Ischemic Heart Disease:
Angina Pectoris

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Learning Objectives

 Contrast and compare chronic stable angina, with acute coronary syndromes unstable angina with respect to presentation, pathophysiology and approach to treatment
 Describe the role and clinical effects of agents used in the management of patients with chronic stable angina (ASA, anti-platelets, nitrates, beta-blockers, and CCBA’s, ACE inhibitors, lipid lowering agents)
 Given a patient case, construct a treatment plan including selection of appropriate medication, sequencing of medications, dose, monitoring parameters and patient instructions.
Angina: Introduction

- Ischemic heart disease accounts for a substantial portion of death, disability and economic loss in most industrialized nations
- Coronary Artery Disease (CAD) is the leading cause of death in the U.S.
- Estimated 6.6M Americans have Angina
- 400,000 new cases diagnosed per year
- 27% of men and 14% of women will develop angina within 6 years of AMI

Angina Defined

- Angina pectoris is a clinical syndrome typically characterized by discomfort in the chest, jaw, shoulder, back or arm. Typically aggravated by exertion or emotional stress and relieved by nitroglycerine
- Typically occurs in patients with CAD involving at least one large epicardial artery

AHA/ACC Guideline Update for the Management of patients with Chronic Stable Angina R. Gibbons Nov 17, 2002
(www.americanheart.org)
Angina General

- Angina pectoris is the development of chest pain due to myocardial ischemia
  - coronary blood flow is inadequate to supply the heart with the needed oxygen and nutrients
  - patients often have underlying coronary artery obstruction
  - diagnosis of angina and its subclassification requires evaluation of the nature of the chest pain and circumstances surrounding its development

Angina Types

- Chronic Stable Angina: - a chronic and predictable development of chest pain upon exertion
- Unstable Angina: - a critical condition characterized by the unpredictable development of chest pain at rest or during minimal exertion. It is either accompanied by an increase in frequency and/or severity of pain within the recent (weeks to 1 or 2 months) past
- Vasospastic Angina or Prinzmetal’s Angina: - is characterized by the unprovoked coronary artery spasm resulting in chest pain.
Angina Types

- **Chronic Stable Angina:** - a chronic and predictable development of chest pain upon exertion
  - Patients rely on antianginal medication throughout the day to perform various degrees of activity however, may prophylax with sublingual nitrates based on anticipated exertions

- **Unstable Angina (UA):** - a critical condition characterized by the unpredictable development of chest pain at rest or during minimal exertion. It is either accompanied by an increase in frequency and/or severity of pain within the recent (weeks to 1 or 2 months) past.
  - Patients with unstable angina are admitted to an acute care setting and managed aggressively with nitrates, beta-blockers, CCBA’s, antiplatelets and anticoagulants.
  - UA is part of the spectrum of acute coronary syndromes (ACS, see ACS lectures)
Angina Types

- Vasospastic Angina or Prinzmetal’s Angina: is characterized by the unprovoked coronary artery spasm resulting in chest pain.
  - Patients with this angina may be relatively young and have few or even no cardiac risk factors
  - The chest pain is often unpredictable and cyclical in nature, sometimes reverting spontaneously into remission.

Other Forms of Ischemia

- Silent Myocardial Ischemia: a phenomenon experienced by a large percentage of patients with ischemic heart disease who for various reasons do not perceive chest pain despite EKG changes consistent with ischemic heart disease.
Events Associated with Ischemia

Exercise Provokes Ischemia

ST Segment Depressions
Myocardial ischemia, demonstrated by stress test
At rest
Incline and speed of treadmill progressively increased
Exercise

ECG changes
Hemodynamic abnormalities
Systolic abnormalities
Diastolic abnormalities
Coronary artery Occlusion
Angina
ISCHEMIA
Time (seconds)
Unstable Angina: Prognosis

- Risk of death or ischemic complications is lower than with MI but higher than with stable angina.
- Prolonged episodes of severe chest pain are important markers of high-risk unstable angina.
Angina Therapy: General

Ranges from intensive medical management (unstable angina) to conservative medical management with the goal of preventing progression to MI or death to death.

Drug therapy may include:
- Antiplatelets: ASA, GPIIb/IIIa and ADP inhibitors
- beta-blockers
- calcium channel blockers
- nitrates
- Anticoagulants: (UFH/LMWH) heparin
- Lipid lowering agents
- ACE inhibitors
- analgesics (morphine)

Angina Therapy: General

Therapy may require cardiac catheterization and myocardial revascularization: (usually unstable angina or advanced stable angina)

- Goal: to risk stratify and place in context the need for CABG or PTCA or stents
Angina Therapy: General

- Therapy may require cardiac catheterization and myocardial revascularization:
- Indications may include
  - failure to stabilize with adequate medical therapy
  - recurrent unstable angina
  - high-risk result from a non-invasive test
  - prior revascularization procedure
  - diagnosis or exclusion of significant CAD with multiple clinical episodes without objective documentation of ischemia

Pharmacologic Therapy Angina

- ASA in absence of contraindications
- B-blockers in pts. With prior MI or without prior MI
- ACE Inhibitors to pts with CAD who also have diabetes and/or LV systolic dysfunction
- LDL-C lowering therapy (target<100mg/dL)
- SI or nitroglycerin spray for immediate relieve of angina
- CCBA or long-acting nitrates for reduction in symptoms (when b-blockers contraindicated)
- CCBA or long-acting nitrates with b-blockers (when b-blockers not successful)
- CCBA and long-acting Nitrates as a substitute for b-blockers if b-blockers leads to unacceptable SEs
Beta-Blockers for Angina

- Beta-Blockers should be started in the absence of contraindications (IV for high-risk patients) or oral for intermediate and low-risk patients for pts with prior MI
- Consider pt. intolerance due to pulmonary disease, especially asthma, LV dysfunction, risk of hypotension or severe bradycardia, diabetes, lipid disorders.

Nitrates for Angina

- Mechanism: reduce cardiac work afterload and preload reduction as well as coronary dilitation and possibly antiplatelet effects.
- Pharmacologic Issues: Variable bioavailability, short half-life, tolerance
- Monitor: SE’s are extension of pharmacologic effects, hypotension, headache, especially post withdrawal
- Other Issues: multiple dosage forms, durations of action, cost, compliance
Nitrates for Angina

- **Outpatient only** - take one sl NTG in response to chest pain if already prescribed NTG, and if pain not relieved in 5 “ call 911 (2004, STEMI Guidelines AHA page e96)
- **Inpatient only** - If symptoms not relieved with 3 sl NTG tablets each taken 5” apart and initiation of B-Blocker therapy (when possible), IV NTG is recommended.
- **Inpatient only** - IV NTG should start at 5-10 mcg/min continuous infusion and titrated up by 10 mcg/min q 5-10 minutes until relief of symptoms or limiting side effects (headache / hypotension SBP <90) or dose exceeds 200 mcg/min
  - Switch to oral nitrates within 24 hours when possible

Nitrate Tolerance

- **Main limitation** of long-term prophylactic nitrate therapy is the development of tolerance (both to hemodynamic effects on exercise capacity)
- **Definition**: decrease in response to a given amount of nitrate or the need of increased amounts of nitrate to maintain a continuous effect
- Tolerance can develop with all forms of nitrate therapy that maintain continuous blood levels of the drug
- Tolerance can develop after only a few doses
- Numerous trials, using exercise testing to assess the efficacy of nitrate therapy, have shown an attenuation of antianginal effect with chronic therapy
**Nitrates**

- **Issues of Metabolism**
  - ISDN has a high first pass effect → low blood levels of ISDN
  - Approx. 26% (F = 26%) enters systemic circ. from po dose
  - Majority of effect from ISDN is IS-5-MN
  - ISMN (F=100%, t1/2 approx. 5 hrs, duration of effect 12 hrs, elimination- hepatic)

**GI Tract**
- ISDN 100%
- Gut Wall
- Circulation ISDN (26%)
- IS-5-MN (64%) [47(a) + 17(b)%]
- 1S-2-MN (19%) [14(a) + 5(b)%]

**Patient Information: Nitrates**

- Discuss issue of tolerance (rational ISDN-ISMN, importance of following instructions)
- Do not crush or chew IMDUR tablets
- Potential for hypotension and headache with all nitrates
- ISMO or ISDN are not choice for immediate anti-anginal effect
- Eccentric dosing (7 hour separation)
- sl NTG -storage, dating, dosing,
Angina Pectoris
“Guideline Review of Key Statements”

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Recommendations for Pharmacotherapy to Prevent MI and Death and to Reduce Symptoms
ACC/AHA 2002 Guideline Update for Chronic Stable Angina (www.americanheart.org)

- **Class I**
  - Aspirin in the absence of contraindications (Level of Evidence: A)
  - Beta-blockers as initial therapy in the absence of contraindications in patients with prior MI (Level of Evidence:A) or without prior MI. (Level of Evidence:B)
  - Angiotensin converting enzyme inhibitors in all patients with CAD who also have diabetes and/or LV systolic dysfunction (Level of Evidence:A)
  - Low-density lipoprotein-lowering therapy in patients with documented or suspected CAD and LDL cholesterol greater than 130 mg/dL, with a target LDL of less than 100 mg/dL (Level of Evidence: A)
  - Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina (Level of Evidence:B)
Recommendations for Pharmacotherapy to Prevent MI and Death and to Reduce Symptoms

ACC/AHA 2002 Guideline Update for Chronic Stable Angina (www.americanheart.org)

- **Class I continued…**
  - **6.** Calcium antagonists or long-acting nitrates as initial therapy for reduction of symptoms when beta-blockers are contraindicated (Level of Evidence: B)
  - **7.** Calcium antagonists or long-acting nitrates in combination with beta-blockers when initial treatment with beta-blockers is not successful (Level of Evidence: B)
  - **8.** Calcium antagonists and long-acting nitrates as a substitute for beta-blocker if initial treatment with beta-blockers leads to unacceptable side effects (Level of Evidence: C)

Recommendations for Pharmacotherapy to Prevent MI and Death and to Reduce Symptoms

ACC/AHA 2002 Guideline Update for Chronic Stable Angina (www.americanheart.org)

- **Class IIa**
  - Clopidogrel when aspirin is absolutely contraindicated (Level of Evidence: B)
  - Long-acting nondihydropyridine calcium antagonists instead of beta-blockers as initial therapy (Level of Evidence: B)
  - In patients with documented or suspected CAD and LDL cholesterol 100 to 129 mg/dL, several therapeutic options are available: (Level of Evidence: B)
    - Lifestyle and/or drug therapies to lower LDL to less than 100 mg/dL
    - Weight reduction and increased physical activity in persons with the metabolic syndrome
    - Institution of treatment of other lipid or non-lipid risk factors: consider use of nicotinic acid or fibric acid for elevated triglycerides or low HDL cholesterol
Recommendations for Pharmacotherapy to Prevent MI and Death and to Reduce Symptoms

ACC/AHA 2002 Guideline Update for Chronic Stable Angina (www.americanheart.org)

- **Class IIa Continued…**
  - 4. Angiotensin converting enzyme inhibitor in patients with CAD or other vascular disease (Level of Evidence:B)
- **Class IIb**
  - Low-intensity anticoagulation with warfarin in addition to aspirin (Level of Evidence:B)
- **Class III**
  - Dipyridamole (Level of Evidence:B)
  - Chelation therapy (Level of Evidence:B)

Choice of Pharmacologic Therapy in Chronic Stable Angina

- Beta-blockers also reduce cardiac events when used as 2^o prevention in post-infarction patients and reduce mortality and morbidity among patients with HTN. On these bases, beta-blockers should be strongly considered as initial therapy for chronic stable angina. Diabetes mellitus is not a contraindication to their use. Nitrates have not been shown to reduce mortality with acute MI or in patients with CAD. Short-acting dihydropyridine calcium antagonists have been reported to increase adverse cardiac events. Long-acting or slow-release dihydropyridines, or nondihydropyridines, have the potential to relieve symptoms in patients with chronic stable angina without enhancing the risk of adverse cardiac events.
### Asymptomatic Patients with CSA to Prevent MI and Death

ACC/AHA 2002 Guideline Update for Chronic Stable Angina (www.americanheart.org)

#### Class I
- Aspirin in the absence of contraindication in patients with prior MI (Level of Evidence:A)
- Beta-blockers as initial therapy in the absence of contraindications in patients with prior MI (Level of Evidence:B)
- Lipid-lowering therapy in patients with documented CAD and LDL cholesterol > 130mg/dL, with a target LDL of <100mg/dL (Level of Evidence:A)
- ACE inhibitor in patients with CAD who also have diabetes and/or systolic dysfunction (Level of Evidence:A)

#### Class IIa
- Aspirin in the absence of contraindications in patients without prior MI (Level of Evidence:B)
- Beta-blockers as initial therapy in the absence of contraindications in patients without prior MI (Level of Evidence:C)
- Lipid-lowering therapy in patients with documented CAD and LDL cholesterol of 100-129mg/dL, with a target LDL of 100mg/dL (Level of Evidence:C)
- Angiotensin converting enzyme inhibitor in all patients with diabetes who do not have contraindications due to severe renal disease (Level of Evidence:B)