Medical Management of Atherosclerosis

Rishad M. Faruqi MD, FRCS (Eng), FRCS (Ed), FACS
Dept. of Vascular Surgery Kaiser Permanente Santa Clara
Clinical Associate Professor University of CA, San Francisco
Clinical Associate Professor Stanford University

Medical Management of Atherosclerosis

- Scope of the problem
- Management of risk factors.
- PHASE program in NCAL
- Impact on vascular surgical practice

Medical Management of Atherosclerosis

- Mortality from cardiovascular disease is declining.
- Overall incidence of MI has not declined.
- Increasing incidence of MI in women.
- Ageing population in developed countries.
- Cardiovascular disease is the leading cause of death worldwide.

Medical Management of Atherosclerosis

“Heart disease and stroke are the leading causes of death in the United States. Although most cardiovascular disease (CVD) is preventable, proven prevention approaches are not being adequately applied in clinical practice.”

–Elias Zerhouni, MD, Director, National Institutes of Health
April, 2004

Medical Management of Atherosclerosis

REACH REGISTRY
Reduction of Atherothrombosis for Continued Health Registry (REACH)
JAMA. March 21, 2007;vol 297, No 11;1197-1206
Medical Management of Atherosclerosis

- 68,236 patients
  - **Group I** with disease (CAD, CVD, PAD): 55,814
  - **Group II** with at least 3 risk factors: 12,422
- 5587 physician practices
- 44 countries
- From 2003-2004

CV Death, MI or CVA rate: 4.24% overall
- **Group I**=4.69%
  - 4.52% (CAD); 5.35% (PAD); 6.47% (CVD)
- **Group II**=2.15%

Add end point “hospitalization for atherothrombotic event”:
- **Gp I**: 15.20% (CAD); 21.14% (PAD); 14.53% (CVD)
- Event rate was directly proportional to the number of vascular beds involved.

What are the main diseases that lead to mortality/morbidity?
- Coronary artery disease
- Cerebrovascular disease
- Peripheral arterial disease
- Aneursym disease
What are the main risk factors?

- Age
- Hyperlipidemia/dyslipidemia
- Diabetes Mellitus
- Hypertension
- Smoking
- CKD

How can we evaluate risk?
Medical Management of Atherosclerosis

**IMPACT OF GENDER ON RISK PROFILE**

- Male non-smoker or non-diabetic male vs. Female smoker or diabetic female

---

**Table 6.** Heart Age/Muscular Age for Women

<table>
<thead>
<tr>
<th>Heart Age/Muscular Age</th>
<th>Heart Age/Muscular Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

**Table 10.** Heart Age/Muscular Age for Men

<table>
<thead>
<tr>
<th>Heart Age/Muscular Age</th>
<th>Heart Age/Muscular Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

---

**Epidemiology**

Systematic Examination of the Updated Framingham Heart Study General Cardiovascular Risk Profile

Anand R. Mann, MD, Donald M. Lloyd-Jones, MD, PhD

- Backward screening has identified risk factors and even patterns of risk factors to be much higher than different family history patterns in men and women. We confirm the need for further risk factor screening and management.

- Conclusion: The inclusion of family history in this study suggests that higher risk factors may be present in men and women. The need for further risk factor screening and management is confirmed. (Correlation, 2005; 101: 349-369).
Medical Management of Atherosclerosis

• Scope of the problem
• Management of risk factors and evidence.
• PHASE program in NCAL
• Impact on vascular surgical practice

Lipid-lowering therapy
• Antiplatelet/antithrombotic therapy
• Antihypertensive therapy

Simvastatin versus placebo in high-risk individuals

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial
Medical Management of Atherosclerosis

- N=20,536
- 40-80 years of age
- CAD or other occlusive disease
- Or DM
- Simvastatin 40 mg versus Placebo
- Analyzed on an “intention to treat basis”
- 5 year follow up
- Mortality, fatal and non-fatal vascular events, cancer and other morbidity.

Medical Management of Atherosclerosis

<table>
<thead>
<tr>
<th>End Point</th>
<th>Drug</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>12.9%</td>
<td>14.7%</td>
<td>0.0003**</td>
</tr>
<tr>
<td>Coronary Death</td>
<td>5.7%</td>
<td>6.9%</td>
<td>0.0005**</td>
</tr>
<tr>
<td>Other vasc death</td>
<td>1.9%</td>
<td>2.2%</td>
<td>0.07*</td>
</tr>
<tr>
<td>Non-vasc death</td>
<td>5.3%</td>
<td>5.7%</td>
<td>0.4 (NS)</td>
</tr>
<tr>
<td>First Event MI</td>
<td>8.7%</td>
<td>11.8%</td>
<td>0.0001**</td>
</tr>
<tr>
<td>First Event CVA</td>
<td>4.3%</td>
<td>5.7%</td>
<td>0.0001**</td>
</tr>
<tr>
<td>Revascularization</td>
<td>9.1%</td>
<td>11.7%</td>
<td>0.0001**</td>
</tr>
</tbody>
</table>

Cancer: No difference
Myopathy incidence was 0.01% in the Simvastatin group.

Overall, about a 25 % reduction in MI, CVA and revascularization, regardless of cholesterol level.

SPARCL
Medical Management of Atherosclerosis

**SPARCL**
- Randomized, blinded, international study
- 4,731 patients stroke or TIA within 1-6 months, LDL 100-190, no coronary disease/cardiac SOE
- Atorvastatin (80 mg/day) vs. placebo
- Fatal or nonfatal stroke over 5 years

**Atorvastatin group (all levels are mg/dL):**
- LDL: 133 → 73
- HDL: 50 → 52
- Triglycerides: 144 → 112

**Placebo group:**
- LDL: 134 → 129
- HDL: 50 → 51
- Triglycerides: 143 → 145

**Fatal or nonfatal stroke over 5 years**
- HR, 0.84 (95% Cl, 0.71-0.99; P = .03)

**Years Since Randomization**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6

**Simvastatin**
- Placebo
- Adjusted P value
  - Major Coronary event: 81 (3.4%) vs. 120 (5.1%); 0.003
  - Any Coronary event: 334 (14.1%) vs. 407 (17.2%); 0.002
  - Major CV event: 123 (5.2%) vs. 204 (8.6%); <0.001
  - Any CV event: 530 (22.4%) vs. 687 (29%); <0.001
  - Death: 216 (9.1%) vs. 211 (8.9%); 0.98

**Outcomes**
- Five-year ARR in nonfatal or fatal stroke of 2.2% (95% CI 0.2-4.2), RRR 16%
- RRR for ischemic stroke 22% (95% CI 6-34%)
- Hemorrhagic stroke increased 2.3% vs. 1.4%
- Five-year ARR in “major cardiovascular events” (stroke + MI + cardiac death) of 3.5%, RRR 20%

**Lancet 2010 Meta-Analysis**
- n=17,000
- 26 RCTs
Medical Management of Atherosclerosis

1 mmol/L = 38.67 mg/dL

1 mmol/L reduction in LDL = 20% in annual risk
2-3 mmol/L reduction in LDL = 50% reduction

Medical Management of Atherosclerosis

• Lipid-lowering therapy
• Antiplatelet/antithrombotic therapy
• Antihypertensive therapy

Medical Management of Atherosclerosis

AHA/ACCF GUIDELINES ON LIPID LEVELS

• Antithrombotic Trialists Collaboration
  – 1994
  – 2002
  – 2009
• CAPRIE Trial
• Cochrane Review Recommendations for bypass graft patency
**Medical Management of Atherosclerosis**

**PRIMARY PREVENTION STUDY OF ASA**

- Double blind, placebo-controlled trial
- ASA = 325 mg every other day OR Placebo
- N=22,071
- Followed for 5 years
- 44% reduction in MI risk in those >50 years
- No change in CVA, or CV mortality
- Trend for increase in h’gie CVA (p = 0.06)

**International study**

- Randomized, double blind study
- Clopidogrel 75 mg versus ASA 325 mg daily
- High risk population (secondary prevention)

**Clinical Implications**

- Antithrombotic therapy protects a wider range of patients at high risk of ischaemic vascular disease than is currently treated (out of range): Should be considered for almost all with suspected acute myocardial infarction, unstable angina, or a history of myocardial infarction, angina, patient ischemic attack, arterial bypass surgery, or angioplasty.
- There is, as yet, no clear evidence that antithrombotic therapy is indicated for routine use in primary prevention: Subjects at low risk of ischemic vascular events.
- Medium-dose aspirin (75-325 mg) in the usual sole agent antiplatelet regimen, and no other regimen appeared significantly more effective at preventing myocardial infarction, stroke, or death.
APT protects against vascular events in high risk groups.
APT should be started immediately and continued long-term in the event of an acute ischemic stroke.
ASA 75-150 mg daily seems to be as effective as higher doses.
Gp IIb/IIIa antagonists can be added to ASA during PCI procedures but come at a higher risk of bleeding.

What about adding Plavix to ASA?
Medical Management of Atherosclerosis

• Patients with recent ischemic CVA/TIA
• ASA+Plavix versus ASA+Placebo
• Non-significant reduction in CV events
• Increased risk of life threatening bleeding with Plavix

N = 15,603
• Established disease OR multiple risk factors
• ASA + Plavix versus ASA + Placebo
• End point: MI, CVA or CV death

Disease | Plavix | Placebo | p value
--- | --- | --- | ---
MI/CVA/CV death | 6.8% | 7.3% | 0.22
Secondary end pts | 16.7% | 17.9% | 0.004
CV Death | 6.9% | 7.9% | 0.046

Risk Factors

<table>
<thead>
<tr>
<th>MI/CVA/CV death</th>
<th>Plavix</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.6%</td>
<td>5.5%</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>3.9%</td>
<td>2.2%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CHARISMA

CONCLUSIONS
In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was nonsignificantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. (ClinicalTrials.gov number, NCT00958077)

ATC 2009
Medical Management of Atherosclerosis

Primary Prevention and ASA:
- 12% RRR in all vascular events (p = 0.0001)
- 20% RRR in non-fatal MI (p = 0.0001)
- No reduction in CVA risk (p = 0.4)
- Increase in hemorrhagic CVA (p = 0.05)
- No reduction in CV mortality (p = 0.7)
- Increased major GI and extracranial hemorrhage (p = 0.0001)

Uncertain net value

Medical Management of Atherosclerosis

Secondary Prevention
- 20% RRR in major vascular events (p = 0.0001)
- 20% RRR in CVA (p = 0.02)
- 20% RRR in MI (p = 0.0001)
- No significant increase in hemorrhagic CVA

ASA 75-325 mg is recommended for secondary prevention

Medical Management of Atherosclerosis

Which antithrombotic agent do you use after a vein bypass?
1-ASA
2-Plavix
3-Coumadin
4-None

Medical Management of Atherosclerosis

Which antithrombotic agent do you use after a prosthetic bypass?
1-ASA
2-Plavix
3-Coumadin
4-None
Medical Management of Atherosclerosis

COCHRANE REVIEWS-2011

- Lipid-lowering therapy
- Antiplatelet/antithrombotic therapy
- Antihypertensive therapy

- ACE Inhibitors (ACEIs)/ AR Blockers (ARBs)
- Beta-blockers (BBs)
  - Role in the peri-operative period

Circulation 1998:97 (22) 2202-2212

Indications for ACE Inhibitors in the Early Treatment of Acute Myocardial Infarction: Systematic Overview of Individual Data From 100 000 Patients in Randomized Trials

Conclusions: These results support the use of ACE inhibitors early in the treatment of acute MI, either to a wide range of patients or selectively in patients with anterior MI and in those at increased risk of death. (Circulation. 1998;97:2202-2212.)

HOPE TRIAL
**Medical Management of Atherosclerosis**

- **N = 9297**
- **CV Disease or DM+1 risk factor**
- **No CHF**
- **Ramipril 10 mg versus Placebo**
- **5 year FU**
- **MI/CVA/CV Death-primary end points**

**HOPE**

<table>
<thead>
<tr>
<th></th>
<th>Ramipril</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end pt</td>
<td>14%</td>
<td>17.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CV Death</td>
<td>6.1</td>
<td>8.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MI</td>
<td>9.9%</td>
<td>12.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CVA</td>
<td>3.4%</td>
<td>4.9%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**EUROPA**

- **N = 13,655**
- **Stable CAD and no CHF**
- **Perindopril 8 mg versus Placebo**
- **FU = 4.2 years**
- **CV Death/MI/Cardiac Arrest-Primary**
- **20% RRR (p = 0.0003)**
- **NNT = 50 for 4 years to prevent one event**

**What’s the story with peri-operative beta blockers?**
Medical Management of Atherosclerosis

**Carp Trial**

**Scip**

**POISE**

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>5.8%</td>
<td>6.9%</td>
<td>0.0399</td>
</tr>
<tr>
<td>MI</td>
<td>4.2%</td>
<td>5.7%</td>
<td>0.0017</td>
</tr>
<tr>
<td>Deaths</td>
<td>3.1%</td>
<td>2.3%</td>
<td>0.0317*</td>
</tr>
<tr>
<td>CVA</td>
<td>1.0%</td>
<td>0.5%</td>
<td>0.0053*</td>
</tr>
</tbody>
</table>

**POISE**

- **RCT**: n = 8351
- 190 hospitals
- 23 countries
- Metoprolol versus Placebo
- Started 2-4 hours preoperatively and continued for 30 days
- Primary end point: CV Death/Non-fatal MI/Cardiac arrest

**POISE**

P value

Primary: 5.8% vs 6.9%, MI: 4.2% vs 5.7%, Deaths: 3.1% vs 2.3%, CVA: 1.0% vs 0.5%

**POISE**

- **P** value
  - Primary: 0.0399
  - MI: 0.0017
  - Deaths: 0.0317*
  - CVA: 0.0053*

**POISE**

- **Meta-analysis**: 33 Trials; 12,306 patients

**POISE**

- **Interpretation**: Evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery. The KCG HIA guidelines committee should soften their advocacy for this intervention until conclusive evidence is available.
Medical Management of Atherosclerosis

- Scope of the problem
- Management of risk factors.
- PHASE program in NCAL
- Impact on vascular surgical practice

### KP-NCAL
- 3.3 million members
- 2.7 million adults
- >5,000 MDs
- 17 medical centers
- 35 OP facilities

Medical Management of Atherosclerosis

**PREVENTING HEART ATTACKS AND STROKES EVERYDAY (PHASE)**

The PHASE program is the cardiovascular risk reduction program instituted in Kaiser Permanente that facilitates large scale implementation of a quartet of lifestyle changes, a quartet of medications, and a trio of treatment goals to reduce the burden of cardiovascular disease in those individuals at very high risk.

Medical Management of Atherosclerosis

### Secondary Prevention Population
Approximately 11% adults in KP-NCAL
- DM Diabetes
- CAD Coronary Artery Disease
- CVA Cerebrovascular Accident or TIA Transient Ischemic Attack
- AAA Abdominal Aortic Aneurysm
- PAD Peripheral Arterial Disease
- CKD Chronic Kidney Disease if age > 50 and – GFR < 30 or – GFR 30-60, plus proteinuria

Medical Management of Atherosclerosis

### 4 Lifestyle Changes

- **Tobacco Cessation**
  - Smoking cessation should be a primary target in the clinical strategy.

- **Physical Activity**
  - Regular, moderate physical activity is recommended for all patients.

- **Healthy Eating**
  - Recommend a diet rich in fruits, vegetables, legumes, nuts, whole grains, and polyunsaturated fats.

- **Weight Management**
  - Weight management reduces multiple risk factors

Medical Management of Atherosclerosis

### 4 Drug Interventions

- **Antithrombotic Medication**
  - Treatment with Aspirin 81-325 mg daily for patients unless contraindicated
  - If contraindicated, consider clopidogrel

- **Lipid Lowering Medications**
  - Treatment with statin is recommended even if LDL-C is <100 mg/dL

- **ACE Inhibition**
  - Treatment with ACE inhibitor long-term unless contraindicated

- **Beta Blockade**
  - Treatment with a beta blocker for members with CAD, PAD, and AAA unless contraindicated
Medical Management of Atherosclerosis

Controlling 3 Risk Factors

• Blood Pressure
  BP 129/79 mm Hg for patients with heart failure, chronic kidney disease (renal insufficiency or proteinuria), and diabetes
  BP 139/89 mm Hg for patients with CAD, PAD, AAA, and CVD

• Lipids
  Statin dose sufficient to bring LDL-C levels < 100 mg/dL
  Statin recommended even if baseline LDL-C is < 100 mg/dL

• Blood Glucose Control
  HgA1c < 7.0 is optimal for members with diabetes

Predicted impact

Risk Reduction for CV Events
Number Needed to Treat

- Tobacco Cessation
  36%
  12

- Physical Activity
  20-24%
  37.46 in 3-5 yrs

- Healthy Eating
  10-75%
  12.93 in 2-3 yrs

- Weight Management
  Improves multiple risk factors

Risk Reduction in CV Events
Number Needed to Treat

- LDL < 100
  16%
  24-32 in 5 yrs

- BP < 139/89
  25%
  29.86 in 5 yrs

- A1C < 9
  10-18%
  but no change in mortality


Ray The Lancet, Volume 373, Issue 9677, Pages 1765-177; Kelly, Ann Int Med 2009

Predicted impact

Risk Reduction in CV Events
Number Needed to Treat

Medical Management of Atherosclerosis

So how are we doing?
Medical Management of Atherosclerosis

• Scope of the problem
• Management of risk factors.
• PHASE program in NCAL
• Impact on vascular surgical practice

Medical Management of Atherosclerosis

• ACAS, ACST and CREST.
• 90% of all carotid interventions in the US are done for asymptomatic disease.
• With improvement in medical management, is intervention justified in asymptomatic carotid disease?

Medical Management of Atherosclerosis

• CREST certainly showed that CEA is superior to CAS.
• Letter to MEDCAC to not expand CAS indications to asymptomatic disease.
• Are the trials for CEA for asymptomatic disease obsolete in the setting of improved medical management?

Medical Management of Atherosclerosis

ACAS

Medical Management of Atherosclerosis

ACST
"A simplified method for bundling fixed doses of a generic statin and an ACEI/ARB was successfully implemented in a large, diverse population in an integrated healthcare delivery system, reducing the risk of hospitalization for MI and stroke."


• In Kaiser Northern California, we estimate the PHASE program prevents 2 CAD/CVD events each day
• 700 heart attacks and strokes prevented in 2007 in the 90,000 Northern California subjects

THANK YOU!