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# CARDIAC PHARMACOLOGY

# OBJECTIVES

- Discuss the guidelines for the treatment of hypertension
- Outline a guideline based approach to a patient with dyslipidemia
- Discuss the medical management of an acute coronary syndrome patient
- Outline an appropriate drug regimen for a patient post myocardial infarction
- Compare and contrast the pharmacologic options for a patient with atrial fibrillation

- Screening should begin at age 18
- Outside readings for accurate diagnosis
- Diagnostic parameters
- Goals

# HTN

HTN

## ACC/AHA 2017 Guidelines

- General population
  - No prior CAD and less than 10% 10 year risk
  - Treat if BP over 140/90
- At risk groups
  - Treat if known CAD (secondary prevention) or 10 year risk is >10%
  - Goal is 130/80
- Elderly with high risk of drug side effects
  - Treatment goal should be tailored to patient

# HTN

- Lifestyle modifications
  - Salt restrictions
  - Weight loss
  - DASH diet
  - Limited alcohol
  - Exercise

# HTN

## Initial drug therapy

- Thiazide type diuretics
- Long acting calcium channel blockers
- Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- Angiotensin II receptor blockers (ARBs)

## Compelling indications

- Post MI
- Heart failure
- Chronic kidney disease
- A-fib
- BPH

## Other considerations

# COMBINATION THERAPY

ACE or ARB plus dihydropyridine CCB

ACE or ARB plus thiazide type diuretic

Start with combo therapy if a patient is more than 20mmHg systolic or 10mmHg above goal at diagnosis

Three drug regimen of ACE or ARB, dihydropyridine CCB and thiazide type diuretic if not controlled on two drug combo

# HTN

- ACE Inhibitor
- ARB
- Calcium Channel Blocker
- Thiazide Diuretic
- Beta Blocker

# HOW DO THEY HELP?

- ACE inhibitor – vasodilator effect (inhibits conversion of ACE I to ACE II)
- ARB – vasodilator effect (inhibits ACE II from binding to receptors)
- Beta Blocker – inhibit inotropic effect, vasodilation (block B1 and B2 receptors)
- CCB – vasodilator effect (inhibits influx of intracellular calcium)
- Thiazide diuretic – volume reduction (inhibits resorption of sodium in the kidney)

- ACE inhibitors → Renal function, K+
- ARBs → Renal function, K+
- Beta Blockers → HR
- CCBs → HR
- Thiazides → Renal function, Electrolytes

# ANY MONITORING NECESSARY?

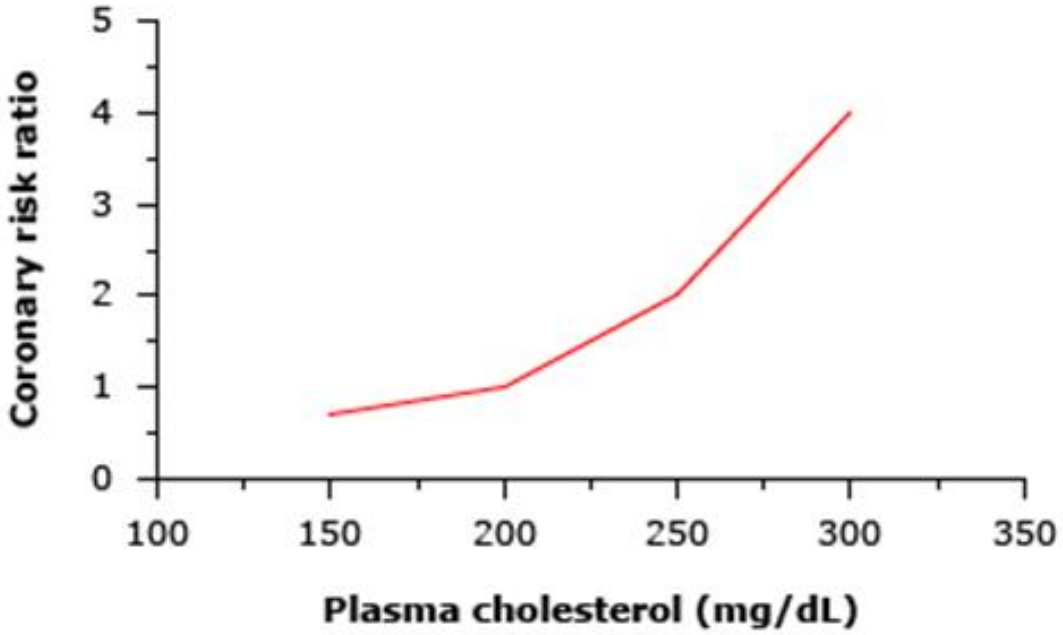
# BENEFITS OF BRINGING BLOOD PRESSURE TO GOAL

| Clinical Event | Average Risk Reduction |
|---|---|
| Stroke | 35 – 40% |
| Myocardial Infarction | 20-25% |
| Heart Failure | 50% |

# DYSLIPIDEMIA

- Screen all adults at establishment of care for baseline.
- Some guidelines recommended every 5 years beginning at age 20.
- Risk assessment and other factors may be a guide.
- ASCVD risk calculator
- Shared decision making.

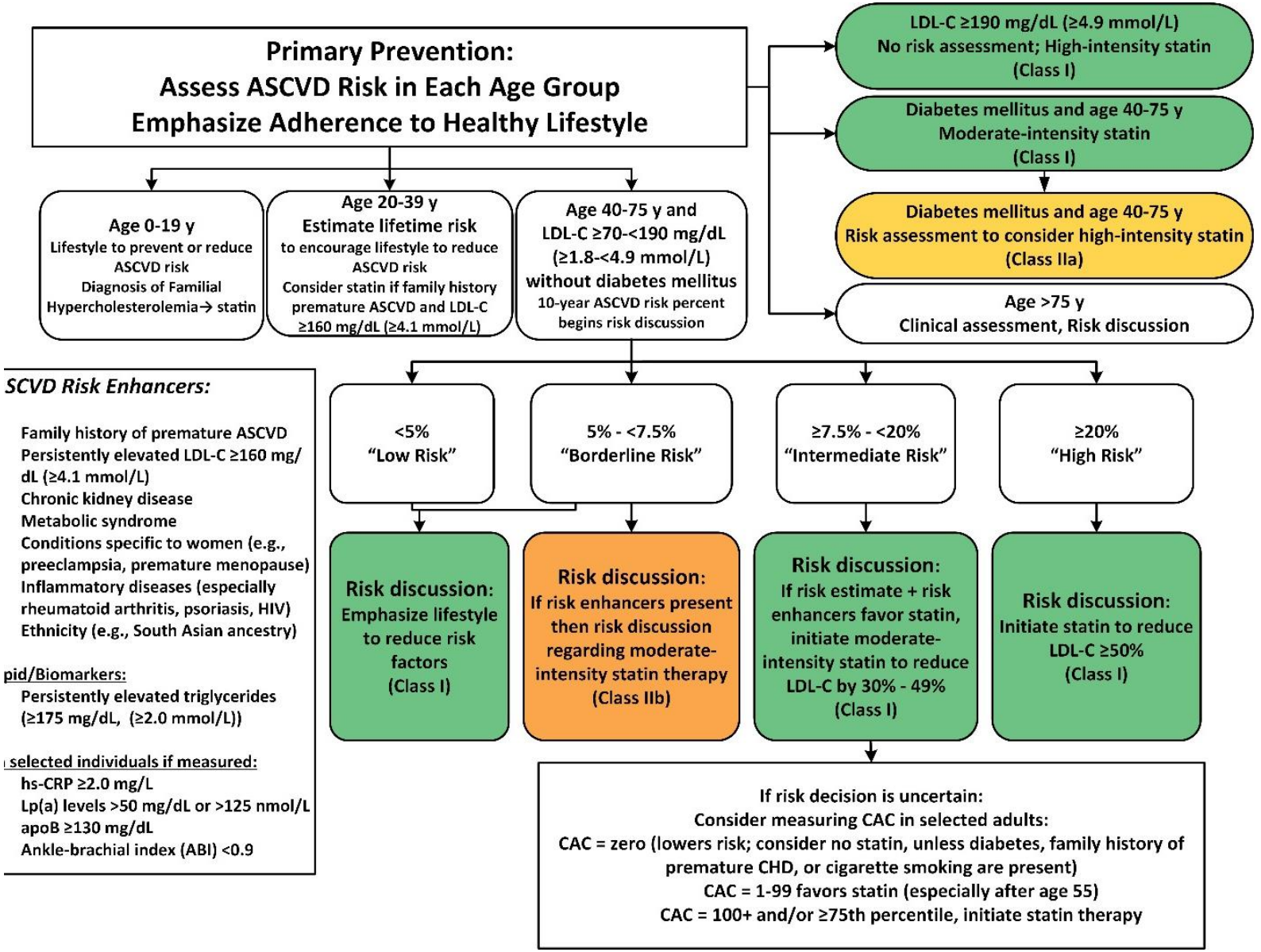
# DYSLIPIDEMIA



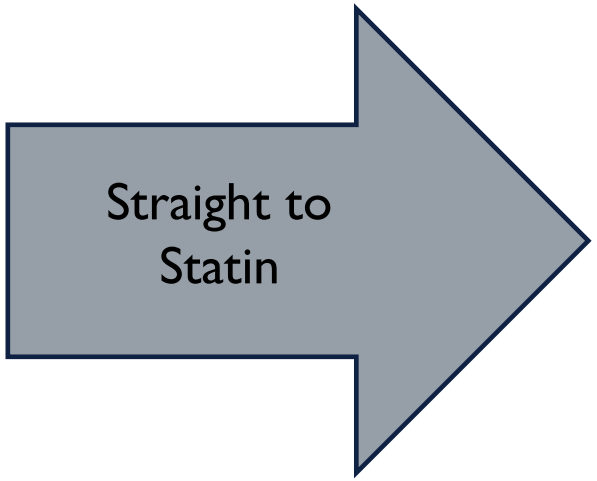

Relation between plasma cholesterol concentration and six-year coronary heart disease risk in 361,662 men (ages 35 to 57) screened during the MRFIT study. There is a continuous, positive, graded correlation between the plasma cholesterol concentration and coronary risk. To convert plasma cholesterol to mmol/L, divide by 38.5.

*Data from: Stamler J, Wentworth D, Neaton JD. Is relationship between*

# DYSLIPIDEMIA



# NO RISK ASSESSMENT NEEDED




- LDL ≥ 190
- 40-75 yrs old with Diabetes


- Age > 75 years old

# DYSLIPIDEMIA

- Lifestyle modifications for all patients
- Statins are first line therapy for tx of dyslipidemia
- No clear role for low intensity statin
- Moderate intensity statin in DM patients between ages 40-75y/o and other patients considered a borderline or intermediate risk category
- High intensity statin for any other patient requiring lipid treatment

# WHAT TO SELECT

## Moderate Intensity

- *Lovastatin 40mg
- *Pravastatin 40mg
- Simvastatin 40mg
- *Atorvastatin 10-20mg
- *Rosuvastatin 5-*10mg

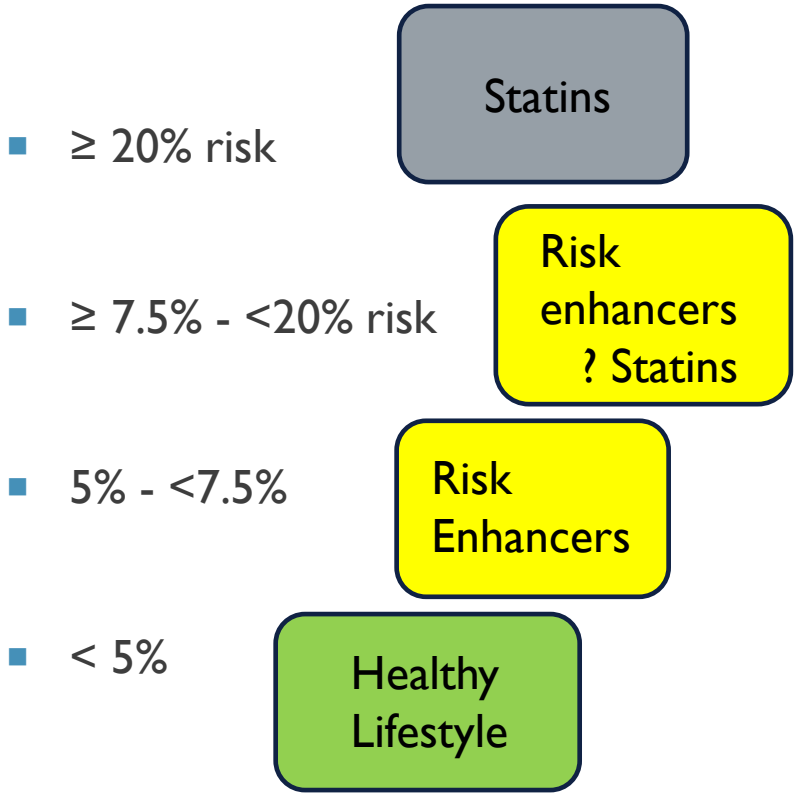
## High Intensity

- Atorvastatin 40-80mg
- Rosuvastatin 20-40mg

# WHAT TO SELECT

- Consider Ezetimibe when not achieving goal with statin therapy alone
- May need to consider three drug therapy
  - PCSK9 inhibitors

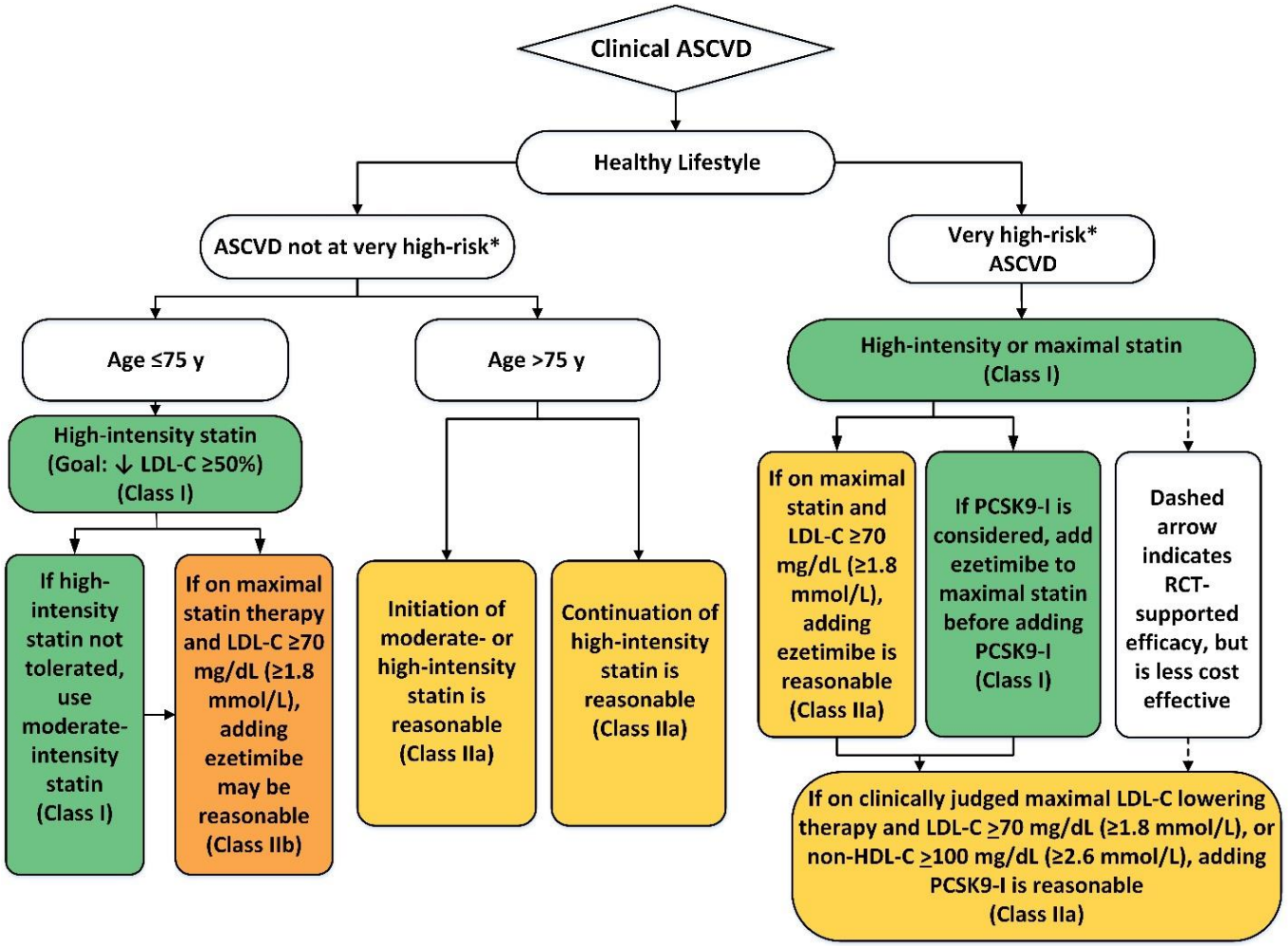
# USE 10-YEAR RISK TO GUIDE "RISK DISCUSSION"




Risk Enhancers

- Metabolic Syndrome
- LDL ≥ 160
- Family History
- Inflammatory Disease
- Women with early menopause or preeclampsia
- South Asian ethnicity
- TGs ≥ 175
- ABI < 0.9

# SECONDARY PREVENTION

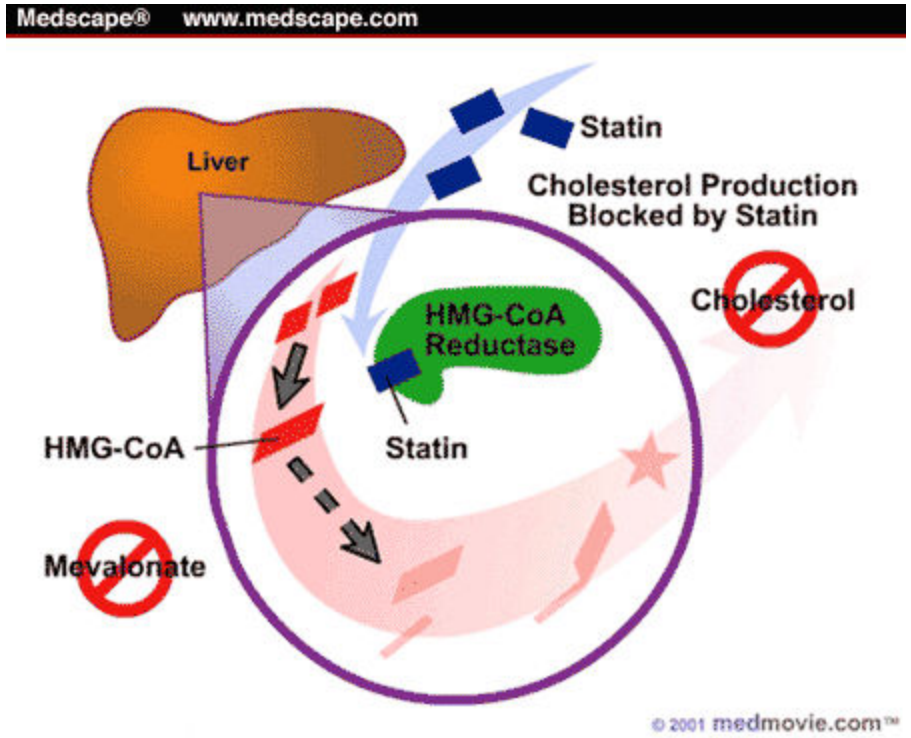



*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk

conditions

# HOW DO STATINS WORK?

Inhibit HMG CoA reductase → rate-limiting step of cholesterol biosynthesis



# STATIN MONITORING

- Check LFTs at baseline
  - Unless chronic liver disease, only need to repeat LFTs for signs/sx of hepatotoxicity; d/c statin if > 3x upper limit of normal
- Document pre-existing muscle symptoms and baseline creatinine kinase (CK)
- If develop severe muscle symptoms- hold statin and check CK
- Repeat fasting lipid panel 4-12 wks after starting or dose change; then every 3-12 months

# DRUG INDUCED HYPERLIPIDEMIA

- Beta Blockers*- may increase TGs and reduce HDL
- Thiazide diuretics*- increase total cholesterol, LDL, and triglycerides
- Oral Contraceptives- increase TGs; effects on HDL and LDL are variable
- Corticosteroids- increase LDL and TGs

*short term effect

- Protease inhibitors- Primarily increase TGs; may decrease HDL
- Immunosuppressants- increase LDL and TGs
- Isotretinoin (Accutane)- increase total cholesterol and TGs

# ACUTE CORONARY SYNDROME

- Prompt recognition of an ACS patient is crucial
- Benefits of any therapy are greatest when provided early

- Elderly – general health, weight, renal function
- Cocaine users – avoid Beta blockade, it may increase vasoconstriction of coronary arteries

# TREATMENT

- All STEMI patients should go to cath ASAP

# ACUTE ACS THERAPY AGENTS

- Antiplatelets
- Anticoagulants
- Beta Blockers
- Pain management
- Oxygen
- Antithrombotic agents
- Statins

# ANTIPLATELET AGENTS

- Aspirin 162-325mg
  - All ACS patients ASAP
- Reduces prostaglandin and thromboxane A2 synthesis by inhibiting cyclooxygenase (COX enzyme)
- Thromboxane A2 is a stimulator for platelet aggregation

# ANTIPLATELET AGENTS

- P2Y12 Inhibitors
  - All ACS patients ASAP (prior to angiography whenever possible)
- Prevent the binding of adenosine phosphate to the P2Y12 platelet receptor, inhibiting platelet activation
- Clopidogrel, Ticagrelor, Prasugrel
  - Ticagrelor 180mg or Prasugrel 60mg should be selected in NSTEMI pts. that will be treated conservatively
  - Ticagrelor 180mg for NSTEMI patients that are expected to undergo PCI within 48 hours
  - Ticagrelor 180mg or Prasugrel 60mg for STEMI patients receiving PCI
  - Clopidogrel 300mg for STEMI patients that will receive fibrinolytics
  - No P2Y12 for STEMI patients that are anticipated to have early CABG
  - Ticagrelor 180mg

CURRENT OASIS-7, TRANSLATE ACS, CURE

# ANTIPLATELET AGENTS

- Glycoprotein IIb/IIIa inhibitors
  - Not recommended for routine use in ACS patients; subgroups only
- Binds to glycoprotein IIb/IIIa receptors therefore reducing platelet aggregation
- Patients that have had dual platelet therapy and have ongoing ischemia
- Used for some patients in whom the angiography shows a giant thrombus or no reflow and in STEMI patients that have been treated with heparin and did not receive a P2Y12 blocker prior to PCI (add after)

# ANTICOAGULANTS

| | |
|---|---|
| Heparin (UFH) | • Indirect thrombin inhibitors: inactivates thrombin, factor Xa (Primarily)<br>• Cannot bind to or inactivate thrombin that is bound within a clot and HIT |
| LMWH | • Inactivates factor Xa |
| Direct Thrombin Inhibitors | • Binds to one or more active sites on the thrombin molecule, deactivating it |
| Synthetic Heparin (Fondaparinux) | • Neutralizes factor Xa |

# ANTICOAGULANTS IN STEMI PATIENTS

- Primary PCI in patients receiving Ticagrelor or Prasugrel → UFH
- Primary PCI in patients receiving Clopidogrel → UFH or bivalirudin
- Fibrinolytics + PCI → UFH
- Fibrinolytics without PCI → Enoxaparin
- No reperfusion → UFH or Enoxaparin

*these recommendations take into consideration numerous trials including HEAT PPCI, CREATE, ASSENT-3, ASSENT-3 PLUS, HORIZONS AMI, EUROMAX and ExTRACT-TIMI 25

# ANTICOAGULANTS IN NSTEACS PATIENTS

- Fodaparinux or Enoxaparin for patients managed conservatively
- UFH for patients managed with invasive strategy within 48 hours
  - Consider bivalirudin or UFH if pt. receiving clopidogrel
  - Mandatory change to UFH or bivalrudin if pt. was started on fondaparinux

* These recommendations consider OASIS-5, ESSENCE, SYNERGY and VALIDATE-SWEDEHEART trials

- Recommended for STEMI patients in whom there will be a delay in primary PCI (>120 minutes)
  - Fibrinolytic therapy should be administered within 30 minutes of pt. arrival/diagnosis
  - It is recommended that most patients receive subsequent angiography and possible PCI of the infarcted artery
  - Fibrin specific agents preferred to streptokinase (tenecteplase)

# FIBRINOLYSIS

AHA/ACC guidelines

# FIBRINOLYSIS – ABSOLUTE CONTRAINDICATIONS

- Prior ICH
- Known structural cerebral vascular lesions
- Malignant intracranial neoplasm
- Ischemic stroke within last 3 months
- Suspected aortic dissection
- Significant closed head or facial injury within last 3 months
- Active bleeding or bleeding diathesis

# BETA BLOCKERS

- All AMI patients within the first 24 hours
- Reduces the size of the infarction and early mortality when started early lowers the risk of death when continued long term
- Decreased oxygen demand
- Reduces remodeling and improves LV hemodynamic function
- Cardioselective beta blockers
  - Metoprolol 25-50mg PO or Atenolol 25-50mg PO

COMMIT/CCS2 trial

# BETA BLOCKERS

- Absolute Contraindications
  - Hemodynamically compromised individuals
  - Patients with heart block beyond 1st degree
  - Patients with a heart rate of <40bpm
  - Patients with active bronchospasm

# PAIN CONTROL

- Nitrates
  - Vessel dilation. May lead to increased perfusion of ischemic area, reduction of preload and afterload, reduction in ventricular wall stress and overall oxygen consumption, enhanced collateral blood flow.
- Sublingual nitro 0.4mg every 5 minutes PRN x 3 doses max
- IV nitroglycerin for continued discomfort (5 to 10 µg/min; relief of symptoms or a mean arterial BP 10% below baseline in normotensive patients or 25-30% for HTN patients, SBP should not fall below 90 mmHg)

- Avoid nitrates in patients with SBP <90 mmHg, significant brady or tachycardia, known or suspected right ventricular infarction, recent phosphodiesterase inhibitor, hypertrophic cardiomyopathy or severe aortic stenosis

# PAIN CONTROL

- Morphine
- 2-4mg (reserved for patients with an unacceptable level of pain)

- Should otherwise be avoided in AMI patients as it is associated with adverse outcomes (higher risk of death than those that do not receive it)

CRUSADE study: 57,039

# OXYGEN

- Patients with arterial saturation <90
- Patients in respiratory distress including those in HF
- Patients at high risk for hypoxia

DETO2X-AMI trial (2017), 6629 patients

# STATINS

- Statin therapy in all ACS patients ASAP
- Goal is LDL-C lowered to approximately 50 mg/dL
- More than just lipid lowering, pleiotropic effects include plaque stabilization, reversal of endothelial dysfunction, decreased thrombogenicity and decreased inflammation
- High intensity statin
  - Atorvastatin 80mg or Rosuvastatin 20-40mg
- Potential intolerance

PROVE IT TIMI-22, MIRACL, IMPROVE-IT, LUNAR trials were considered in these recommendations.

- Antiplatelet agents
- Beta Blockers
- ACE Inhibitors
- Aldosterone Antagonists
- Statins
- Nitroglycerin

# LONG TERM AGENTS

- Appropriate use of medications upon discharge may reduce 6 month mortality by up to 90%.
- *Antiplatelet therapy
- Nitro
- *ACE Inhibitors
- *Beta Blockers
- *Statins
- Aldosterone agonists

# LONG TERM MANAGEMENT – SECONDARY PREVENTION

# ANTIPLATELET THERAPY

- DAPT
- ASA and Ticagrleor is preferred
- One year

- ASA 75-100mg daily
- Ticagrelor 90mg BID
- Prasugrel 10mg daily
- Clopidogrel 75mg daily

# BETA BLOCKERS

- Long term Beta Blocker therapy is recommended (minimum of three years)
- Optimal agent, dose and duration not well known
- Long acting agent is recommended for purposes of adherence
  - Metoprolol Succinate 50-100mg daily or Atenolol 25-50mg BID
- If pt. has heart failure with reduced EF consider carvedilol or metoprolol succinate
- Consider contraindications as discussed previously

# STATINS

- High intensity statins for all
  - Atorvastatin 80mg or Rosuvastatin 20-40mg
- Goal of 50 mg/dL

# ACE INHIBITORS

- ~80% of patients with CVD will benefit from ACE inhibition
  - Known to reduce cardiovascular mortality
- HTN, hx of AMI, HF, LV EF lower than 40%, DM, proteinuric kidney disease

- Oral administration at low doses with BP monitoring
- Captopril 6.25mg to a max of 50mg TID, Enalapril 2.5mg to max of 20mg BID or Lisinopril 2.5mg to a max of 10mg Daily

# ALDOSTERONE ANTAGONISTS

- Aldosterone antagonists for post MI patients without significant renal dysfunction or hyperkalemia that are on therapeutic doses of ACE inhibitor and BB that have LV EF <40 and have DM or HF
- Eplerenone 25mg daily increased to 50mg daily after first month
- Monitor K+ and renal function

# OTHERS

- Annual flu vaccine
- Reduce modifiable risk factors not discussed
  - Smoking, EtOH consumption, excess weight, sedentary lifestyle, diet

# ATRIAL FIBRILLATION

- Rate control vs. rhythm control
- Rate agents
- Rhythm agents
- When to use anticoagulants
- What anticoagulants to use

# RATE VS. RHYTHM: WHICH IS BETTER?

- Not mutually exclusive
- Morbidity and mortality data are similar
- Symptoms may be better with rhythm control
- Return to NSR may prevent irreversible structural and electrical remodeling that can occur with longstanding AF

# RHYTHM CONTROL

- Patients will require rate control initially with AV nodal blocking agent prior to conversion
- Cardioversion can occur electrically or through pharmacologic means
- Rhythm maintenance may be achieved with a variety of medications
  - Selection of the medication should be based on patient characteristics
    - Other cardiac conditions: CHD, Heart failure, LVH

# RHYTHM CONTROL

- Amiodarone
- Dofetilide
- Flecainide
- Propafenone
- Sotalol
- Dronedarone

## Expectations

- Reduce frequency and duration of episodes, improve quality of life, reduce hospitalizations

## Concerns

- Proarrhythmia and bradyarrhythmia

# RHYTHM CONTROL

# RATE CONTROL

- Beta Blockers
  - Use in acute and chronic settings
- Non-dihydropyridine CCB
  - Use in acute and chronic settings
- Digoxin
- Amiodarone
- Combo therapy

# CHRONIC RATE CONTROL AGENTS

- Beta Blockers
  - Atenolol*, Metoprolol, Timolol, Pindolol, Nadolol*
- CCBs
  - Verapamil, Diltaizem
  - Clinical cautions
- Digoxin
  - Reserved for certain cases
- Amiodarone
  - Maintenance therapy after rhythm conversion and also helps with rate control

# ANTICOAGULATION

Calculate a $CHA_2DS_2$-VASc Score

| | |
|---|---|
| Score of 2 or more should have anticoagulation | Discuss anticoagulation option in score of 1 and some 0 |

DOAC is preferred when anticoagulation is needed

# DIRECT ORAL ANTICOAGULATION

- Dabigatran
- Apixiban
- Edoxaban
- Rivaroxaban

# MUST NOT MISS ADVERSE REACTIONS

Thank you!