What’s the Latest in Stable Ischemic Heart Disease?

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Objectives

• Describe the epidemiology and pathophysiology of ischemic heart disease.

• Construct appropriate treatment regimens for ischemic heart disease by integration of patient specific characteristics, drug-drug interactions, and the potential for adverse drug reactions
# Epidemiology of CHD

## Prevalence
- Estimated 15.4 million (6.4%) adults ≥20 years old
- 8.8 million (7.9%) males vs. 6.6 million (5.1%) females

## Significance
- Makes up more than half of all cardiovascular events
- Leading cause of death in the U.S. (1 out of every 6 deaths)

## Lifetime Risk of Developing CHD (after age 40)
- 49% or almost 1 out of 2 men
- 32% or almost 1 out of 3 women

## Total Estimated Costs (2009)
- $195.2 billion
- Projected to increase by 100% by 2030

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# Pathophysiology

- RBC
- LDL
- Extracellular Matrix Accumulation
- Foam Cell
- Coronary Artery
Balancing Act

Myocardial Oxygen Supply

Myocardial Oxygen Demand

Wall Tension
Contractility
Heart Rate

Blood Flow

Classification - Etiology

Noncardiac
Angina Pectoris
Variant (Prinzmetal)
Silent Ischemia
Chronic Stable Angina
Acute Coronary Syndrome
Unstable Angina
Non ST-segment elevation MI (NSTEMI)
ST-elevation MI (MI)
**Diagnostic Process**

- **Suspicion**
  - Resting electrocardiogram
  - Thorough history and physical

- **Noninvasive**
  - Stress test: exercise v. drug
  - Imaging: perfusion, MRI, CT

- **High-risk?**
  - High-risk: angiography
  - Low-risk: medical therapy

**Patient Counseling**

- Importance of medication adherence
- Understanding of cardiovascular risk reduction and risk factor modification
- Introduction to self-monitoring
- Information on how to recognize worsening angina symptoms and when to seek medical attention

*J Am Coll Cardiol* 2012;60:e44–e164
### Treatment Goals

- **Reduce CV death rates**
- **Prevent complications (AMI, HF)**
- **Minimize or eliminate symptoms (Quality of life)**
- **Minimize costs***

*AMI = acute myocardial infarction  
HF = heart failure

*Eliminating avoidable adverse effects of tests and treatments, preventing hospital admissions, and eliminating unnecessary tests and treatments.

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### Approach to Treatment

- **Identify and treat conditions that contribute or complicate SIHD.**
- **Effectively modify risk factors for SIHD.**
- **Education**
- **PCI or CABG when there is clear evidence of the potential to improve patients’ health status and survival.**
Treatment Overview

- High-risk SIHD?
  - Yes: Angiography +/- Revascularization
  - No: Begin GDMT

  - Angina: Anti-anginal drug therapy → Success → Continue to monitor
  - Failure: Angina → Aggressive Risk Factor Modification

  - All patients

Aggressive Risk Factor Modification

- Reduce CV death rates
- Prevent complications of SIHD
Modifiable Risk Factors - Worldwide

- Poor diet
- Smoking
- Dyslipidemia
- Impaired psychological well-being
- Diabetes
- Alcohol
- Obesity
- Hypertension

Aggressive Risk Factor Modification

- Smoking cessation
- Hyperlipidemia: Follow current guidelines; moderate – high intensity statin therapy
- Diabetes: Follow current guidelines; individualize A1C goals
- Weight loss
- Increase exercise
- High blood pressure: Follow current guidelines
Lifestyle Modifications

**Class I**
Maintain a BMI of 18.5 to 24.9 kg/m², and maintenance of a waist circumference less than 40 inches in men and less than (35 inches) in women. The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline.

*(Level of Evidence: C)*

**Class IIa**
Adherence to a diet that is low in saturated fat, cholesterol, and *trans* fat; high in fresh fruits, whole grains, and vegetables; and reduced in sodium intake, with cultural and ethnic preferences incorporated.

*(Level of Evidence: B)*

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Physical Activity

**Class I**
At least 30-60 minutes of moderate-intense aerobic activity such as brisk walking for a minimum of 5 days and preferably all days of the week, supplemented by an increase in daily lifestyle activities.

*(Level of evidence: B)*

**Class I**
Cardiac Rehabilitation or medically supervised programs and physician-directed, home-based programs for at-risk patients at first diagnosis.

*(Level of evidence: A)*

**Class IIa**
Complementary resistance training at least 2 days per week

*(Level of evidence: C)*

*J Am Coll Cardiol 2012;60:e44–e164*
**Smoking Cessation**

**Class I**
Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD.

*(Level of Evidence: A)*

- Reduces mortality risk by 30%; benefits within 2 years
- Nicotine replacement and bupropion first line agents
- Varenicline: probably safe but monitor closely
- Meta-analysis: lower mortality but higher MACE
  - Cardiovascular mortality: varenicline 0.05% (2/4190) vs. placebo 0.07% (2/2812)
  - MACE: Varenicline 0.31% (13) vs. placebo 0.21% (6)

http://www.fda.gov/Drugs/DrugSafety/ucm330367.htm

**Antiplatelet Therapy**

**Class I**

1. Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with SIHD

*(Level of Evidence: A)*

2. Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD.

*(Level of Evidence: B)*

**CLASS IIb**

Treatment with aspirin 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD.

*(Level of Evidence: B)*

**Class III: No Benefit**

Dipyridamole is not recommended as antiplatelet therapy for patients with SIHD.

*(Level of Evidence: B)*

*J Am Coll Cardiol 2012;60:e44–e164*
ACE Inhibitors

Class I
1. ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF 40% or less, or CKD, unless contraindicated. 
(Level of Evidence: A)

2. ARBs are recommended for patients with SIHD who have hypertension, diabetes mellitus, LV systolic dysfunction, or CKD and have indications for, but are intolerant of, ACE inhibitors. 
(Level of Evidence: A)

- Based largely on HOPE trial (placebo)
- ALLHAT showed equivalence to most other classes
- Would follow more recent hypertension guidelines

Immunizations

Class I
Influenza Vaccine should be administered annually
(Level of evidence: B)

- Acute infections can increase the risk of cardiovascular events by as much as five fold
- Flu vaccine may reduce the risk of cardiovascular events by as much as 50%

Pneumococcal and other vaccines

- No data to support their use for solely preventing CV events at this time
Management of Anginal Symptoms

Enhance well-being, activity level and
Improve quality of life

Beta-blockers

Class I
Beta blockers should be prescribed as initial therapy for relief of symptoms in patients with SIHD.
(Level of Evidence: B)

- Reduces mortality rate in low EF heart failure and post-MI

- No difference in SIHD versus calcium channel blockers
  - CV mortality: OR 0.97 (95% CI 0.67-1.38)
  - 0.31 (95% CI, 0.00-0.62; P = .05) fewer episodes of angina per week with beta-blockers than with calcium channel blockers
  - Higher rates of adverse events (mostly nifedipine)

- Insufficient data to compare to long-acting nitrates

J Am Coll Cardiol 2012;60:e44–e164
JAMA. 1999;281:1927-1936
Beta-blockers: Recent Evidence

Meta-analysis of 102,003 patients post-MI

- 60 Trials, stratified by reperfusion era

Only found mortality benefit in pre-reperfusion era patients

- Increase risk of cardiogenic shock

Limited by significant heterogeneity

- Reperfusion era patients = old thrombolytics


Beta-blockers: Recent Evidence

Registry of 26,793 patients on beta-blockers after first event

- ACS, acute MI, UA or PCI/CABG identified through ICD-9
- 19,843 were started within 7 days

Overall reduction in death and MI

- HR for mortality of 0.90 (95% CI 0.84 to 0.96)
- Benefit limited to recent MI patients

Reinforces previous notions

- Conducted in contemporary era (2000-2008)
- Limited by non-randomized study design

Calcium Channel Blockers

**Class I**
Calcium channel blocker should be prescribed for relief of symptoms when beta blockers are contraindicated or cause unacceptable side effects in patients with SIHD. *(Level of Evidence: B)*

Calcium channel blockers, in combination with beta blockers, should be prescribed for relief of symptoms when initial treatment with beta blockers is unsuccessful in patients with SIHD. *(Level of Evidence: B)*

**Class IIa**
Treatment with a long-acting non-dihydropyridine calcium channel blocker instead of a beta blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD. *(Level of Evidence: B)*

J Am Coll Cardiol 2012;60:e44–e164

Nitrates

**Class I**
Long-acting nitrates should be prescribed for relief of symptoms when beta blockers are contraindicated or cause unacceptable side effects in patients with SIHD. *(Level of Evidence: B)*

Long-acting nitrates, in combination with beta blockers, should be prescribed for relief of symptoms when initial treatment with beta blockers is unsuccessful in patients with SIHD. *(Level of Evidence: B)*

Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD. *(Level of Evidence: B)*

J Am Coll Cardiol 2012;60:e44–e164
Ranolazine

Mechanism originally based on inhibition of FA oxidation but now postulated that it works through inhibition of the late Na⁺ current ⇒ reduction in intracellular Ca²⁺/Na⁺ ⇒ increased myocardial relaxation during diastole

Has not been shown to delay or reduce mortality or other major adverse cardiac events (MERLIN-TIMI 36)

Efficacy established in four key clinical trials

MARISA  CARISA  ERICA  MERLIN-TIMI 36

Ranolazine: Recent Evidence

Evaluation of Ranolazine in Patients With Type 2 Diabetes Mellitus and Chronic Stable Angina
Results From the TERISA Randomized Clinical Trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ranolazine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina Frequency (attacks/week)</td>
<td>Mean ± SD</td>
<td>4.3 (4.0–4.5)</td>
<td>3.8 (3.6–4.1)</td>
</tr>
<tr>
<td>Nitroglycerin use (doses/week)</td>
<td>Mean ± SD</td>
<td>1.7 (1.6–1.9)</td>
<td>2.1 (1.9–2.3)</td>
</tr>
</tbody>
</table>

Ranolazine

Class IIa
Ranolazine can be useful when prescribed as a substitute for beta blockers for relief of symptoms in patients with SIHD if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or if initial treatment with beta blockers is contraindicated.
(Level of Evidence: B)

Ranolazine in combination with beta blockers can be useful when prescribed for relief of symptoms when initial treatment with beta blockers is not successful in patients with SIHD.
(Level of Evidence: A)

- No effect on BP or HR!
- Cost is a barrier
- Multiple drug-drug interactions

J Am Coll Cardiol 2012;60:e44–e164

Ranolazine Interactions

- Do not use with strong CYP3A inhibitors
  - Ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir
- Limit the dose to 500 mg twice daily in patients on moderate CYP3A inhibitors
  - Diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice
- Concomitant use with P-gp inhibitors, such as cyclosporine, may result in increases in ranolazine concentrations.
- Do not use with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John’s wort
Ranolazine Interactions

- Effects of ranolazine on other drugs metabolized by CYP3A
  - Limit the dose of simvastatin in patients to 20 mg once daily
  - Dose adjustment of other sensitive CYP3A substrates (e.g., lovastatin)
    and CYP3A substrates with a narrow therapeutic range (e.g.,
    cyclosporine, tacrolimus, sirolimus) may be required

- Drugs Transported by P-gp
  - Increased exposure to digoxin. The dose of digoxin may have to be
    adjusted.

- Drugs Metabolized by CYP2D6
  - The exposure to CYP2D6 substrates may be increased and lower doses
    of these drugs may be required.

- Drugs Transported by OCT2
  - When ranolazine 1000 mg twice daily is co-administered with
    metformin, metformin dose should not exceed 1700 mg/day. Monitor
    blood glucose levels and risks associated with high exposures of
    metformin.

Ranolazine: Cost-effective?

Cost-Effectiveness of Ranolazine Added to Standard-of-Care
Treatment in Patients With Chronic Stable Angina Pectoris

- Markov model based on ERICA trial

- Assumed cost-effectiveness = ICER <$50,000 per QALY
- Assumed monthly cost of 1000 mg bid = $397

- Results: ICER = $32,682/QALY for ranolazine
- Loss of cost-effectiveness = increase >32% over base

Am J Cardiol 2014;113:1306-1311.
Angina Symptom Control

Initiate beta-blocker as first line therapy
- Not for vasospastic
- Especially if post-MI or HF

Add calcium blocker
- First line if CI for beta-blocker
- Use non-DHP with caution in combination with beta-blocker

Add long-acting nitrate
- Good alternative if intolerance to other agents
- Ranolazine last line if failure/CI to other agents

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Alternative Therapy: Chelation

<table>
<thead>
<tr>
<th>2012 Recommendation</th>
<th>2014 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III: No Benefit</td>
<td>Class IIb</td>
</tr>
<tr>
<td>Chelation therapy is not recommended with the intent of improving symptoms or reducing cardiovascular risk in patients with SIHD (Level of Evidence: C)</td>
<td>The usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with SIHD. (Level of Evidence: B)</td>
</tr>
</tbody>
</table>

- Infusions of disodium EDTA = removal of toxins
- One small study showed reduction in MACE
  - 222 (26%) patients in the chelation group and 261 (30%) patients in the placebo group
  - Limited by small size, high drop out rate (18%)
- Potential toxicity: renal failure, hypocalcemia
Refractory Angina

<table>
<thead>
<tr>
<th>2012 Recommendation</th>
<th>2014 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIb</td>
<td>Class IIb</td>
</tr>
<tr>
<td>EECP may be considered for relief of refractory angina in patients with SIHD.</td>
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</tr>
</tbody>
</table>

- EECP = Enhanced External Counterpulsation
- Limited benefit in angina symptoms
  - Small, short-term randomized trials (2)
  - Observational, non-randomized studies (13)
- Potential for harm: leg pain and skin abrasions
- Need additional study


Revascularization: Who and When?

<table>
<thead>
<tr>
<th>Extent of Coronary Artery Disease</th>
<th>5-year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel, 75%</td>
<td>93%</td>
</tr>
<tr>
<td>1-vessel, 95%</td>
<td>91%</td>
</tr>
<tr>
<td>2-vessel</td>
<td>88%</td>
</tr>
<tr>
<td>2-vessel, both 95%</td>
<td>86%</td>
</tr>
<tr>
<td>1-vessel, &gt;95% proximal LAD lesion</td>
<td>83%</td>
</tr>
<tr>
<td>2-vessel, &gt;95% proximal LAD lesion</td>
<td>79%</td>
</tr>
<tr>
<td>3-vessel</td>
<td>79%</td>
</tr>
<tr>
<td>3-vessel, &gt;95% proximal LAD lesion</td>
<td>59%</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2012;60:e44–e164
Revascularization: Improve Survival

- Unprotected left-main or 3-vessel
  - CABG > PCI
- 2-vessel with proximal LAD
  - CABG >> PCI (uncertain benefit)
- 1-vessel without proximal LAD
  - No CABG or PCI (Class III: Harm)

Revascularization: Improve Symptoms

- ≥1-vessel + symptoms despite medication
  - CABG and PCI (both 1A recommendations)
- ≥1-vessel + symptoms with intolerance or contraindications to medication
  - CABG and PCI (both class IIa, level B)
- No anatomic or physiological criteria
  - No CABG or PCI (Class III: Harm)
Revascularization: New Recommendations

<table>
<thead>
<tr>
<th>2012 Recommendation</th>
<th>2014 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class IIa</strong></td>
<td><strong>Class I</strong></td>
</tr>
<tr>
<td>CABG is probably recommended in preference to PCI to improve survival in patients with multi-vessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery. <em>(Level of Evidence: B)</em></td>
<td>1. A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD. <em>(Level of Evidence: C)</em></td>
</tr>
<tr>
<td></td>
<td>2. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multi-vessel CAD when likely to improve survival...particularly if a LIMA graft can be anastomosed to the LAD artery, and provided the patient is a good candidate for surgery. <em>(Level of Evidence: B)</em></td>
</tr>
</tbody>
</table>


Ivabradine: Latest Evidence

*Original Article*

**Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure**

Kim Fox, M.D., Ian Ford, Ph.D., Philippe Gabriel Steg, M.D., Jean-Claude Tardif, M.D., Michal Tendera, M.D., and Roberto Ferrari, M.D., for the SIGNIFY Investigators

*New Engl J Med* 2014; DOI: 10.1056/NEJMoa1406430
Components of Successful Treatment

- Optimal control of risk factors
- Complete or nearly complete elimination of anginal symptoms
- Return to normal activities or functional capacity of Class I Angina
- Minimal to no side effects of therapy

**Goals modified according to clinical characteristics and preferences of each patient**

Questions?