2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce Atherosclerotic Risk in Adults

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Goals of the Guidelines

- National Heart, lung and Blood Institute (NHLBI) collaborated with ACC/AHA to develop guidelines:
  a.) assess CV risk,
  b.) lifestyle modifications to reduce CV risk
  c.) management of blood cholesterol and obesity in adults
- Data collected until July 2013 from high quality RCT
- RCT- Well designed, Well executed that achieved high certainty about the estimate of effect and further research unlikely to change our confidence in the estimate of the effect.
Expert Panel (16 members)

- PCPs
- Cardiologists
- Endocrinologists
- Experts in Lipidology, epidemiology and guideline development
Update Clinical practice recommendations for the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease.

Used RCTs, systematic reviews of RCTs and meta-analysis from RCTs

Both primary and secondary prevention in men and women aged 21 years and older
Strategy to use drug therapy

- Older strategies advocated
  - Treat to cholesterol target
  - Lower cholesterol the better
  - Risk based treatment

However only one strategy has been evaluated in multiple RCTS-
  - Fixed Dose cholesterol medications to reduce ASCVD risk
Focus on ASCVD risk reduction (4 groups)
Panel was unable to find RCT to support treating to a target LDL or non-HDL level
Use Pooled Cohort Equations to estimate 10 year ASCVD risk
Safety recommendations
Role of Biomarkers and Non-invasive tests
Future Updates
RCTS- identified consistent reduction of ASCVD events from Statins for primary and secondary prevention
Exception- no reduction in NYHA class II-IV heart failure and hemodialysis patients
Compared fixed dose statins vs. placebo or untreated controls or high dose statins (>50% LDL reduction) vs moderate dose statins (30-50% reduction)
Trials were NOT designed to evaluate effect of titrated dose to achieve target LDL or non HDL levels
Panel was unable to find RCT evidence to support titration as recommended by ATP III
Other considerations

RCTs did find that use of niacin to lower non HDL levels once target LDL achieved- did NOT further reduce ASCVD outcomes
Expert Panel conclusions

- Extensive RCT evidence
- Appropriate intensity statin therapy should be used to reduce ASCVD risk in patients most likely to benefit
- Lifestyle – foundation for risk reduction
  - Heart healthy diet
  - Regular exercise
  - Avoid tobacco
  - Maintenance of healthy weight
4 Major Statin benefit groups

- Patient with ASCVD
  - ACS, hx of MI, Stable or unstable angina, Coronary or Peripheral revascularization, TIA/CVA, PAD
- LDL > 190 mg/dl
- Diabetes aged 40-75 with LDL 70-190 mg/dl
- No ASCVD or DM with LDL- 70-189 mg/dl and 10 year risk of ASCVD > 7.5%
  - Calculate 10 year ASCVD risk- Pooled Cohort equations–
  - http://my.americanheart.org/cvriskcalculator
Statin

- RCTs support use of statins in both nonfatal and fatal ASCVD
- High level of evidence that statins reduce total mortality in secondary prevention settings
- Primary prevention- moderate evidence reduce total mortality
Treat to Target
Lowest is Best

- Widely used for last 15 years
- No data to suggest what target should be
- Do not know magnitude of ASCVD risk reduction achieved with one target vs. another
- Does NOT account for potential adverse effects when using multidrug therapy
A New Perspective

- Treat to target paradigm was deliberated over 3 years
- LDL < 70 for secondary prevention
- LDL < 100 for primary prevention
- However the RCTS clearly show that it is the MAXIMUM tolerated statin intensity in those groups to show benefit
- AIM HIGH- Niacin lowered non HDL, APO-B, Lpa and TG- did NOT further reduce ASCVD in pt with LDL 40-80 on statins
Using LDL targets—may result in under-treatment with evidence based statin therapy or over treatment with non-statin drugs not shown to reduce ASCVD in RCTs.

E.g—secondary prevention—LDL -78 mg/dl on Atorvastatin 80 mg qd.- no data suggests adding non-statin drug will provide incremental benefit.

- AIM high- futility of adding niacin
- ACCORD- futility of adding fenofibrate in Diabetics
Biomarkers and Non-invasive tests

Unclear situations
- LDL > 160
- Genetic dyslipidemias
- Family hx of premature ASCVD- (onset in first degree male relative > 55 years old and >65 in female)
- HsCRP- > 2.0
- CAC score > 300 Agatston units- or >75% percentile for age/gender/ethnicity
- ABI < 0.9rt
Focus on treatments proven to reduce ASCVD

Never intended to be comprehensive approach to lipid management

Future considerations

- Rx of Hypertriglyceridemia
- Use on Non HDL in rx decisions
- Whether APO-B, Lpa or LDL particle size are useful in guiding Rx
- How lifetime risk can guide optimal age for initiating statins
- Subgroups with heart failure or hemodialysis- migh benefit from statin therapy
- Statin associated new onset diabetes
- Efficacy and safety of statins in HIV/solid organ transplant patients
- Role of pharmocogenetic testing
Panel reviewed 19 RCTs
- Majority of studies confirmed efficacy of single dose fixed statin in improving clinical outcomes
- 4S- trial (37% had simvastatin raised from 20-40 mg/qd– but no RCT ever showed treating to a target LDL of 100 or 70

What is evidence for LDL and non HDL goals for secondary prevention of ASCVD
What is Evidence for LDL and non HDL goals for primary prevention of ASCVD

- Panel reviewed 6 RCTs
- 4 studies confirmed single fixed dose statin lowered LDL levels and improved clinical outcomes
- AFCAPS-TEXCAPS trial- 50% titrated from Lovastatin 20-40 mg/qd to achieve LDL < 110
- MEGA trial- Pravastatin could be uptitrated from 10-20 mg to achieve total cholesterol of < 220 mg/dl
- No RCTS evaluated titration to LDL < 100 or < 70
- No RCTs reported on tratment of non HDL goals
What is evidence of impact on lipid levels, effectiveness and safety of specific cholesterol modifying drugs in primary and secondary prevention:

- Single or multi-drug combinations
  - Statins
  - Nicotinic acid
  - Fibtrates
  - Bile acid sequestrants
  - Ezetimibe
  - Omega 3- fatty acids
Safety considerations

- Predisposing characteristics to statin adverse effects:
  - Impaired renal or hepatic function
  - Prior statin intolerance or muscle disorder
  - Unexplained ALT elevations > 3x ULN
  - Age > 75
  - Concomitant use of drugs affecting statin metabolism
  - ? Prior hemorrhagic CVA
  - ? Asian ancestry
CK should NOT be measured routinely (Strong)
Measure CK if muscle symptoms (Expert)
Check baseline ALT (Moderate)
Check ALT if symptoms (Expert)
Decrease statin if LDL < 40 (twice)– Weak
Harmful Initiate Simvistatin 80 or titrate to 80 (moderate)
If on statins, eval for DM per DM screening guidelines and do lifestyle modifications if develop DM on statins (moderate)
Caution of statins in age >75, HIV and solid organ transplant on complex meds (expert opinion)

If muscle symptoms (severe)
- Stop statin and evaluate CK, creatinine, UA for myoglobinuria
- Mild to mod symptoms
  - Stop statin
  - Eval for hypothyroid, renal or hepatic impairment, Rheum d/o, PMR, Vit D def or primary muscle d/o.
Safety

- Mild to mod muscle symptoms
  - If causal relationship- d/c original statin, wait for all symptoms to resolve and try another statin at low dose (titrate as allowed to achieve mod or high dose per guidelines (Expert)

- Confusional state or memory impairment
  - eval for nonstatin related causes as well as possibility of statin association- (Expert)
Statins and Diabetes

- Modestly increase the excess risk of DM-2
- The potential for ASCVD risk reduction on statins outweighs risk of DM-2 except in lowest risk populations
Monitoring of Statin therapy

- Fasting lipids at baseline
- Followed by second lipid panel in 4-12 weeks to assure adherence of therapy
- Then check every 3-12 months as clinically indicated
- Do not add non-statin unless rare circumstances
  - High risk patients (ASCVD, LDL > 190, DM or age 40-75)
  - With less than anticipated response to statins or statin intolerance
Age > 75

- Continue statin beyond age 75 who are taking and tolerating
- Moderate intensity statin for secondary prevention in ASCVD patients age 75 and older (not high intensity)
- Few data for age > 75 and primary prevention
Conclusions

- 4 statin benefit groups
  - ASCVD
  - LDL >190
  - Age 40-75 + DM with LDL 70-189- without known ASCVD
  - Age 40-75 (no DM or ASCVD LDL 70-189 but have ASCVD risk > 7.5% over 10 years)
  - Use Pooled Cohort Equations to calculate risk