. Ranolazine

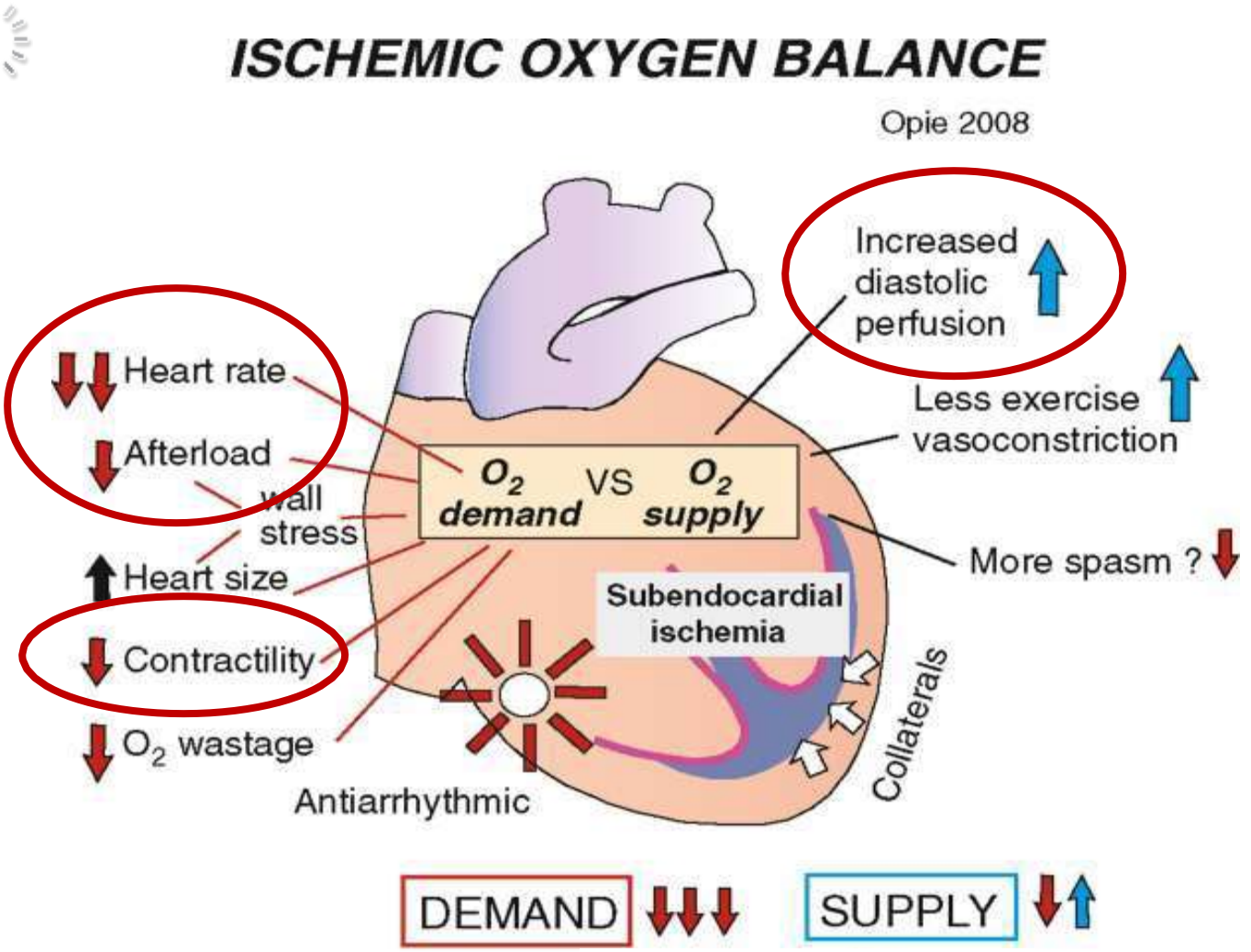


- Treatment goals:
  - Reduce symptoms of cardiac ischemia
  - Improve physical function and quality of life

Beta-Blockers

- ACC/AHA recommends to prevent MI and death:
  - BB should be started and continued for 3 years in all patients with normal LV function after ACS
  - BB should be used in all patients who have LV dysfunction (EF < 40%) with HF or prior MI in absence of contraindications (carvedilol, metoprolol succinate, bisoprolol)
  - BB may be considered as chronic therapy in all other patients with CHD (like SIHD/CCS) or other vascular disease

ACC/AHA 2012 SIHD Guidelines; 2019 ESC CCS Guidelines



Adapted from Drugs for the Heart 7th Edition, Figure 1-4.

Clinical Benefits of BB

- MOA: block adrenergic stimulation (NE release) to decrease cardiac work and myocardial oxygen consumption
- Decrease HR, contractility, and SBP at rest and during exercise to delay or avoid ischemic threshold by decreasing myocardial oxygen demand
- Cardioprotective benefits:
  - Improve survival rate in patients with recent MI, HF
  - Improve survival rate and prevent stroke and HF in patients with HTN
- Antiarrhythmic and antihypertensive properties
- Lack of tolerance to pharmacologic effects

FDA Approved Drugs	Selectivity	Usual Dose for Angina	Elimination
Atenolol	β_1 < 100 mg	50-200 mg daily	Kidney
Bisoprolol	β_1	5-20 mg daily	Liver and Kidney
Carvedilol	α, β_1, β_2	25-50 mg 2 x daily	Liver
Metoprolol succinate, tartrate	β_1 < 100 mg	50-200 mg/day	Liver
Nadolol	β_1, β_2	40-80 mg daily	Kidney
Propranolol	β_1, β_2	80-320 mg/day	Liver

Titrate to:

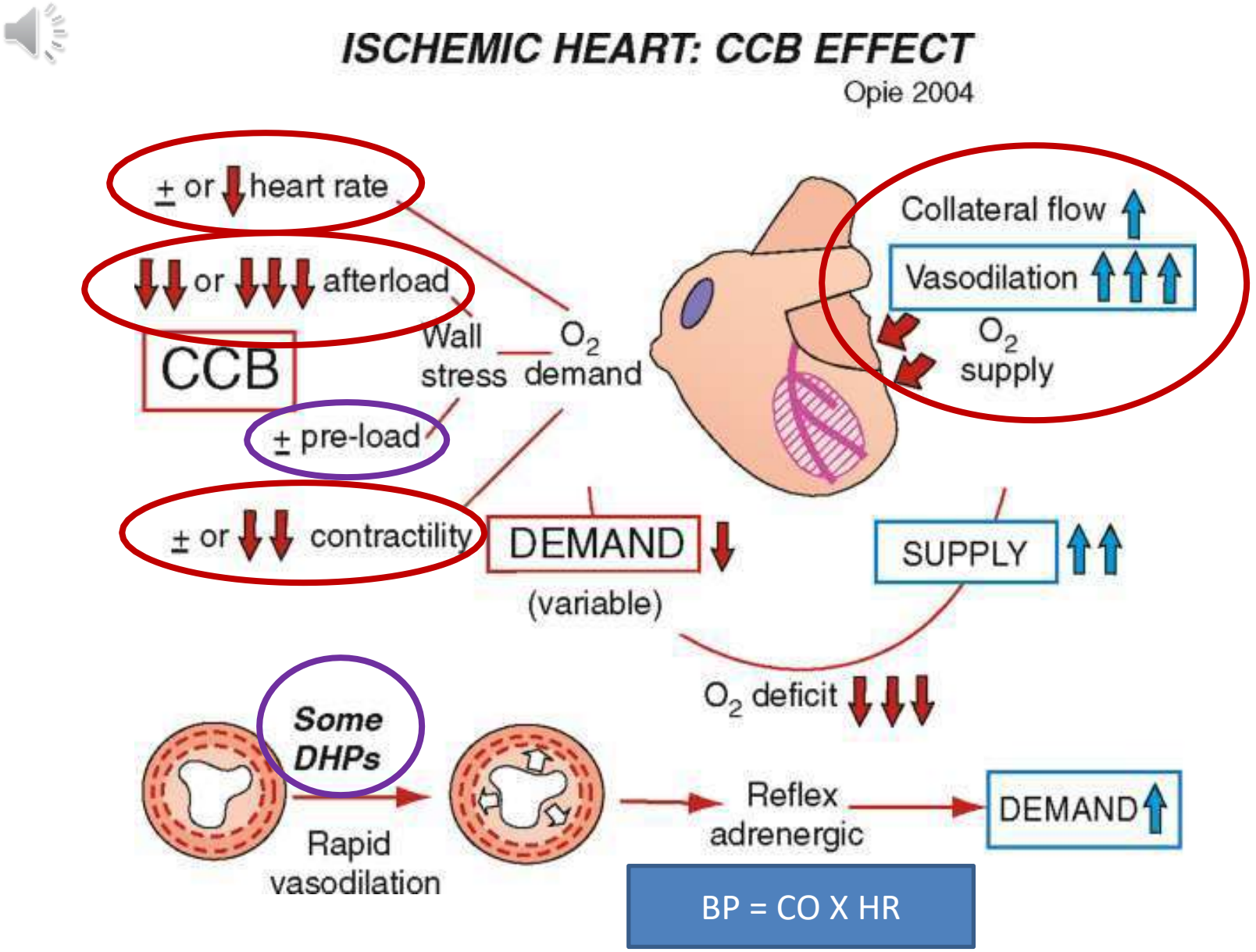
Beta-Blockers: Key Points

- Educate about side effects!
- Exercise intolerance may need coaching, encouragement
- Separate BID dosing by 12 hours
- Take carvedilol with meals if orthostasis occurs
- Metoprolol succinate BID dosing
- Monitor use of SL NTG
- Monitor BP and HR at home
- Must be tapered off!

Calcium Channel Blockers

- ACC/AHA recommends for the relief of symptoms:
  - Non-DPH CCB indicated as initial treatment for reduction of symptoms when BB contraindicated or cause unacceptable side effects
    - DPH CCBs can also be used but do not decrease HR like non-DPH CCBs
  - DPH CCB used in combination with BB when initial treatment with BB unsuccessful
  - CCB indicated as treatment for reduction of symptoms in patients with vasospastic angina

ACC/AHA 2012 SIHD Guidelines; 2019 ESC CCS Guidelines



Adapted from Drugs for the Heart 7th Edition, Figure 3-6.

Clinical Benefits Of CCBs

- MOA: Block transmembrane calcium currents in vascular smooth muscle to cause arterial vasodilation
- Direct vasodilation of R1 and R2 arteries to increase myocardial oxygen supply
- Decrease myocardial oxygen demand by reduction of systemic vascular resistance and systolic pressure
- Negative inotropic effects to decrease myocardial oxygen demand (Non-DHP)
- Antiarrhythmic effects (Non-DHP)
- No effect on exercise capacity
- Lack of tolerance to pharmacologic effects

CCB Classifications

- Dihydropyridines
  - Potent vasodilators, no conduction inhibition, little to no negative inotropic effects
    - May cause reflex tachycardia that increases demand
- Non-DHP
  - Moderate vasodilators, significant SA and AV node conduction inhibition, negative chronotropic and inotropic effects
    - Should not be used in patients with HFrEF

How do you determine which CCB to use?

CCB Dosage for Angina

Dihydropyridine

~~Nifedipine IR 10-30 mg TID~~

Nifedipine SR 30-180mg/day

Amlodipine 5-10 mg/day

Felodipine 5-10 mg/day

Isradipine 2.5-10 mg BID

~~Nicardipine IR 20-40 mg TID~~

Nicardipine SR 30 mg BID

Non-DHP

Diltiazem CD 180-360 mg/day

Verapamil SR 120-480 mg/day

CCBs: Key Points

- Educate about side effects!
- Lower extremity edema very common with DHP
- Monitor for important drug-drug interactions
- Monitor use of SL NTG
- Monitor BP and HR at home

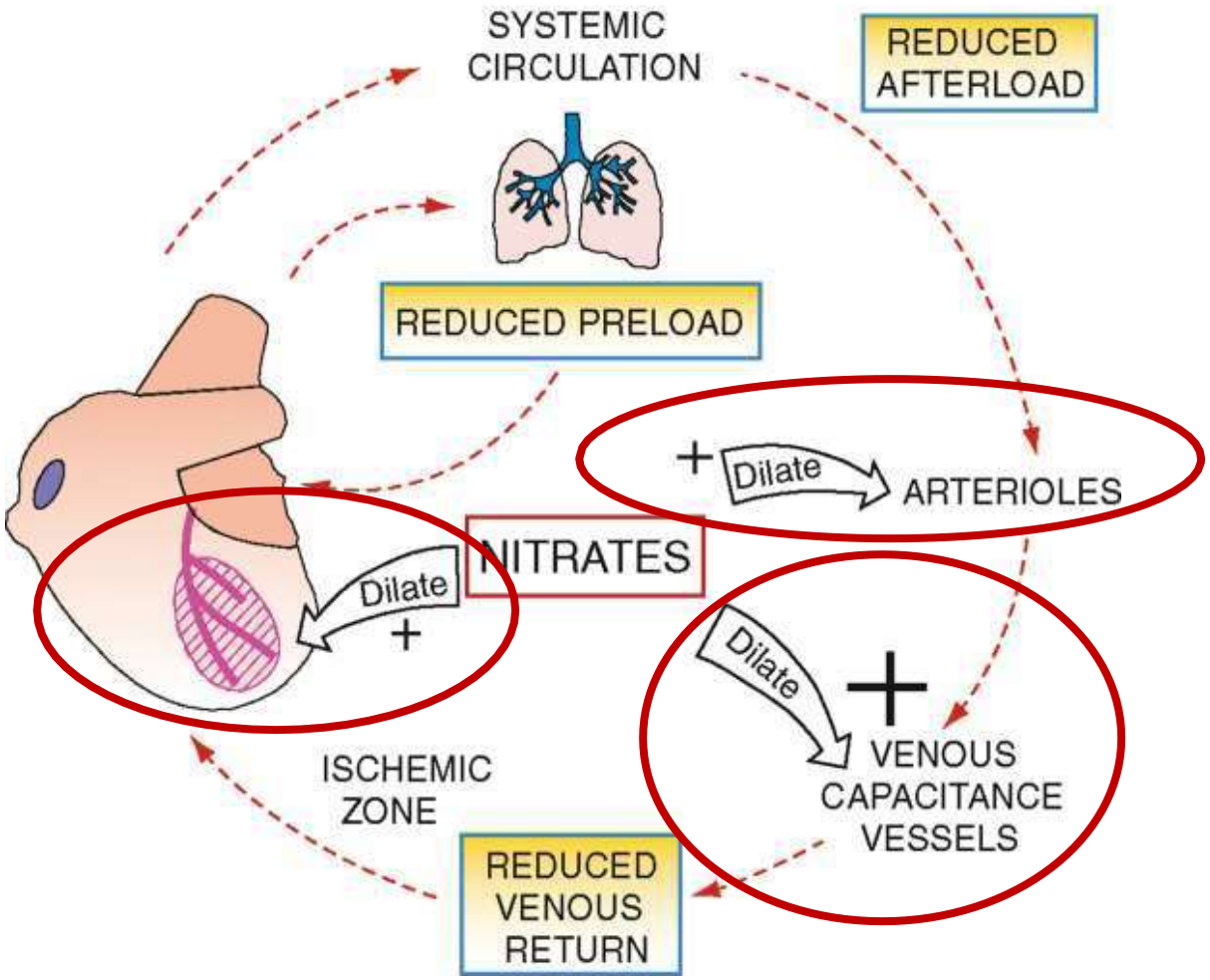
Nitrates

- ACC/AHA recommends for relief of symptoms:
  - Long-acting nitrates are indicated as initial treatment with non-DHP CCB for reduction of symptoms when BB is contraindicated
  - Long-acting nitrates are indicated in combination with BB when initial BB therapy is unsuccessful
  - Long-acting nitrates (in combo with non-DHP CCB) indicated as treatment for reduction of symptoms in patients with vasospastic angina
  - Short-acting nitrates (sublingual tablet or spray) indicated for immediate relief of angina

ACC/AHA 2012 SIHD Guidelines; 2019 ESC CCS Guidelines

ACTION OF NITRATES ON CIRCULATION

Opie 2008



Adapted from Drugs for the Heart 7th Edition, Figure 2-3

Clinical Benefits of Nitrates

- Direct vasodilation of R1 and R2 arteries to increase myocardial oxygen supply
- Decrease myocardial oxygen demand by reducing LV volume and arterial pressure
- Improve exercise tolerance and time to onset of angina
- **Greater anti-anginal effects when combined with BB or non-DHP CCB**

Nitrate MOA Review

- Nitrates are converted to nitric oxide that increases intracellular cyclic GMP levels. Increased GMP decreases intracellular calcium release by sacroplasmic reticulum to produce vascular smooth muscle relaxation.
- Tolerance develops quickly to anti-anginal effects
  - Theoretical mechanisms:
    - Decreased availability of sulfhydryl groups
    - Activation of RAAS
    - Activation of SNS
    - Increased intravascular volume
    - Generation of free oxygen radicals that decrease NO
- **Only recommended method to manage nitrate tolerance is to:**

Drug	Route	Dose	Duration of Effect
NTG	Sublingual tablets	0.3-0.6 mg	20-30 minutes
	Sublingual spray	0.4 mg	Similar to SL tabs
	2% Ointment	0.5-2” q6 hrs	3-8 hours
	Patch	0.2-0.6 mg/hr	8-12 hours
	Intravenous	5-200 mcg/min	3-5 min, Tolerance develops in 7-8 hours

Which NTG route of administration has the fastest onset of action?

Adapted from Cardiovascular Pharmacotherapeutics 3rd Edition, Table 8-4

Drug	Route	Dose	Duration of Effect
Isosorbide Dinitrate (ISDN)	Oral	5-80 mg TID	2-6 hours
	SR	40 mg BID	10-14 hours
Isosorbide Mononitrate (ISMN)	Oral	20 mg BID (doses separated by 7-8 hours)	3-6 hours
		60-240 mg qday	10-14 hours

Adapted from Cardiovascular Pharmacotherapeutics 3rd Edition, Table 8-4

Side Effects

- Hypotension
- Orthostatic hypotension
- Syncope
- Dizziness
- Headache
- Flushing
- Reflex tachycardia
- Palpitations
- Methemoglobinemia
- Nitrate tolerance

SEX

Sex and CHD

- Decreased sexual activity and function can be common in patients with CVD.
  - Medications vs medical conditions?
- CV drugs that improve symptoms and survival should not be withheld because of concerns about the potential impact on sexual function.
- Phosphodiesterase type-5 (PDE-5) inhibitors are useful for the treatment of ED in patients with stable CVD.

Levine et al. AHA Scientific Statement. Circ 2012; 125:1058-72.

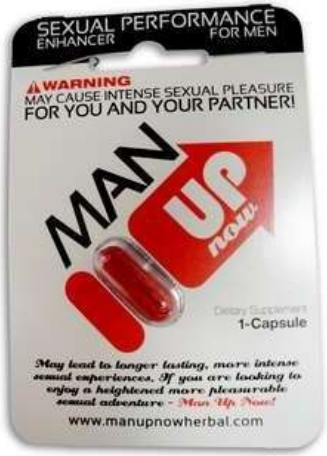
Nitrate Drug Interaction

- Nitrates are contraindicated with sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis)
  - Selective inhibitor of cyclic GMP-specific phosphodiesterase type-5, resulting in smooth muscle relaxation, vasodilation, and enhanced penile erection
  - Co-administration of nitrates with these agents significantly increases the risk of potentially life-threatening hypotension

Levine et al. AHA Scientific Statement. Circ 2012; 125:1058-72.

Nitrate Drug Interaction Continued

- PDE5 Inhibitors are contraindicated with nitrate therapy
  - Sildenafil and Vardenafil:
  - Tadalafil:
- Caution patients with CVD regarding the potential for adverse events with the use of herbal medications with unknown ingredients that are taken for treatment of sexual dysfunction.



Levine et al. AHA Scientific Statement. Circ 2012

Counseling Pearls

Sublingual tablets/spray:

- **All patients with CHD should have for rescue**
- Store in original glass container with lid on tightly
- Tabs reformulated- do not expire in 6 months after bottle opened!
- Note expiration date, use clear tape to protect label from wearing off
- Protect from light, heat, cold

ACC/AHA 2012 SIHD Guidelines

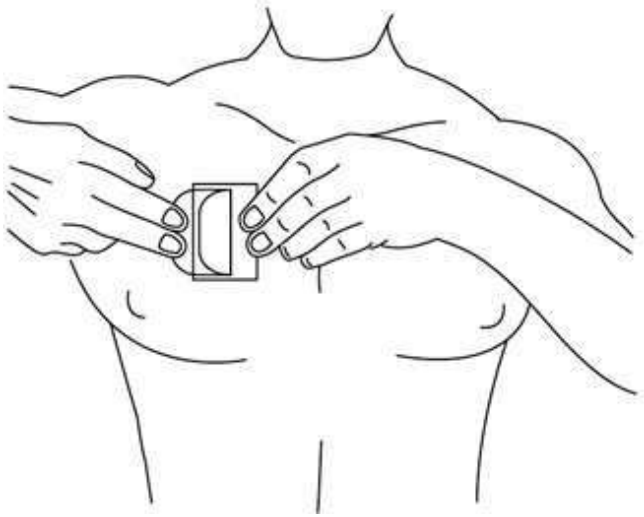
Counseling Pearls Continued

Sublingual tablets/spray:

- Always sit down when using
- Dry mouth may delay absorption
- Expect headache and flushing
- **Directions: 1 tablet or spray SL q5min x 3 tabs *for exacerbation of SIHD (CCS)***
- **If taking a third tablet, call 911**
- *Different dosing strategy in patients who have previously experienced ACS*
- For exertional chest pain, take one tablet 5-10 minutes before activity

Patient Information Continued

- Patches
  - Rotate patch sites on “hair-free” skin
  - Need 10-12 hour nitrate-free interval
  - Do not cut patches



- Tablets
  - Need 8-12 hour nitrate-free interval
  - Do not stop abruptly

Nitrates: Key Points

- Educate about side effects!
- Tolerance develops to side effects
- Must have nitrate-free period every day
- Should carry SL NTG with for rescue
- Monitor use of SL NTG
- Monitor BP and HR at home
- Must be tapered off!

Ranolazine (Ranexa)

American Heart Association. Learn and Live.

- ACC/AHA recommends for relief of symptoms:
  - Recommended as a substitute for BB if:
    - Initial BB therapy is contraindicated
    - Initial BB therapy leads to unacceptable side effects
    - Initial BB therapy is ineffective
  - Recommended in combination with BB when initial BB therapy is not successful

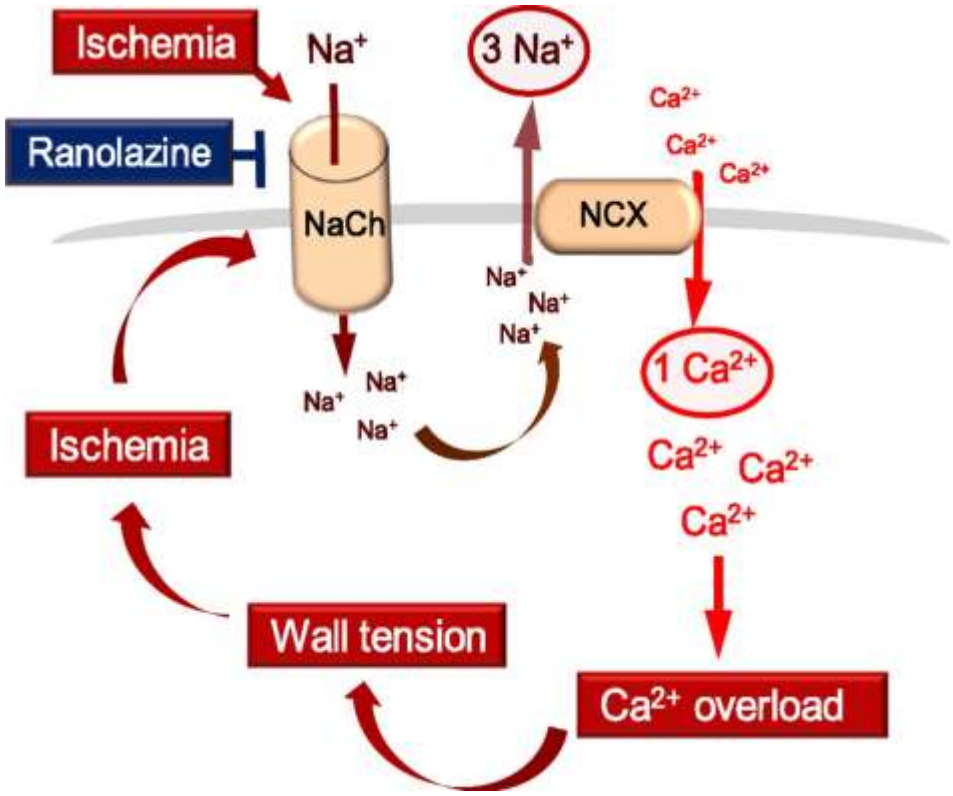
ACC/AHA 2012 SIHD Guidelines; 2019 ESC Guideline

Ranolazine

- FDA approved as initial treatment for SIHD (CCS)
  - Commonly used with BB, CCB, and long-acting nitrates for refractory angina despite maximal doses of other anti-anginal medications
    - May provide additional benefit in patients with MVD or DM
  - Not indicated in patients with ACS
- MOA: see next slide
  - Inhibits late sodium entry into the myocardial cell to decrease calcium entry (sodium-calcium exchanger) to decrease wall tension (myocardial oxygen demand)
- Therapeutic benefits do not depend on HR, BP, or SVR lowering

Ranolazine MOA

- In ischemic myocardium, late inward sodium currents increase intracellular sodium.
- Increased intracellular sodium leads to increased intracellular calcium through sodium-calcium exchanger.
- Calcium overload in ischemic cells leads to impaired relaxation of ventricles.



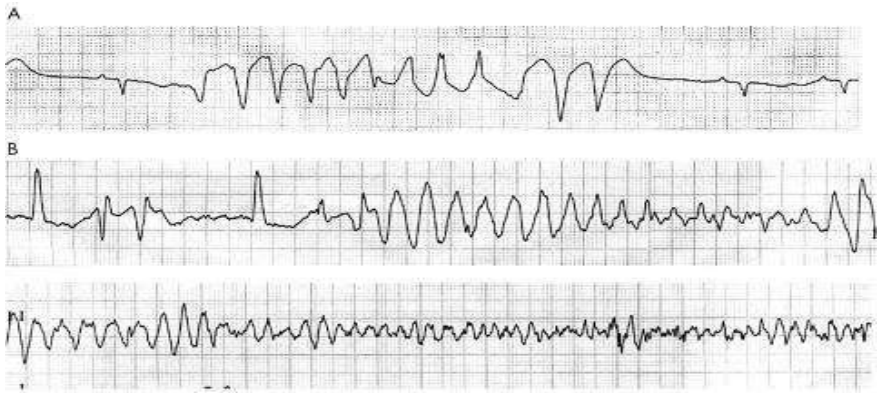
Ranolazine Dosing

- Dosing: 500 mg BID, increase to 1000mg BID if needed for continued angina (max dose)

- Side Effects:
  - Dizziness, HA, nausea, constipation, asthenia, dose dependent QTc prolongation
  - Patients with several renal impairment (CrCl < 30 ml/min), increased risk for acute renal failure
  - Contraindicated in patients with liver cirrhosis

Ranolazine Dosing Continued

- Drug interactions:
  - Metformin- see increased concentrations by inhibiting metabolism, increased risk of SE (nausea, diarrhea)
    - Max metformin dose: 1700mg/day
  - Use with caution with other drugs that prolong QTc interval or patients with prolonged QTc
    - Increased risk for torsades de pointes (TdP)
    - Class Ia or III antiarrhythmics (except for amiodarone)



Ranolazine Dosing Continued

- Drug interactions continued:
  - Contraindicated with strong CYP 3A4 inhibitors or inducers
    - Strong inhibitors: clarithromycin, antiretroviral meds, azole antifungal agents
  - Reduce dose with moderate inhibitors
    - Moderate inhibitors: erythromycin, diltiazem, verapamil, grapefruit juice (MAX dose 500mg BID)

Ranolazine: Key Points

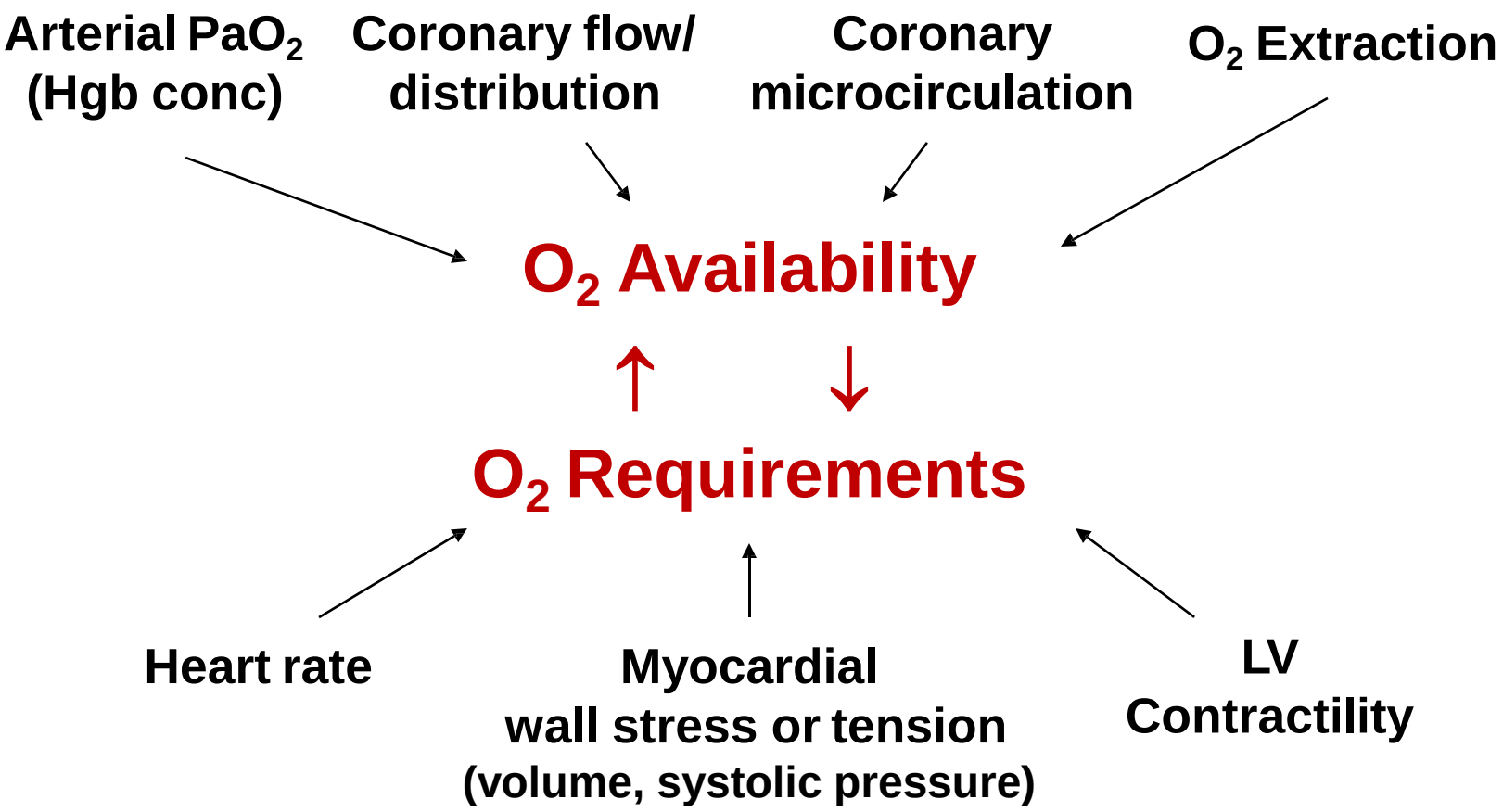
- Educate about side effects!
- Keep appointments for EKG checks
- Monitor for important drug-drug interactions
- Monitor use of SL NTG
- Monitor BP and HR

Anti-Anginal Selection in SIHD

	Macrovascular Disease	Microvascular Disease	Vasospastic Disease
Beta blockers	1st line	1st line	Avoid
CCB	2nd line	2nd line	1st line
Long-acting NTG	2nd line	2nd - 3rd line	Add on therapy
Short-acting NTG	Yes!	Yes!	Yes!
Ranolazine	Add on therapy	Add on therapy	

ACC/AHA 2012 SIHD Guidelines; 2013 ESC SCAD Guidelines

How do anti-anginal drugs prevent angina?



Thank-you!