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Observations on US CVD Prevention Guidelines

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What are Guidelines?

Evidence Base for Guidelines

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommen-

Tricoci, JAMA 2009

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Evidence Base for Guidelines

Table 2. Distribution of Class of Recommendation and Level of Evidence in Current Guidelines

Guidelines	Year	No./Total (%)						
		Class of Recommendations[a]			Level of Evidence[b]			
		I	II	III	A	B	C	None
Disease guidelines								
Atrial fibrillation[7]	2006	41/111 (36.9)	55/111 (49.5)	15/111 (13.5)	13/111 (11.7)	33/111 (29.7)	65/111 (58.6)	0/111
Heart failure[28]	2005	66/129 (51.2)	44/129 (4.1)	19/129 (14.7)	34/129 (26.4)	25/129 (19.4)	70/129 (54.3)	0/129
Peripheral artery disease[33]	2005	147/237 (62.6)	68/237 (28.1)	22/237 (9.4)	36/237 (15.3)	142/237 (60.4)	59/237 (25.1)	0/237
STEMI[45]	2004	248/422 (58.8)	123/422 (29.1)	51/422 (12.1)	57/422 (13.5)	167/422 (39.6)	199/422 (47.2)	0/422
Perioperative evaluation[40]	2007	13/50 (26.0)	27/50 (54.0)	10/50 (20.0)	6/50 (12.0)	28/50 (56.0)	16/50 (32.0)	0/50
Secondary prevention[44]	2006	38/48 (79.2)	10/48 (20.8)	0/48	11/48 (22.9)	33/48 (68.8)	4/48 (8.3)	0/48
Stable angina[47]	2002	78/235 (33.2)	98/235 (41.7)	59/235 (25.1)	15/235 (6.4)	92/235 (39.1)	128/235 (54.5)	0/235
Supraventricular arrhythmias[48]	2003	61/147 (41.5)	77/147 (52.4)	9/147 (6.1)	9/147 (6.1)	55/147 (37.4)	83/147 (56.5)	0/147
Unstable angina[51]	2007	187/298 (62.8)	82/298 (27.5)	29/298 (9.7)	70/298 (23.6)	139/298 (46.8)	88/298 (29.6)	0/298
Valvular heart disease[55]	2008	156/320 (48.8)	124/320 (38.8)	40/320 (12.5)	1/320 (0.3)	93/320 (29.1)	226/320 (70.6)	0/320
Ventricular arrhythmias and sudden cardiac death[52]	2006	103/217 (47.5)	100/217 (46.1)	14/217 (6.5)	21/217 (9.7)	69/217 (31.8)	127/217 (58.5)	0/217
Summary of disease guidelines, median (IQR), %		48.8 (39.2-60.7)	38.8 (28.6-47.8)	12.1 (8.0-14.1)	12.0 (8.1-19.1)	39.1 (30.8-51.4)	54.3 (30.8-57.5)	0
Summary of all guidelines, median (IQR), %		46.4 (33.2-57.1)	41.0 (29.1-50.7)	13.1 (9.4-20.0)	11.4 (5.8-16.2)	39.4 (31.3-57.1)	47.5 (25.9-56.9)	0

Tricoci, JAMA 2009

CLINICAL PRACTICE GUIDELINES WE CAN TRUST

Committee on Standards for Developing
Trustworthy Clinical Practice Guidelines

Board on Health Care Services

Robin Graham, Michelle Mancher, Dianne Miller Wolman,
Sheldon Greenfield, and Earl Steinberg, *Editors*

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From 2011 IOM Report: Making Guidelines Better

To be trustworthy, guidelines should:

- Be based on a systematic review of the existing evidence;
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups;
- Consider important patient subgroups and patient preferences, as appropriate;
- Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest;
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and
- Provide ratings of both the quality of evidence and the strength of the recommendations; and
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

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

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease

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NHLBI Charge to the Expert Panel

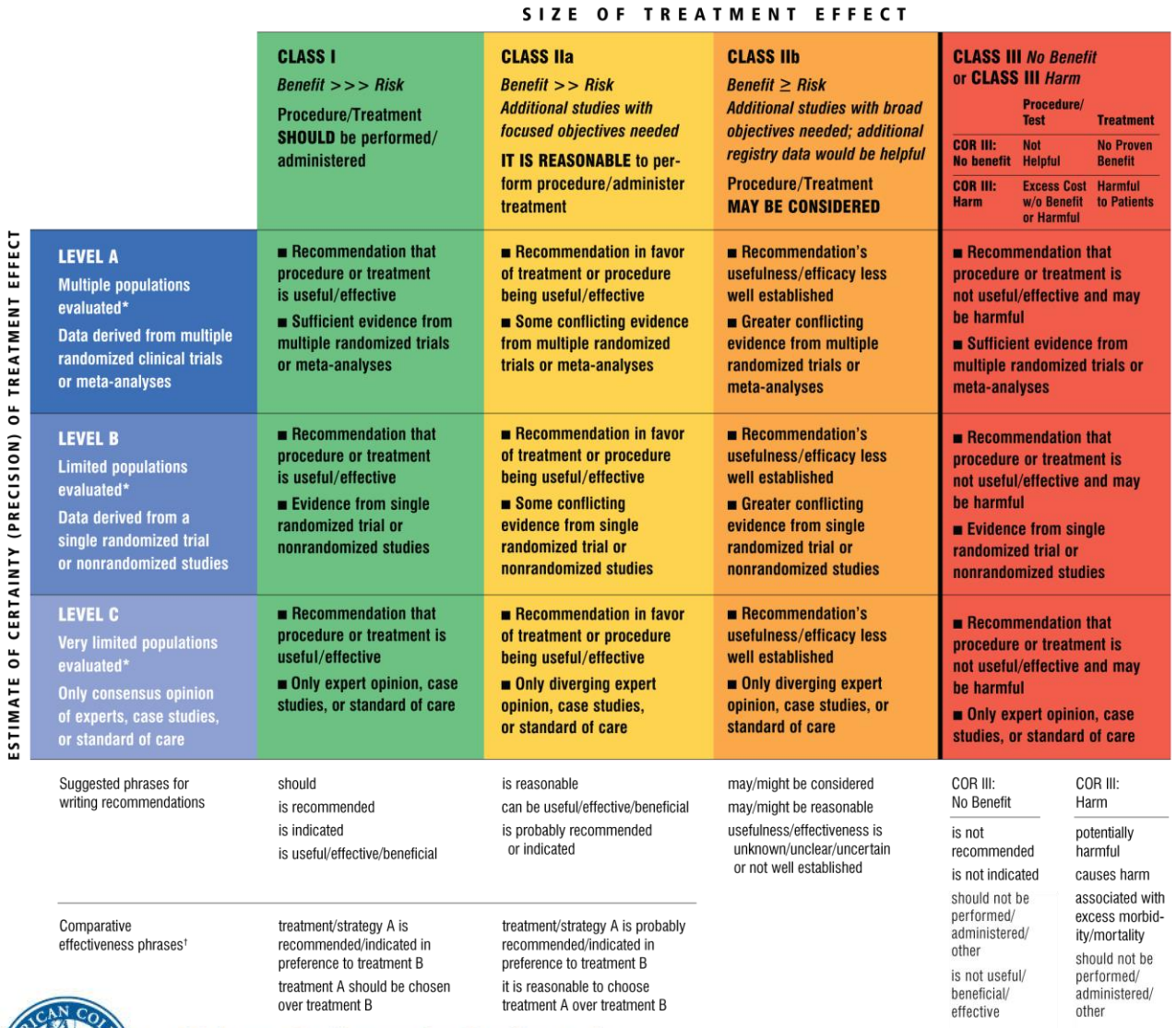
Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk

- Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
  - Cholesterol Panel: 3 CQs
  - Risk Assessment Work Group: 2 CQs
  - Lifestyle Management Work Group: 3 CQs
- RCTs and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality
- Develop recommendations based on RCT evidence

Systematic Review Process

- The Expert Panel constructed CQs relevant to clinical practice.
- The Expert Panel identified (a priori) inclusion/exclusion (I/E) criteria for each CQ.
- An independent contractor developed a literature search strategy, based on I/E criteria, for each CQ.
- ***An independent contractor executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ.***
- The date for the overall literature search was from January 1, 1995 through December 1, 2009.
- However, RCTs with the ASCVD outcomes of MI, stroke and cardiovascular death published after that date were eligible for consideration until July 2013.

Classification of Recommendations and Levels of Evidence



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit — is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm — potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Guideline Scope

- Focus on *treatment of blood cholesterol to reduce ASCVD risk in adults*
- Emphasize adherence to a heart healthy lifestyle
    - See Lifestyle Management Guideline
- Identify individuals *most likely to benefit* from cholesterol-lowering therapy
    - 4 statin benefit groups
- Identify safety issues

4 Evidence-Based Statin Benefit Groups

- Clinical ASCVD
- LDL–C ≥190 mg/dL without secondary cause
- Primary prevention/Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL
- Primary prevention/No Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL, ASCVD risk ≥7.5%*

* Requires risk discussion with clinician before statin prescription. Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator.

New Perspective on LDL–C & Non-HDL–C Goals

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
- Strong evidence that *appropriate intensity of statin therapy* should be used to reduce ASCVD risk *in those most likely to benefit*
- Quantitative comparison of statin benefits with statin risk
- Nonstatin therapies – did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy

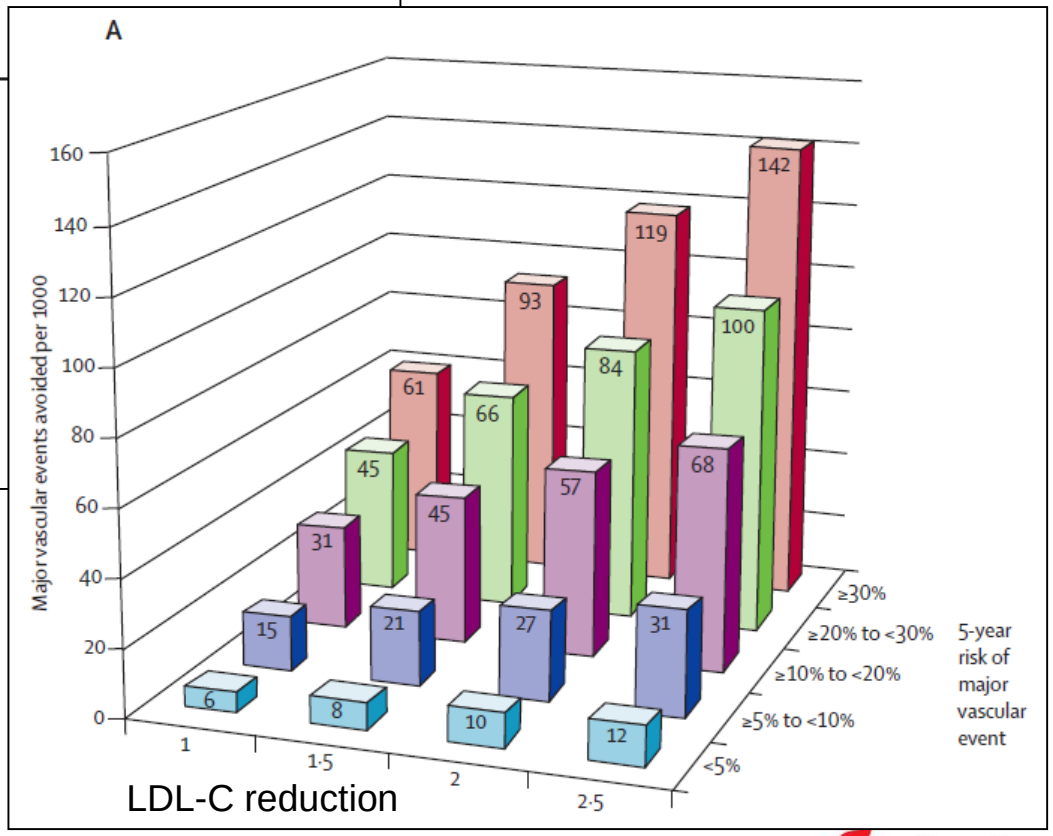
Why Not Continue to Treat to Target?

***Major difficulties*:**

1. Current RCT data do not indicate what the target should be
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
4. Therefore, unknown net benefit from treat-to-target approach

CTT 2012
RRR Similar; Absolute Risk Rules

5-year MVE risk at baseline	Events (% per annum)		RR (CI) per 1·0 mmol/L reduction in LDL cholesterol	Trend test
	Statin/more	Control/less		
Participants without vascular disease				
<5%	148 (0·35)	229 (0·53)		
≥5% to <10%	487 (1·02)	716 (1·53)		
≥10% to <20%	854 (2·52)	1003 (2·98)		
≥20% to <30%	294 (4·40)	351 (5·28)		
≥30%	121 (7·29)	126 (8·16)		
Subtotal	1904 (1·44)	2425 (1·84)		



Primary Prevention
Global Risk Assessment

- To estimate 10-year *ASCVD* risk
  - New Pooled Cohort Risk Equations
  - White and black men and women
- More accurately identifies higher risk individuals for statin therapy
  - Focuses statin therapy on those most likely to benefit
  - You may wish to avoid initiating statin therapy in high-risk groups found not to benefit (higher grades of heart failure and hemodialysis)

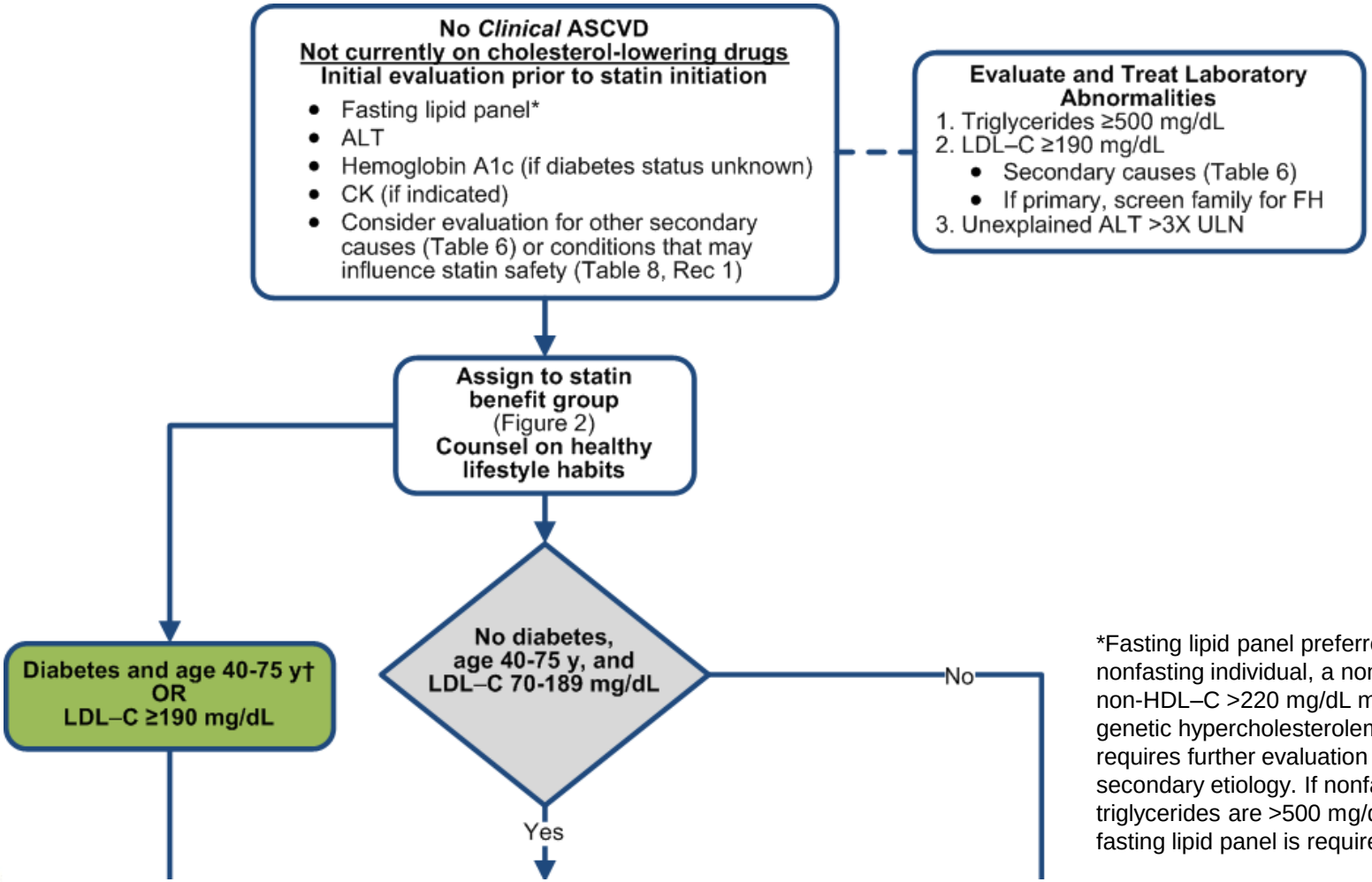
Primary Prevention
Statin Therapy

- Thresholds for initiating statin therapy derived from RCTs (not from calculator)

- Before initiating statin therapy, clinicians and patients engage in a discussion of the potential for ASCVD risk reduction benefits, potential for adverse effects, drug-drug interactions, and patient preferences

Primary Prevention

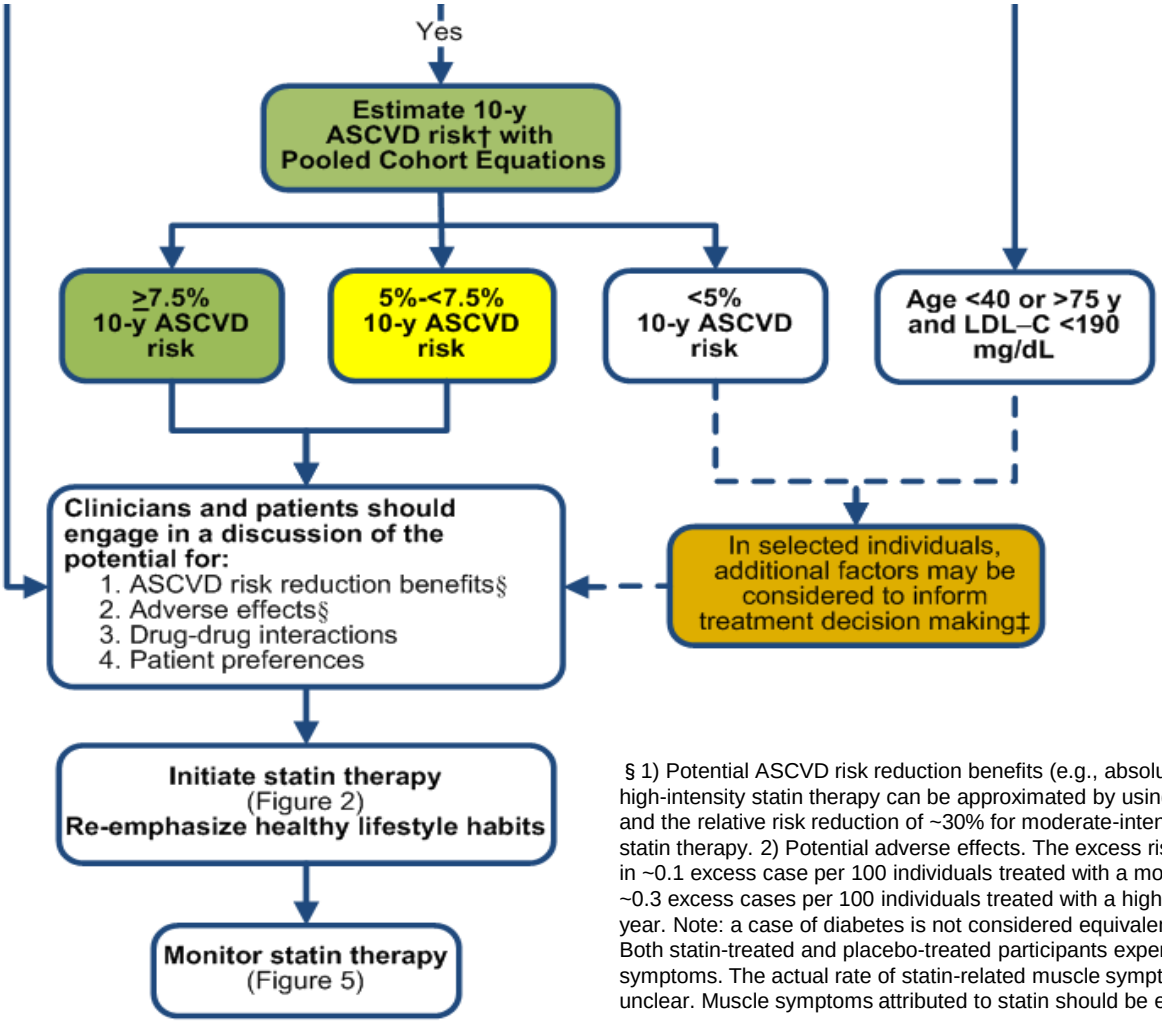
Initiating Statin Therapy



*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL–C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.

Primary Prevention

Initiating Statin Therapy (con't)



†The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.

‡These factors may include primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, sensitivity-C-reactive protein ≥2 mg/L ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity (For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.

§ 1) Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: a case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.

Individuals Not in a Statin Benefit Group

- In those not clearly in a statin benefit group, additional factors may inform treatment decision-making:
  - *Family history of premature ASCVD*
  - *Elevated lifetime risk of ASCVD*
  - *LDL–C ≥160 mg/dL*
  - *hs-CRP ≥2.0 mg/L*
  - *Subclinical atherosclerosis*
    - *CAC score ≥300/75%ile or ABI<0.9*
- Discussion of potential for ASCVD risk reduction benefit, potential for adverse effects, drug-drug interactions, and patient preferences

Monitoring & Safety

- Measure LDL-C on therapy to assess adherence, need for further lifestyle modification, potential need for additional therapy in high-risk patients

- Safety
  - RCTs & meta-analyses of RCTs used to identify important safety considerations
  - Allow estimation of **net benefit** from statin therapy
    - ASCVD risk reduction versus adverse effects
- Expert guidance on management of statin-associated adverse effects, including muscle symptoms

Three Principles

- Do not focus on LDL cholesterol levels as drug therapy goals
- Use proven medications to reduce ASCVD risk
  - Individualize after that
- Make decisions on drug treatment in primary prevention based on the patient
  - Risk discussion with patient is required
  - Assessment of absolute benefits and harms

JBS3 and ACC/AHA

- Systematic reviews on critical questions
- Very similar identification of evidence base in terms of process and outcomes
- Similar approaches to risk assessment
  - 10-year and lifetime risk estimation
  - QRISK2 vs Pooled Cohort Equations
    - Traditional RF inputs, slightly different endpoints
  - Do not recommend routine screening with novel markers, but perhps in some subgroups

JBS3 and ACC/AHA

- Similar approaches to risk communicaition and treatment
  - Starts with risk tool and a risk/benefit discussion about intensity of prevention efforts
  - Similar RRR means select patients based on higher absolute risk
  - Broader base for pharmacotherapy
    - Increased sensitivity and lower specificity given marked efficacy and benign low-cost drug (statins)
    - Statins >>> other classes

JBS3 and ACC/AHA

- Consideration of statins for those with 10-year risk >10% (JBS) or 7.5% (ACC/AHA)
  - Nearly identical thresholds considering difference in endpoints of interest
  - ACC/AHA focuses on statin intensity
  - JBS focuses on 2 doses of atorvastatin based on C-E analysis

JBS3 and ACC/AHA

- "In conclusion, the new British and American guidelines have much in common. This should come as no surprise since they are both based on the same scientific foundation. The fact that totally different committees, in different societies, working separately and independently came to nearly identical conclusions and recommendations suggests to me that bias did not greatly play a role in either's conclusions. It is, as we would hope, that the science drives the outcome of clinical practice guidelines."

Greenland, Heart, In press