Best Practices in Lipid Management
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Disclosures

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Secondary Prevention with App for
Home-based Cardiac Rehabilitation

Consultant, AliveCor, mobile ECG
What goes wrong in atherosclerosis?
CVD Risk Factors

- Age
- Family history
- Gender
- Post-menopausal

- Hypertension
- Diabetes mellitus
- Dyslipidemia
- Obesity
- Sedentary lifestyle
- Smoking
- Stress

MODIFIABLE
Risk Factors for Coronary Disease

- “Classic” risk factors are identifiable.
- Risk factors work synergistically.
  - But likely account for only ~50% of one’s lifetime risk for cardiovascular disease.
  - The balance must therefore derive from the environment and unmeasured genetic elements.

Cholesterol

- A fatty, waxy substance found in body cells
- Thought to play key biologic roles
- Made by the liver; also comes from animal-based food we eat
- There is “good” and “bad” cholesterol.
Normal cholesterol metabolism
Support for the LDL-C hypothesis

TOP TWO KILLERS

By AMERICAN HEART ASSOCIATION NEWS

The total number of Americans dying from heart disease rose in recent years following decades in decline. Cancer deaths have nearly tripled since 1950 and continue to climb.

Source: Centers for Disease Control and Prevention
Published Aug. 24, 2016
Common misconceptions about the 2013 ACC/AHA Cholesterol guidelines

- Require initiation of statin for 10 year risk > 7.5%
- They are “set and forget”
- There is no role for non-statin agents
- There can be no compromise about statin dosing
- They are not useful for people > 75 yo
- They wildly overestimate risk
- Orthogonal data is useless
The “Dream” Cholesterol Profile*

- Total cholesterol < 200
- LDL (“bad”) < 100 (or even better, < 70)
- HDL (“good”) ≥ 60 (women) and ≥ 50 (men)
- Triglycerides < 100
Dietary Patterns

- Mediterranean Diet
  - BP
  - lipids

- DASH Diet
  - BP
  - lipids
2015-2020 Dietary Guidelines

A healthy dietary pattern is higher in:

- Vegetables
- Fruit
- Whole grains
- Seafood
- Legumes
- Nuts
- Low- and non-fat dairy products
2015-2020 Dietary Guidelines

Make half your plate fruits and vegetables
Make half your grains whole grains
Move to low-fat and fat-free daily
Vary your protein
Reduce sodium, saturated fats and sugar

Scientific Report of the 2015-2020 Dietary Guidelines Advisory Committee
Working towards a healthy diet

• Healthy dieting is also associated with reduced cardiovascular risk
  – High intakes of fruits and vegetables
  – Portion control
  – High fiber intake
  – Less simple sugars
  – Mediterranean diets- high in monounsaturated fat (vs trans or saturated fats)
  – Limited intake of red meat
  – Omega-3 fatty acids
2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol

Emphasize heart-healthy lifestyle at all ages

Healthy lifestyle is the primary intervention for metabolic syndrome: Weight management, stress reduction, smoking cessation, consistent daily exercise, healthy diet emphasizing plants.
Figure 3. 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Shown are standardized 10-year cumulative incidence rates for coronary events in the three prospective cohorts, according to lifestyle and genetic risk. Standardization was performed to cohort-specific population averages for each covariate. The I bars represent 95% confidence intervals.

Genetics does not equal destiny!!!
Primary Prevention

Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history of premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin (Class IIa)

Age >75 y
Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 mmol/L
- apolipoprotein B ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

Risk discussion:
Emphasize lifestyle to reduce risk factors (Class I)

<5%
“Low Risk”

5% - <7.5%
“Borderline Risk”

≥7.5% - <20%
“Intermediate Risk”

≥20%
“High Risk”

Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion:
Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy
In patients with clinical ASCVD, reduce LDL with high-intensity statins to reduce risk

Clinical ASCVD includes: stroke/TIA, CAD/CABG/PCI/ACS, PAD and AA
CAC CT can help clarify risk
Secondary Prevention in Patients with ASCVD

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*

Age ≤75 y
High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)
- If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
- If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)

Age >75 y
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-i is reasonable (Class IIa)

If PCSK9-i is considered, add ezetimibe to maximal statin before adding PCSK9-i (Class I)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective

Stanford Medicine
Very high risk goal: <70 mg/dl

If not at goal with maximum statins, add ezetimibe 10 mg daily.
If not at goal with statins/ezetimibe, add PCSK9 inhibitors
Severe primary hypercholesterolemia with LDL $\geq 190$, begin high intensity statin therapy

If not at goal of LDL $<100$ with maximum statins, add ezetimibe 10 mg daily.
If not at goal with statins/ezetimibe, consider PCSK9 inhibitors
Aged 40-75 with DM and LDL $\geq 70$, start moderate dose statins

If multiple risk factors are present, use high-intensity statins.
Very High-Risk of future ASCVD events, start high dose statins

Age &ge;65
Heterozygous FH
DM, HTN, CKD, current smoker
Persistently elevated LDL.100 despite statin and ezetimide
Hx CHF
Aged 40-75 without DM and LDL $\geq 70$, at 10 yr risk of $\geq 7.5\%$, start moderate dose statins

If FH of premature ASCVD, LDL $\geq 160$, metabolic syndrome, CKD, hx preeclampsia or premature menopause, chronic inflammatory disorders, South Asian or Filipino, TG $\geq 175$, hsCRP $\geq 2$, Lp(a)$\geq 50$ mg/dl, initiate statins at risk of 5% or greater
Aged 40-75 without DM and LDL \( \geq 70 \), at 10 yr risk of \( \geq 7.5\% \), start moderate dose statins

Consider CAC CT is risk status uncertain.
If zero, without smoking, FH, or DM, then may hold off.
Do not use baby ASA unless CAC \( \geq 100 \) or \( \text{Lp}(a) > 50 \text{ mg/DL} \)
Coronary Artery Scanning

- SEVERE CALCIFICATION
Repeat lipid panels 4-12 weeks after statin initiation or dose adjustment.

Repeat lipid panel every 3-12 months as needed to assess if at goal.
Major Recs for Statins

- Clinical ASCVD*
- LDL–C >190 mg/dL
- Primary prevention – Diabetes
- Primary prevention – No Diabetes†:
  - ≥7.5%‡ 10-year ASCVD risk

* Abbreviations: ASCVD = Atherosclerotic Cardiovascular Disease
† For individuals aged 40-75 years with diabetes type 1 or 2
‡ 10-year ASCVD risk with Pooled Cohort Equations

Figure 2. Major recommendations for statin therapy for ASCVD prevention

- Clinical ASCVD
- LDL–C >190 mg/dL
- Primary prevention – Diabetes
- Primary prevention – No Diabetes†:
  - ≥7.5%‡ 10-year ASCVD risk

ASCVD prevention benefit of statin therapy may be less clear in other groups
In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.
Case 1

- 39 year old Hispanic man presents with MI (NSTEMI, troponin peak 0.2)
- Risk factors:
  + smoking
  + cholesterol
  - hypertension
  - diabetes
  + family history of early CAD
Case 1
Lipid panel:

- Total Cholesterol  472 (H)
- Triglyceride       155 (H)
- HDL-C             53
- LDL-C             412 (H)

Severe elevation of LDL cholesterol
FH is common and devastating

- Modern genetic studies support a prevalence of ~1 in 250
- 50% of untreated men will have MI by age 50
- Causes 2-4% of heart attacks before age 60
- Cost $100s of millions
Lifelong exposure to high LDL causes early onset coronary disease
Management

- Diet/lifestyle changes important
  - Reduce saturated fat
  - High soluble fiber: 10-20g/day
  - Dietitian referral

- Statins are the mainstay of therapy
  - Many will require 2 or more drugs

- Treat other risk factors (HTN, smoking)

- **DO NOT USE STANDARD TOOLS TO ESTIMATE HEART DISEASE RISK**
Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above

Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up

Long-term mortality end points at 20 years of follow-up, overall, and stratified by LDL-C levels

**Figure 2.** Coronary heart disease risk: Kaplan-Meier curves during the randomized trial period stratified by LDL-C.
**Intensity of Statin Therapy**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)-80 mg Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20-40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
PCSK9 inhibitors: Triumph of modern genetic revolution

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Marianne Abifadel1,2, Mathilde Varret1, Jean-Pierre Rabès1,3, Delphine Allard1, Khadija Ougesram4, Marine Devilliers4

Exon 4 mutation control
AAGAAC-CTCTGGCAG NDA
NDA-CTCTGGCAG AAGAAC

Individual HC60-II-2
NDA-CTCTGGCAG AAGAAC
AAGAAC-CTCTGGCAG NDA

890T=C (P215L)

Cumulative Incidence [%]

Days since Randomization

Hazard ratio, 0.47 (95% CI, 0.28–0.78)

P=0.003

Standard therapy

Praluent (alirocumab), the first in a potential blockbuster class of cholesterol-reducing agents, was FDA-approved on Friday, July 24, 2015.

**Praluent use is approved** in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease (ASCVD) such as heart attacks or strokes, who require additional lowering of LDL cholesterol.

The FDA approved Amgen’s Repatha (evolocumab) for U.S. marketing on August 27, 2015. Repatha injection is indicated for use in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD), such as heart attacks or strokes, who require additional lowering of LDL cholesterol.

Prior to full approval, Repatha underwent FDA advisory committee review on Wednesday, June 10th, 2015. The FDA committee voted 11-4 in favor of FDA approval, including a 15-0 approval for homozygous familial hypercholesterolemia (HoFH).
LDLR recycling

With PCSK9 inhibitor
Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.

The 4 “higher risk” statin benefit groups

- 4 statin benefit groups
  - Secondary prevention
  - LDL > 190 mg/dl
  - Diabetes
  - 10 year risk > 7.5% with new “Pooled cohort/Omnibus risk calculator”

- No “treatment targets”

- With a few exceptions (like potentially using ABI, CAC) recommend against most imaging studies or non-traditional biomarkers

Age 40-75
“Of 1000 people treated with a statin for five years, 18 would avoid a major CVD event which compares well with other treatments used for preventing cardiovascular disease.”

Thus need to treat 55 people for 5 years to prevent major CVD event.

“Taking all years together...48 (95% CI 39–57) fewer participants having major vascular events per 1000 among those with pre-existing CHD at baseline.”

Thus need to treat 20 people for 5 years to prevent major CVD event.
- All cause mortality reduced by 12% for each 40 mg/dl decrease in LDL-C
  - 19% reduction in CHD death
- Secondary prevention: 14 fewer CHD deaths per 1000 participants
  - NNT = 71
- Primary prevention: 4 fewer CHD deaths per 1000 participants
  - NNT = 250
Case 2

- 53 yo M, asymptomatic, overweight
  - TC 220, LDL 160, HDL 35, TG 100
  - BP 135/85, not on meds
  - Not diabetic
  - Not smoker

- What to do?
Case 2

• 53 yo M, asymptomatic, overweight
  – TC 220, LDL 160, HDL 35, TG 100
  – BP 135/85, not on meds
  – Not diabetic
  – Not smoker
  – What to do?

• Omnibus 10 year 8.0%, lifetime 46%
  – Framingham 10 year “hard outcomes” 9%, Framingham 10 year for all CVD 16%
• Therefore initiate high dose statin
Case 2

• 53 yo M, asymptomatic, overweight
  – TC 220, LDL 160, HDL 35, TG 100
  – BP 135/85, not on meds
  – Not diabetic
  – Not smoker

  – What to do?

  • Trial rosvastatin 20 mg or atorvastatin 40 mg qd
  • If LDL not at goal, increase dose
  • If not at goal, add ezetimide 10 mg qd
  • If not at goal; consider PSK9I
Case 3

• 33 yo F, asymptomatic
  – Life insurance physical:
    • BP 102/75
    • TC 280, LDL 210, HDL 50, TG 100
    • Not diabetic
  – Mother had MI at age 55
  – What to do?
Case 3

• 33 yo F, asymptomatic
  – Life insurance physical:
    • BP 102/75
    • TC 280, LDL 210, HDL 50, TG 100
    • Not diabetic
  – Mother had MI at age 55
  – What to do?

• DO NOT USE RISK CALCULATOR

This is Familial Hypercholesterolemia

• Initiate high dose statin
• Plan B supplemental contraception
• Screen relatives
Case 3

- 33 yo F, asymptomatic
  - Life insurance physical:
    - BP 102/75
    - TC 280, LDL 210, HDL 50, TG 100
    - Not diabetic
  - Mother had MI at age 55
  - What to do?

- Trial rosvastatin 20 mg or atorvastatin 40 mg qd
- If LDL not at goal, increase dose
- If not at goal, add ezetimibe 10 mg qd
- If not at goal; consider PSK9I
Case 4

- 67 yo African American woman
  - TC 220, LDL 125, HDL 50, TG 75
  - Non smoker
  - Non diabetic
  - BP 120/75 but on therapy

- What to do?
Case 4

- 67 yo African American woman
  - TC 220, LDL 125, HDL 50, TG 75
  - Non smoker
  - Non diabetic
  - BP 120/75 but on therapy

- Omnibus risk calculator 10 year risk 9.7%
  - Framingham 10 year “hard outcomes” 5% risk

- Therefore initiate high potency statin
Case 4

- 67 yo African American woman
  - TC 220, LDL 125, HDL 50, TG 75
  - Non smoker
  - Non diabetic
  - BP 120/75 but on therapy

- Trial rosvuastatin 20 mg or atorvastatin 40 mg qd
- If LDL not at goal, increase dose
- If not at goal, add ezetimibe 10 mg qd
- If not at goal; consider PCSK9 Inhibitors
Case 4

- 67 yo African American woman
  - TC 220, LDL 125, HDL 50, TG 75
  - Non smoker
  - Non diabetic
  - BP 120/75 but on therapy

Start on atorvastatin 80mg

- Myalgias: “nocebo”
- Eventually tolerates only rosuvastatin 5mg/day
- Repeat LDL 105
- What to do?
- Add ezetimibe 10 mg qd
Case 5

- 45 yo obese M
  - T2D
  - SBP 135/90 but on therapy
  - TC 210, LDL 140, HDL 35, TG 180
  - Non-smoker
Case 5

- 45 yo obese M
  - T2D
  - SBP 135/90 but on therapy
  - TC 210, LDL 140, HDL 35, TG 180
  - Non-smoker

- The question is moot
- Has diabetes
- Initiate high potency statin regimen
Case 5

• 45 yo obese M
  – T2D
  – SBP 135/90 but on therapy
  – TC 210, LDL 140, HDL 35, TG 180
  – Non-smoker

• Trial rosuvastatin 20 mg or atorvastatin 40 mg qd
• If LDL not at goal, increase dose
• If not at goal, add ezetimide 10 mg qd
• If not at goal; consider PSK9I
Case 6

60 yo M with prior MI s/p PCI to LAD
- Hx HTN on ACE-I
- Pre-event lipids
  - TC 200, LDL 165, HDL 45
- Former smoker
- Not diabetic
- On ASA, clopidogrel

Started on atorvastatin 80mg/day
- Tolerates well
- Repeat lipids
  - LDL 80

What to do?
Case 6

- 60 yo M with prior MI s/p PCI to LAD
  - Hx HTN on ACE-I
  - Pre-event lipids
    - TC 200, LDL 165, HDL 45
  - Former smoker
  - Not diabetic
  - On ASA, clopidogrel

- Started on atorvastatin 80mg/day. Tolerates med
- Repeat lipids
  - LDL 80
- What to do?
  - Consider ezetimide 10 mg qd
Case 7

• 44 yo M
  – Smoker
  – BP 135/75
  – TC 260, LDL 170, HDL 40

– What to do?
Case 7

- 44 yo M
  - Smoker
  - BP 135/75
  - TC 260, LDL 170, HDL 40
  - What to do?

- Omnibus 10 year risk 5.2%
- Lifetime risk 70%
- Smoking cessation
- Consider statin
- Consider coronary calcium scan
Case 8

• 57 yo F
  – Non smoker
  – DM type II
  – BP 135/75
  – TC 260, LDL 170, HDL 40
  – “intolerant of statins”: muscle aches with atorvastatin
Case 8

- 57 yo F
  - Non smoker
  - DM type II
  - BP 135/75
  - TC 260, LDL 170, HDL 40
  - “intolerant of statins”: “Nocebo”/ muscle aches with atorvastatin

- Trial hydrophilic statin, rosvuavastatin 10 mg ONCE A WEEK
- If tolerated, increase frequency
- If not tolerated, consider PCSK9 Inhibitors
Case 9

• 49 yo F
  – Nonsmoker
  – BP 125/75
  – LDL 125 HDL 50
  – Lp(a) 103 mg/DL
  – FH early MI in mother, MGF

  – What to do?
Case 9

- 49 yo F
  - Nonsmoker
  - BP 125/75
  - LDL 125 HDL 50
  - Lp(a) 103 mg/DL
  - FH early MI in mother, MGF

- What to do?

- Add statin to reduce LDL to 35-45 range
- Add ASA 81 mg daily
- Currently no treatment options for Lp(a)