

Novas guidelines de tratamento dislipidemia ACC/AHA

Razões que a razão desconhece?

In 1913, Anichkov and his student Chalatov observed that feeding hypercholesterolemic diets to rabbits led to atherosclerotic lesions.

Much science has supported the key role of cholesterol in the pathogenesis of atherosclerosis.



FIGURE 8. A 1945 photograph of Lieutenant General Nikolai Anichkov of the Russian Army Medical Corps. (Photograph courtesy of Anichkov's grandson, Professor Nikolai Anichkov of Saint Pecersburg.)

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

Published on line November, 12 2013





Institute of Medicine Report: Quality Chasm

"In its current form, habits, and environment, American health care is incapable of providing the public with the quality health care it expects and deserves."

Design Rule 5: Current: Decision making is based on training and experience. New: Decision making is based on evidence. Patients should receive care based on the best available scientific knowledge. Care should not vary illogically form clinician to clinician or from place to place.

Institute of Medicine, Crossing the Quality Chasm: A New Health System for the Twenty-first Century. Washington: National Academy Press, 2001

!!!46 total recommendations, 20 of which are graded 'E,' meaning they are based on expert opinion!!!

Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.")

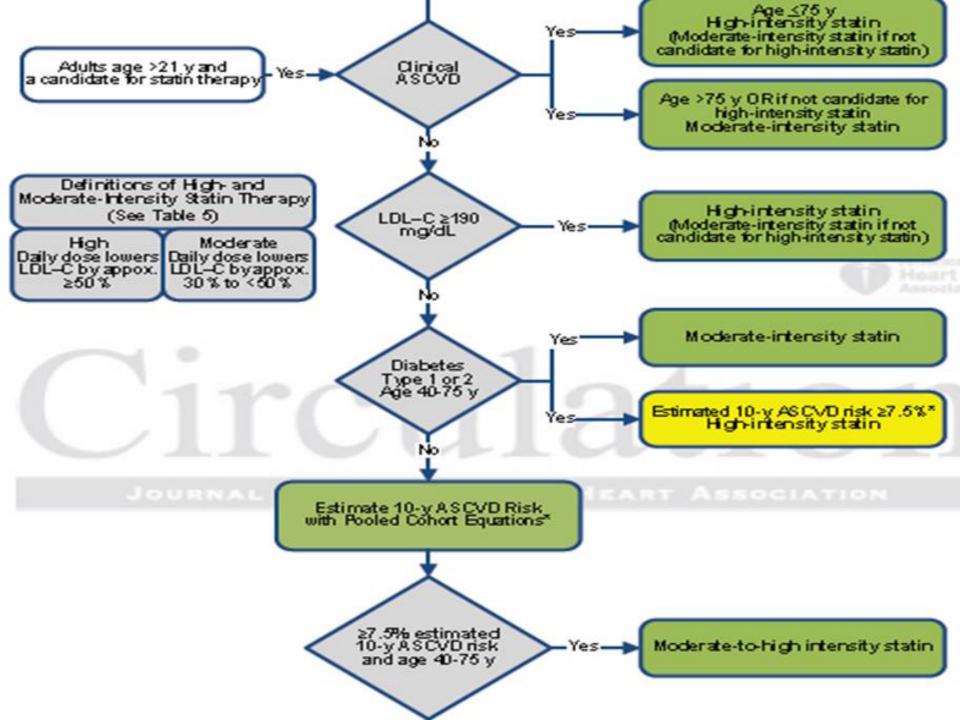
Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation.

Further research is recommended in this area.

WHAT'S NEW

A New Perspective on LDL-C and/or Non-HDL-C Treatment Goals

- The Expert Panel was unable to find RCT evidence to support continued use of specific LDL—C and/or non-HDL—C treatment targets.
- The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.
- Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.



Use of LDL targets may result in undertreatment with evidence-based statin therapy or overtreatment with nonstatin drugs that have not been shown to reduce ASCVD events in RCTs (even though the drug may additionally lower LDLand/or non-HDL).

Summary of treatment thresholds and targets based on Framingham Risk Score (FRS), modified by family history

Risk level	Initiate therapy if:	Primary target (LDL-C)	Alternate target		
High FRS ≥20%	Consider treatment in all (Strong, High)	 ≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate) 	 Apo B ≤0.8 g/L or Non-HDL-C ≤2.6 mmol/L (Strong, High) 		
Intermediate FRS 10-19%	 LDL-C ≥3.5 mmol/L (Strong, Moderate) For LDL-C <3.5 mmol/L consider if: Apo B ≥1.2 g/L OR Non-HDL-C ≥4.3 mmol/L (Strong, Moderate) 	• ≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate)	 Apo B ≤0.8 g/L or Non-HDL-C ≤2.6 mmol/L (Strong, Moderate) 		
Low FRS <10%	 LDL-C ≥5.0 mmol/L Familial hypercholesterolemia (Strong, Moderate) 	• ≥50% decrease in LDL-C (Strong, Moderate)	N/A		



Managing lipids - reducing cardiovascular disease risk

Published in NPS News

Date published: 01 February 2011 (i)

Use absolute risk to inform treatment in primary prevention

Start people without cardiovascular disease who are otherwise at high cardiovascular risk on a statin dose with a moderate LDL-lowering effect. 6,11,14 In primary prevention, simvastatin 40 mg, atorvastatin 10 mg, or pravastatin 40 mg reduced the relative risk of major coronary events by 25% to 35%. 40,42,53,54 Rosuvastatin 20 mg reduced cardiovascular events in a primary prevention trial, but the long-term safety of this dosing regimen for this population has not been established. 55

Treat to a target LDL cholesterol < 2.5 mmol/L in primary prevention¹, taking into account the person's cardiovascular risk score, co-morbidities, life-expectancy and their preferences.⁶ A lower target LDL cholesterol < 2 mmol/L may be appropriate for some high risk groups, such as people with diabetes.⁶ No trials have compared moderate LDL-lowering regimens with more intensive regimens in people without cardiovascular disease, so the benefits and safety of intensive statin therapy have not been directly evaluated in this population.⁶

Treat intensively in secondary prevention

Start people with stable cardiovascular disease on a statin dose with a moderate LDL-lowering effect (e.g. simvastatin 40 mg or atorvastatin 10 mg), then treat to a target LDL cholesterol < 2 mmol/L. ^{1,6} Consider a statin dose with a greater LDL-lowering effect for people with acute coronary syndrome (atorvastatin 80 mg or simvastatin 80 mg were used in trials^G). ⁶

Intensive lowering of LDL cholesterol is beneficial in secondary prevention, even if the target LDL cholesterol cannot be achieved. 1,6,51 High doses of statins (e.g. atorvastatin 80 mg) reduce the relative risk of major cardiovascular events by a further 15% compared with moderate doses (e.g. pravastatin 40 mg) for people with cardiovascular disease. 47 However, high statin doses are associated with higher incidences of myopathy (0.03% versus 0.9% with simvastatin 20 mg versus 80 mg)⁵² and elevated liver enzymes (0.4% versus 1.5% with less intensive versus more intensive regimens). 51 Monitor people taking high statin doses closely for muscle effects and for changes to liver enzymes. 51



ADA Guidelines: Dyslipidemia and Lipid Management (1 of 2)

Lipid Screening

- Measure fasting lipids at least annually in adults with diabetes
 - Every 2 yrs for adults with low-risk lipid values (LDL-C <100 mg/dL, HDL-C >50 mg/dL, TG <150 mg/dL)

Goals

No overt CVD	LDL-C <100 mg/dL (2.6 mmol/L)
Overt CVD	LDL-C <70 mg/dL (1.8 mmol/L)*
Alternative goal if goals not achieved on maximal statin therapy	30–40% LDL-C reduction from baseline

^{*}Using high-dose statin therapy; statins contraindicated in pregnancy

AACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS' GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROSIS

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the AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis

Table 12 Lipid Goals for Patients at Risk for Coronary Artery Disease

(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])

Lipid Parameter	Goal	EL
TC, mg/dL	<200	EL 1
LDL-C, mg/dL	<100; <70 (all very high risk patients)	EL 1
HDL-C, mg/dL	As high as possible, but at least >40 in both men and in women	EL 1
Non-HDL-C, mg/dL	30 above LDL-C goal	EL 1
TG, mg/dL	<150	EL 1
Apo B, mg/dL	<90 (patients at risk of CAD, including those with diabetes) <80 (patients with established CAD or diabetes plus ≥1 additional risk factor)	EL 4

Abbreviations: apo, apolipoprotein; EL, evidence level; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

National Cholesterol Education Program Adult Treatment Panels (ATP)

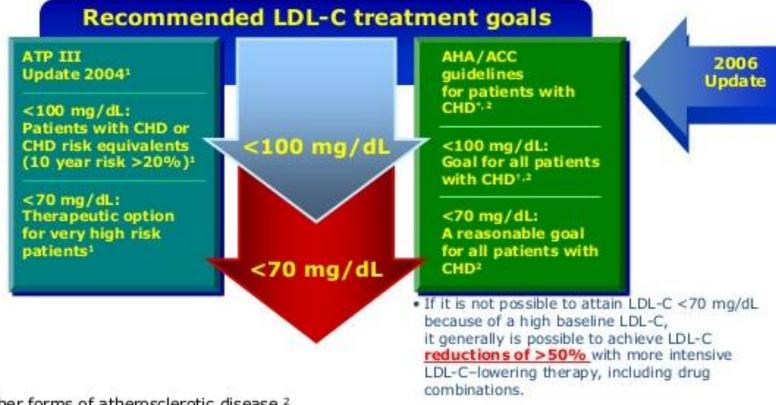
ATP I

- LDL-C primary target:
 - High risk >160 mg/dL or
 2130 mg/dL and 2 or more
 risk factors (RFs)— <130
 mg/dL considered desirable
- HDL-C considered a major RF but not considered for screening purposes — concerns re: measurement accuracy and science base
- Population guide also published

ATP II

- 1993: Emphasized risk status as a guide to treatment intensity.
- Recommended HDL-C screening
- Set <100 mg/dL for LDL-C goal in those with overt disease
- Emphasized physical activity and weight reduction to enhance diet therapy

LDL-C Goals for High Risk Patients



^{*}And other forms of atherosclerotic disease.2

- Grundy SM et al. Circulation 2004;110:227-239.
- 2. Smith SC Jr et al. Circulation 2006; 113:2363-2372.

^{*}Factors that place a patient at very high risk: established cardiovascular disease plus: multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (e.g., cigarette smoking); metabolic syndrome (triglycerides ≥200 mg/dL + non-HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.¹</p>

Evolution of NHLBI Supported Guidelines

NCEP ATP I 1988 NCEP ATP II 1993 NCEP ATP III 2001 Updated NCEP ATP III 2004 AHA/ACC Update 2006 2* Prev. Guidelines

More Intensive Treatment Recommendations

1

Framingham
MRFIT
LRC-CPPT
Coronary
Drug Project
Helsinki Heart
CLAS

1

Angiographic trials (FATS, POSCH, SCOR, STARS, Ornish, MARS) Meta-analyses (Holme, Rossouw) Î

4S WOSCOPS CARE LIPID AFCAPS/ TexCAPS



HPS
PROVE-IT
ASCOT-LLA
PROSPER
ALLHAT-LLT



TNT IDEAL



Issue date: May 2008 (reissued March 2010)

Lipid modification

Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Primary prevention	No target level for total or LDL cholesterol	Initiate simvastatin (Zocor), 40 mg daily, if CHD risk is ≥ 20
		percent (routine measurement of lipid levels is not
	"fire and forget"	necessary)
Secondary prevention	< 78 mg per dL (2.02 mmol per L)	Initiate simvastatin, 40 mg daily, as soon as possible
		Consider increasing dosage to 80 mg daily if LDL
		cholesterol goal is not achieved
		Consider a higher-intensity statin in patients with acute

coronary syndrome

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Conflicts of Interest

2 main types

- Financial
- Intellectual

Per IOM 2011:

- Whenever possible GDG members should not have COIs.
- Members with COIs should represent not more than a minority of the GDG.
- The chair or co-chairs should not be a person(s) with COIs.
- Funders should have no role in CPG development.

"Majority of panelists on controversial new cholesterol guideline have current or recent ties to drug manufacturers"
- BMJ 2013;347:16989

Neil Stone, MD (chairman)

- Abbott, AstraZeneca, Merck, Pfizer, Sanofi-Aventis and Schering-Plough
- "I will not take industry funding for 2 years after release of the guidelines"
- Jennifer Robinson, MD (Co-chair)
 - Financial ties to several statin manufactures while on panel from 2008-2013
- 6 of 8 panelist with financial ties during service on the panel!

Why a new risk predictor?

- Previously used <u>Framingham</u> risk score was not felt to be adequate because of its "derivation in an <u>exclusively White</u> sample population and the limited scope of the outcome (in determining CHD alone)."
- Other risk scores also suffered from "nonrepresentative or historically dated populations, limited ethnic diversity, narrowly defined endpoints, endpoints influenced by provider preferences (e.g., revascularizations), and endpoints with poor reliability (e.g., angina and heart failure [HF])."
- Broader outcomes of interest
 - ASCVD: first occurrence of nonfatal myocardial infarction or CHD death, or fatal or nonfatal stroke

Clinical prediction rule development

Step 1. Derivation

Identification of factors with predictive power

Step 2. Validation

Evidence of reproducible accuracy

Narrow Validation

Application of a rule in a similar clinical setting and population as in Step 1

Broad Validation

Application of a rule in multiple clinical settings with varying prevalence of disease

Step 3. Impact Analysis

Evidence that rule changes physician behavior and improves patient outcomes

Development of the Pooled Cohort Risk Assessment Equations

Derivation

- Used several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies,
- including the ARIC study,
 Cardiovascular Health Study, and
 the CARDIA study, combined
 with applicable data from the
 Framingham Original and
 Offspring Study cohorts
- Sex-and race-specific proportional hazards models that included the covariates of age, treated or untreated systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), current smoking (Y/N), and diabetes (Y/N).

Validation

- Calculated area under the receiver operating curve (Cstatistic) for discrimination and the calibration chi-squared statistic
- External validation done in external cohorts consisting of Whites and African Americans from the Multi-Ethnic Study of Atherosclerosis (MESA) and the REasons for Geographic And Racial Differences in Stroke study (REGARDS) and contemporary cohorts from ARIC and Framingham.

Validation

- Discrimination
 - Accurately determine if a person has or doesn't have disease
 - C-statistic or AUC

- Calibration
 - How well do predicted risk estimates match observed risk in external populations

Omnibus_Risk_Estimator

Risk Factor	Units			
Sex	M (for males) or F (for females)			
Age	years			
Race	AA (for African Americans) or WH (for whites or others)			
Total Cholesterol	mg/dL			
HDL-Cholesterol	mg/dL			
Systolic Blood Pressure	mm Hg			
Treatment for High Blood Pressure	Y (for yes) or N (for no)			
Diabetes	Y (for yes) or N (for no)			
Smoker	Y (for yes) or N (for no)			

Risk score doesn't take into account family history of premature cardiovascular disease, triglycerides, waist circumference, body-mass index, lifestyle habits, and smoking history.

Validation

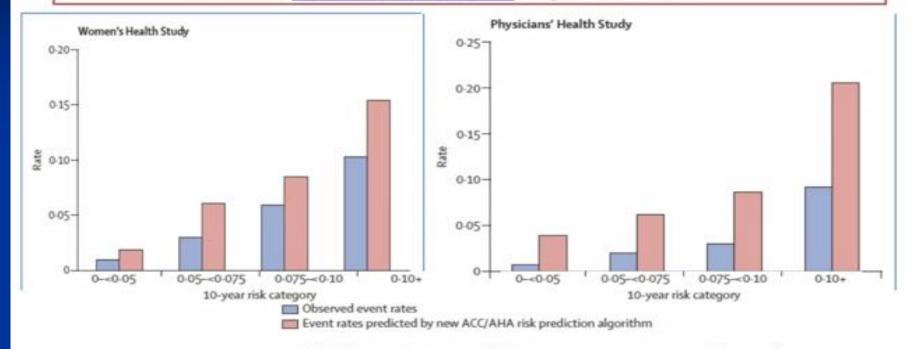
(http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437741.48606.98/suppl/DC1)

	Women			Men				
	Algorithm	Validation Cohorts		Algorithm	Validation Cohorts			
	Derivation Cohort	Contemporary (4)	MESA (5)	REGARDS (6)	Derivation Cohort	Contemporary (4)	MESA (5)	REGARDS (6)
White					0.0			
Total N	11.240	6,509	1.273	6,333	9,098	5.041	1,184	5.296
Events(1)	683	400	37	101	1,032	539	57	218
Events(2)	722.9	426.7	38.4	120.7	1,095.2	580.9	59.7	250.2
Exp Events(3)	723.5	549.4	49.9	153.9	1,098.5	798.9	94.9	306.4
C- statistic	0.8058	0.7377	0.7109	0.6599	0.7462	0.6843	0.7044	0.5950
Callb. Chi-sq	6.43	45.50	14.56	44.93	4.86	84.45	21.43	66.71
African American								
Total N	2,641	1,367	978	5.275	1,647	735	799	2.969
Events(1)	235	127	28	126	194	107	36	136
Events(2)	248.7	131.3	30.1	147.1	213.8	114.0	38.3	162.5
Exp Events(3)	250.6	173.5	59.4	217.5	212.5	120.8	72.3	180.7
C- statistic	0.8182	0.7068	0.7684	0.6625	0.7130	0.7109	0.6689	0.5564
Calib. Chi-sq	7.25	15.96	18.51	48.22	6.71	12.62	24:40	46.23

C statistic: range 0.5 - 1.0 ("reasonable" > 0.7, "strong" > 0.8)

External Validation

The Lancet, Volume 382, Issue 9907, Pages 1762 - 1765



 How many of the 33 million expected to have risk >7.5% actually have risk that is much lower?

Guideline risk-assessment calculator overestimated risk, when tested in MESA and REGARDS

"It is possible that as many as 40 to 50 percent of the 33 million middle-aged Americans targeted by the new guidelines for statin therapy do not actually have risk thresholds exceeding the 7.5 percent level suggested for treatment"

Ridker and Cook

"We recognize a potential for overestimates, especially at the high end of risk"

Dr. David Goff, co-chairman of the guidelines' risk assessment WG

"We're surrounded by a real disaster in terms of credibility"

Peter Libby, chairman of CV department of medicine, Brigham and Women's Hospital.

ATP III vs ACC/AHA

Panel followed the "rules" for guideline development published by a committee of the Institute of Medicine (IOM), emphasizing the necessity for "evidence-based medicine".

ATP III panel used of all types of relevant science: RCTs, epidemiological data, genetic and metabolic studies, in vivo and in vitro investigations.

New guidelines mean that clinicians have to use clinical judgement to make clinical decisions instead of having science-based guidance to inform clinical choices.

ACC/AHA guidelines promote lifestyle intervention without RCT evidence, breaking their own evidence-based rules

ACC/AHA guidelines recomend high-intensity statins in pts with ASCVD, substantially ↓ risk. Pts with high baseline LDL will not receive full benefit of LDL lowering because non-statin drugs are not explicitly recommended.

RCT evidence on statin efficacy and scientific evidence on LDL lowering efficacy are not in accord.

Although there are similarities between ATP III and ACC/AHA guidelines, the two are fundamentally different. ATP III is the summation of several decades of research on the relation of atherogenic lipoproteins to ASCVD, based on the concept that lowering atherogenic lipoproteins will prevent ASCVD.

ACC/AHA guidelines, under the influence of an IOM paradigm, are transformed into statin treatment instructions.

ACC/AHA guidelines depend entirely on RCTs, are not to be considered comprehensive cholesterol guidelines. Physician must rely on clinical judgment, making ATP III still useful

Scott Grundy

NLA – National Lipid Association

We provided our comments but after multiple revisions ultimately felt that the document presented - although important and constructive - does not go far enough to address gaps in clinical care and therefore decided not to endorse them as guidelines.

We understand the constraints that the NHLBI panel had in limiting their review to only high quality randomized controlled trials but also believe that other important types of clinical evidence should not have been excluded. We also do not find evidence-based support for the Panel's recommendation for removing LDL (and Non-HDL) treatment targets.

.... We question the need to remove such important and well-known clinical performance metrics that have been so widely endorsed by the clinical community

Further we find there to be an absence of discussion regarding other therapeutic options for patients on high-dose statins but which still exhibit high residual risk and/or significantly elevated LDL-C levels.

There also needs to be more discussion on managing special populations such as older patients above age 75, those with familial hypercholesterolemia, those who are statinintolerant, and younger high risk patients under age 40.

New cholesterol guidelines: Worth the wait?

CHAD RAYMOND, DO

LESLIE CHO, MD

MICHAEL ROCCO, MD^a

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CLINICAL ASCVD

Limitations of the new guidelines

Make follow-up LDL-C levels irrelevant, seeming to assume that there is no gradation in residual risk and, thus, no need to tailor therapy to the individual.

Patients no longer have a goal to strive for or a way to monitor their progress.

Ignore the pathophysiology of coronary artery disease and evidence of residual risk in patients on both moderate intensity and high-intensity statin therapy.

Ignore the potential benefits of treating to lower LDL-C or non-HDL-C goals, thus eliminating consideration of multidrug therapy.

Do not address patients with recurrent cardiovascular events already on maximal tolerated statin doses.

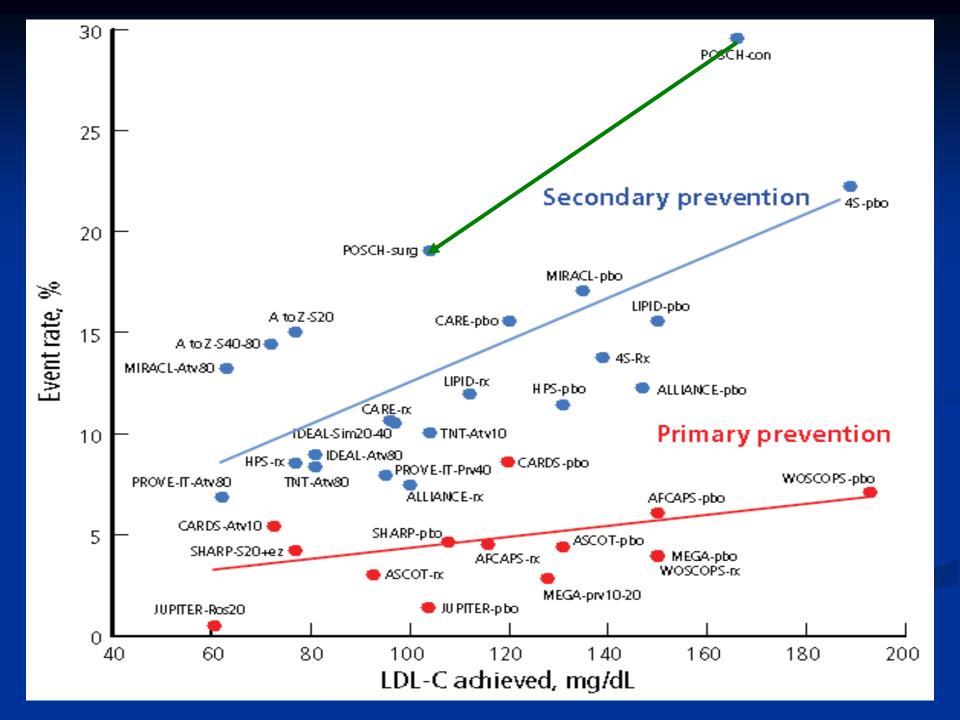
Undermine the potential development and use of new therapies for dysplipidemia in patients with ASCVD.

In a patient at high risk, would you be comfortable with an LDL-C value of 110 mg/dL on maximum statin therapy?

Genetic data show that LDL particle and the LDL receptor pathway are mechanistically linked to ASCVD pathogenesis, with lifetime exposure as a critical determinant of risk.

RCTs of statins and other studies of cholesterollowering show a reproducible relationship between the LDL-C level achieved and absolute risk.

There's a strong rationale for targeting LDL-C and establishing goals for lowering its levels. We believe that removing LDL-C goals is a fundamental flaw of the new guidelines.



$LDL-C \ge 190 mg/dL$

Limitations of the new guidelines

Mention only that one "may consider" adding a second agent if LDL-C remains above 190 mg/dL after maximum-dose therapy. Patients with **familial hypercholesterolemia** or other severe forms of hypercholesterolemia typically end up on multidrug therapy to further reduce LDL-C.

Absence of RCT data to show an additive value of second and third lipid-lowering agents does not mean these agents do not provide benefit (The absence of evidence isn't the evidence of absence)

Absence of RCT data in a given scenario should not be interpreted as evidence of lack of benefit (primary-prevention patient under age 40 with elevated LDL-C below the 190 mg/dL cutoff who otherwise is healthy and without risk factors).

By disregarding all evidence that is not from RCTs, expert panel fails to account for the extensive pathophysiology of ASCVD, which often begins at a young age and takes decades to develop.

Prevention only works if started

DIABETES,40–75 y, LDL-C 70–189, NO CLINICAL ASCVD

Limitations of new guidelines

High-intensity statin therapy is indicated, but, using the new risk calculator, some pts may receive overly aggressive treatment, thus increasing the possibility of statin side effects.

The guidelines do not address patients younger than 40 or older than 75.

Diabetic patients have a high residual risk of ASCVD events, even on statin. Yet the guidelines ignore the potential benefits of more aggressive LDL-lowering or non-LDL secondary targets for therapy.

ADA and AACE recommend LDL-C goal < 70 mg/dL in high risk pts, non-HDL-C less than 100 mg/dL, an apoB < 80 mg/dL, and an LDL particle number < 1,000 nmol/L.

AGE 40–75, LDL-C 70–189, NO ASCVD, 10-YEAR RISK ≥ 7.5%

Limitations of the new guidelines

New risk calculator is controversial (potential for overtreatment, particularly in older pts).

Potential for undertreatment, particularly in patients with an elevated LDL-C but whose 10-year risk is less than 7.5% because they are young.

Do not address patients younger than 40 or older than 75.

Do not take into account some traditional risk factors, such as family history, and nontraditional risk factors such as CRP, measured by ultrasensitive assays, Lp(a), and apo B.

60-year-old African-American man with no risk factors

(TC 150 mg/dL, HDL 45, systolic blood pressure of 125 mmHg, no diabetic or smoker)

10-year risk of 7.5 percent

Mid-60s woman with LDL cholesterol 180 mg/dL would have a 10-year heart attack and stroke risk of 4 %

Too low to qualify her for statin use under the new guidelines, but someone whom most of us would "definitely treat" with statin.

Patients could have a completely normal lipid profile, with normal triglycerides, HDL cholesterol, and LDL cholesterol, but because of age, smoking or blood pressure, guidelines will now recommend treatment

Problematic for physicians and patients because just last week you would have said their LDL-cholesterol levels of 80 or 90 mg/dL was optimal.

"If experts are having this debate over the new guideline, what are practitioners and patients going to think?

They may hold back on these medications even though they've been shown in recent trials to prevent 20 percent of heart attacks and strokes in those who have certain risk factors such as diabetes, high inflammation levels, and elevated cholesterol. We'll have a failure to apply the scientific knowledge that we acquired with great effort over the past 20 years."

"This is a tectonic shift in thinking that's hard to explain.

I worry about this causing confusion, because we've been telling patients for two decades, "know your numbers" and "treat to a certain level".

There will be some significant confusion until we educate everybody about what we are asking them to do.

It is difficult to implement a guideline that on one hand used RCTs exclusively for recommendations, but on the other hand used an untested risk calculator to guide therapy

I hope that the European Society of Cardiology will consider the principles of these guidelines closely and agree that it is time to abandon the focus on LDL-C concentrations









Queimar gordura

Ingerir muitos líquidos



