

Managing Dyslipidemia and ASCVD Risk:

Confusion, Controversy...Consensus

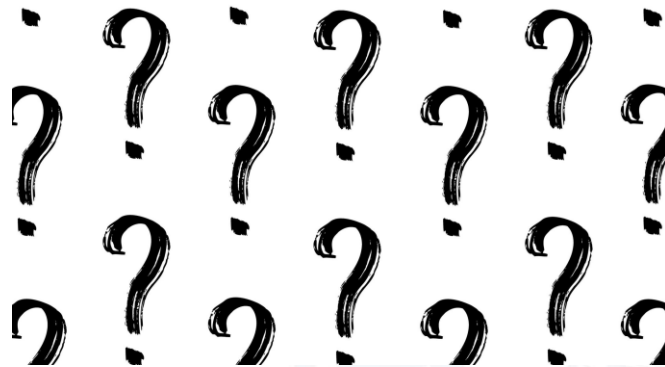
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Charleston, SC



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Management of dyslipidemia for cardiovascular risk reduction

Where questions, controversy, and confusion remain...



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Confusions and Controversies...

- Risk assessment tools: Which one(s) in which patients?
- Lipoprotein targets of therapy: What target and according to whom?
 - LDL-C, non-HDL-C, apo B, LDL-P
- Statin dosing: Fixed dose/intensity or dose titration?
- Lipoprotein goals of therapy: To use or not to use...that is the question.
- Monitoring of response to therapy: The most misunderstood concept.
- Assessing response to therapy: When is enough...enough?
- Safety and efficacy of very low levels of atherogenic lipoproteins: How do we know if therapy has gone too far?
- PCSK9 inhibitors: Waiting for the evidence...



Guidelines for the Management of LDL-related ASCVD Risk

- Multiple guidelines published by numerous professional societies committed to ASCVD prevention



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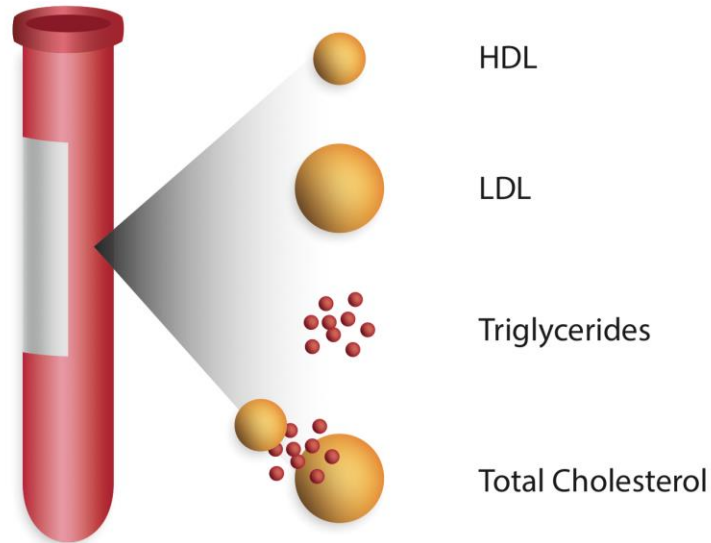


Guidelines: What is the same...

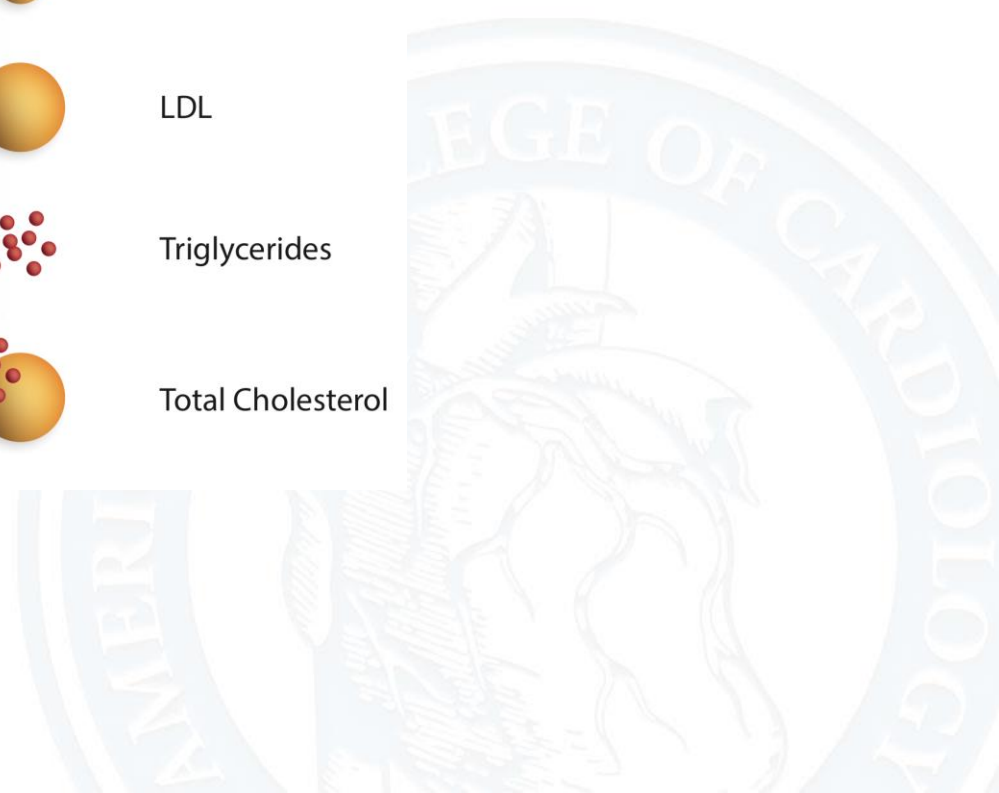
- Intensity of therapy is guided by level of ASCVD risk.
- Statin therapy is first line therapy in all at-risk patients, regardless of how “at-risk” is defined.
- Response to therapy should be monitored.
- Inadequate response to therapy should be addressed.
- Combination therapy may be considered in high-risk patients.



Monitoring...



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Monitoring therapy

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Table 36 Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy

Testing lipids

How often should lipids be tested?

- Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where concomitant drug treatment is suggested such as ACS and very high-risk patients.

How often should a patient's lipids be tested after starting lipid-lowering treatment?

- 8 (\pm 4) weeks after starting treatment.
- 8 (\pm 4) weeks after adjustment of treatment until within the target range.

How often should lipids be tested once a patient has reached the target or optimal lipid level?

- Annually (unless there is adherence problems or other specific reasons for more frequent reviews).

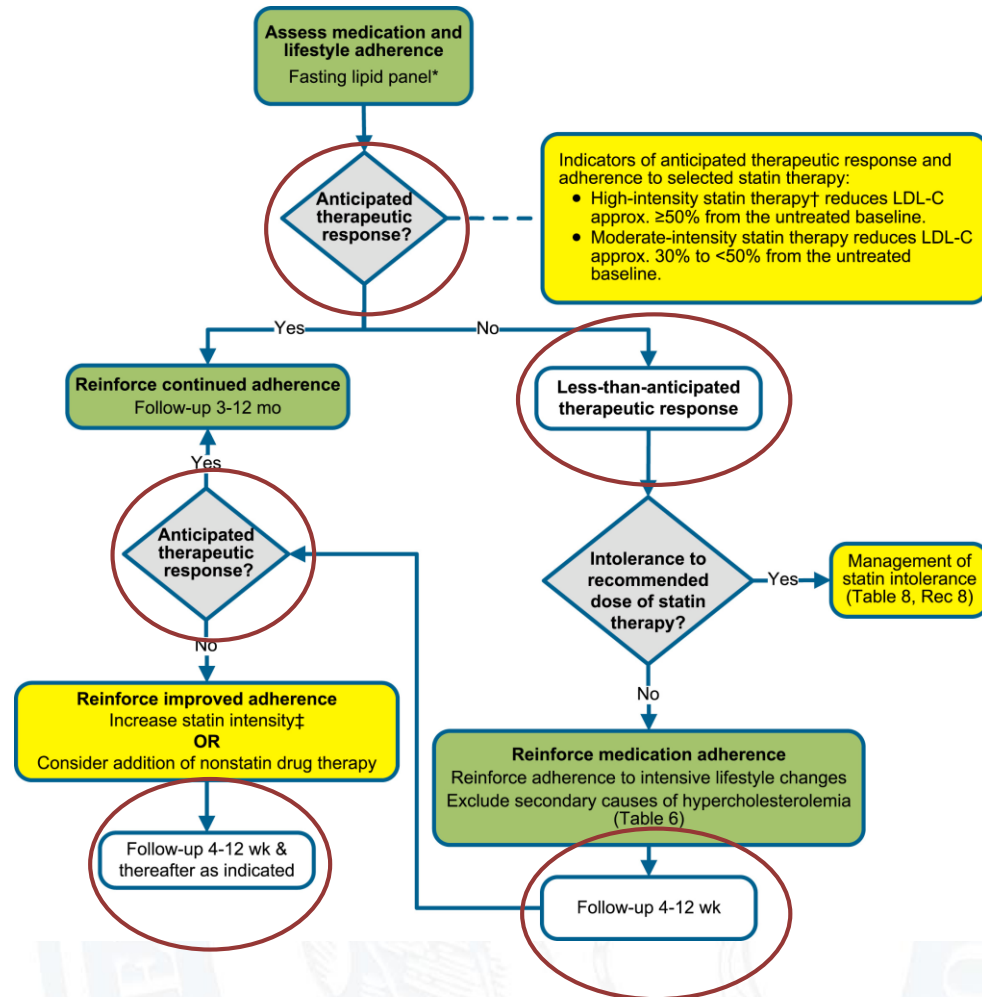
European Heart Journal doi:10.1093/eurheartj/ehw272



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Monitoring response to statin therapy... so misunderstood

- “A high level of RCT evidence supports the use of an initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and calculated LDL-C), followed by a second lipid panel **4 to 12 weeks after initiation of statin therapy**, to determine a patient’s adherence. Thereafter, assessments should be performed **every 3 to 12 months** as clinically indicated.”



Monitoring therapy

- National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia: Part 1

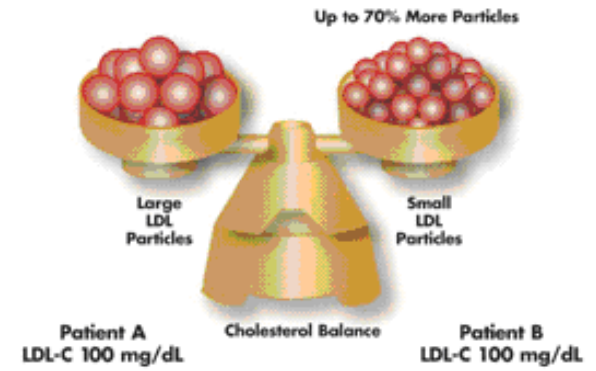
7. The measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy.

Results from RCTs of a variety of atherogenic cholesterol-lowering therapies as well as results from observational studies have generally found that lower on-treatment atherogenic cholesterol levels are associated with lower ASCVD risk.^{8,49,50,98,106} Treatment goals and periodic monitoring of atherogenic cholesterol are useful for allowing a clinician to match the aggressiveness of lipid-lowering therapy to a patient's absolute risk for an ASCVD event and for assessing the adequacy of a patient's response and adherence to therapy. Treatment goals and monitoring of atherogenic cholesterol are particularly valuable tools in patient-clinician communication.

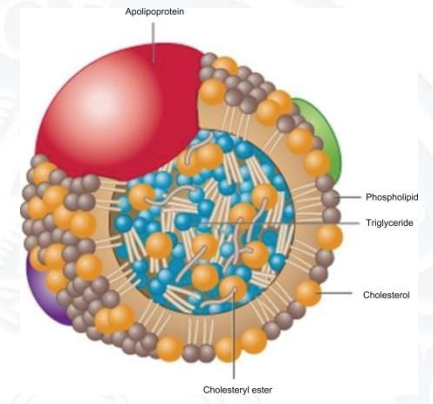
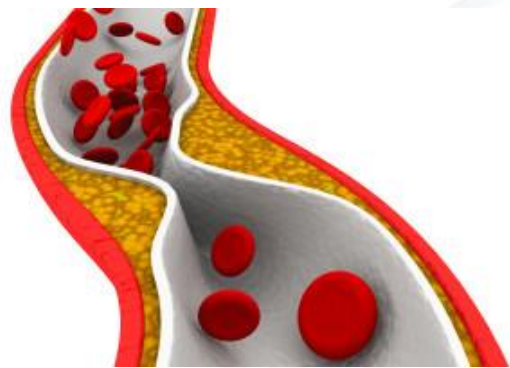
J Clin Lipidol 2014;8:473–488



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Targets, goals, and thresholds...oh, my!



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Targets, goals, and thresholds...oh my!

- Target of therapy: the lipoprotein measurement you want to affect with treatment
 - LDL
 - apo B
 - Non-HDL
 - VLDL
 - LDL-P



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Targets, **goals**, and thresholds...oh my!

- Goals of therapy: the lipoprotein level you want to achieve with treatment
 - Absolute LDL-C
 - apo B
 - Non-HDL
 - LDL-P



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Targets, goals, and **thresholds...oh my!**

- Lipoprotein thresholds: the lipoprotein level at which you may consider treatment intensification, though modification of therapy is NOT mandated
 - Absolute LDL-C
 - Percent LDL-C reduction
 - apo B
 - Non-HDL-C
 - LDL-P



Lipoprotein targets of therapy

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias
 - Primary: LDL-C
 - Secondary: non-HDL-C or apoB
 - Not recommended: HDL-C, ratios

Table 9 Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease

Recommendations	Class ^a	Level ^b	Ref ^c
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

European Heart Journal doi:10.1093/eurheartj/ehw272



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Lipoprotein targets of therapy

- 2014 International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia
- Primary: LDL-C
- Non-HDL-C is an alternate target and has growing advantages.
 - Includes atherogenic cholesterol-rich VLDL remnants
 - Does not require fasting for accurate measurement.
 - In future guidelines non-HDL-C will replace LDL-C as the better target of treatment.
- Total apo B is an optional target, but is not recommended as a primary target treatment.
 - Issues of cost, lack of standardization, and lack of consensus on its use stand in the way of making apo B the primary treatment target.
- A low HDL-C is a target of intervention, but predominately through lifestyle therapies.



An International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia



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http://www.athero.org/download/IASPPGuidelines_FullReport_2.pdf

Lipoprotein targets of therapy

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Full Report

Terry A. Jacobson, MD*, Matthew K. Ito, PharmD, Kevin C. Maki, PhD, Carl E. Orringer, MD, Harold E. Bays, MD, Peter H. Jones, MD, James M. McKenney, PharmD, Scott M. Grundy, MD, PhD, Edward A. Gill, MD, Robert A. Wild, MD, PhD, Don P. Wilson, MD, W. Virgil Brown, MD

- Primary: non-HDL-C
- Although LDL-C has traditionally been the primary target of therapy...the NLA Expert Panel's consensus view is that non-HDL-C is a better primary target for modification than LDL-C.

J Clin Lipidol 2014;8:473–488



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Lipoprotein targets of therapy

- 2013 ACC/AHA Blood Cholesterol Guideline
- “RCT evidence to support the use of specific LDL-C or non-HDL-C targets was **not** identified. The focus is on the intensity of the statin therapy....”

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C on average, by approximately $\geq 50\%$	Daily dose lowers LDL-C on average, by approximately 30 to $< 50\%$	Daily dose lowers LDL-C on average by approximately $< 30\%$
Atorvastatin 40*-80* mg Rosuvastatin 20*-40** mg	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	Simvastatin 10** mg Pravastatin 10*-20* mg Lovastatin 20* mg Fluvastatin 20**-40** mg Pitavastatin 1** mg

J Am Coll Cardiol. 2014;63:2889-2934



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Lipoprotein goals of therapy...



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Lipoprotein goals of therapy

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias
 - Primary: LDL-C
 - Secondary: non-HDL-C or apoB
 - Not recommended: HDL-C, ratios

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class ^a	Level ^b	Ref ^c
In patients at VERY HIGH CV risk ^d , an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C ^e is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk ^d , an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C ^e is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk ^d an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

European Heart Journal doi:10.1093/eurheartj/ehw272



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Lipoprotein goals of therapy...

- 2014 International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia



**An International Atherosclerosis Society Position Paper:
Global Recommendations for the
Management of Dyslipidemia**

- The IAS does not specifically prescribe “treatment goals” for atherogenic lipoproteins.
- Identifies *optimal* levels and makes the general statement that the intensity of lipid-lowering therapy should be adjusted to long-term risk.
- Guidelines leave to *clinical judgment* and *national recommendations* on intensities of therapies.



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Lipoprotein goals of therapy...

- 2013 ACC/AHA Blood Cholesterol Guideline

- The Expert Panel was unable to find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dL or <70 mg/dL, nor were any RCTs comparing 2 LDL-C treatment targets identified.

- No statin RCTs reporting on-treatment non-HDL-C levels were identified.

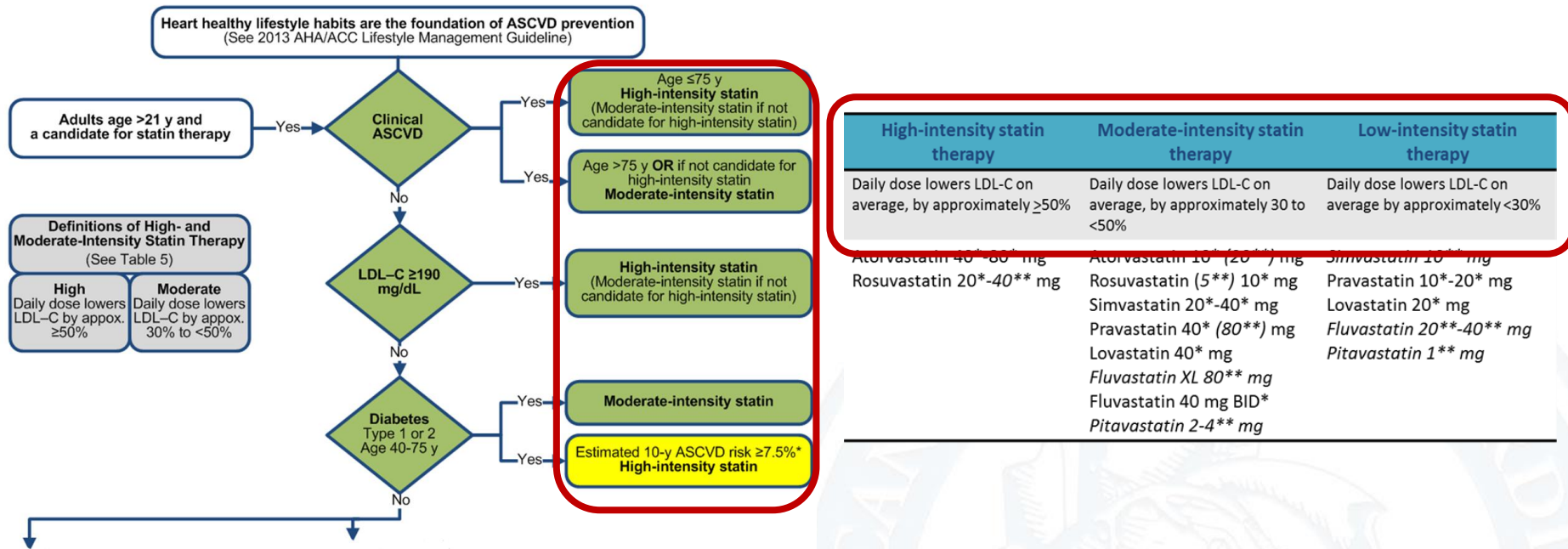
J Am Coll Cardiol. 2014;63:2889-2934



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Lipoprotein ~~goals~~ of therapy...

2013 ACC/AHA Blood Cholesterol Guideline



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Lipoprotein goals of therapy...

- National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia
- “...treatment goals are useful as means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event.
- Moreover, treatment goals facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives...”

Table 3 Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

Risk category	Criteria	Treatment goal		Consider drug therapy	
		Non-HDL-C mg/dL	LDL-C mg/dL	Non-HDL-C mg/dL	LDL-C mg/dL
Low	<ul style="list-style-type: none"> • 0–1 major ASCVD risk factors • Consider other risk indicators, if known 	<130	<100	≥190	≥160
Moderate	<ul style="list-style-type: none"> • 2 major ASCVD risk factors • Consider quantitative risk scoring • Consider other risk indicators* 	<130	<100	≥160	≥130
High	<ul style="list-style-type: none"> • ≥3 major ASCVD risk factors • Diabetes mellitus (type 1 or 2)[†] <ul style="list-style-type: none"> ◦ 0–1 other major ASCVD risk factors and ◦ No evidence of end organ damage • Chronic kidney disease stage 3B or 4[‡] • LDL-C ≥190 mg/dL (severe hypercholesterolemia)[§] • Quantitative risk score reaching the high-risk threshold 	<130	<100	≥130	≥100
Very high	<ul style="list-style-type: none"> • ASCVD • Diabetes mellitus (type 1 or 2) <ul style="list-style-type: none"> ◦ ≥2 other major ASCVD risk factors or ◦ Evidence of end-organ damage[¶] 	<100	<70	≥100	≥70



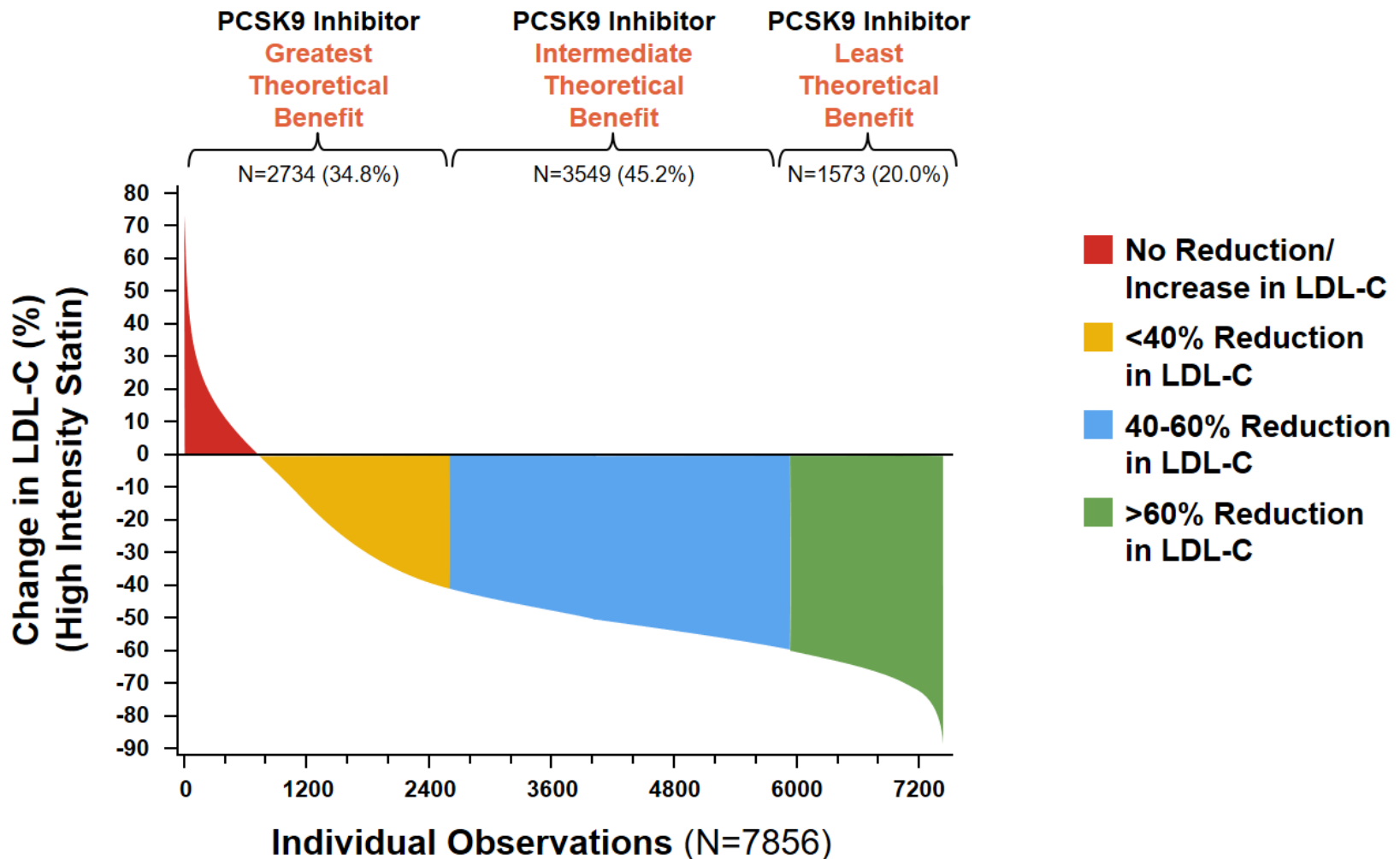
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Assessing response to therapy...



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LDL-C Response Variability to High-Intensity Statin Therapy and Implications for the Allocation of PCSK9 Inhibitors



Assessing response to therapy...

- 2016 ESC/EAS Guidelines for the

Has patient achieved expected *absolute* LDL-C goal levels?

- Secondary: non-HDL-C or apoB
- Not recommended: HDL-C, ratios

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class ^a	Level ^b	Ref ^c
In patients at VERY HIGH CV risk ^d			
(100 mg/dL), or a reduction of at least 50% if the baseline LDL-C ^e is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk ^d an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

European Heart Journal doi:10.1093/eurheartj/ehw272



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Assessing response to therapy...

- 2014 International Atherosclerosis Society Global
- The IAS does not specifically prescribe “treatment goals” for atherogenic

Clinical judgment and national recommendations may be used to determine adequacy of reduction in atherogenic lipoproteins.

intensities of therapies.



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Assessing response to therapy...

Table 3 Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

Risk category	Criteria	Treatment goal	Consider drug therapy
		Non-HDL-C mg/dL LDL-C mg/dL	Non-HDL-C mg/dL LDL-C mg/dL
			≥190
			≥160
			≥160
			≥130
			≥130
			≥100
			≥100
			≥70
	<ul style="list-style-type: none"> • Diabetes mellitus (type 1 or 2) ○ ≥2 other major ASCVD risk factors or ○ Evidence of end-organ damage¹ 	<70	≥70

Has patient achieved expected *absolute* non-HDL-C and/or LDL-C goals levels?

- National Lipid Association Recommendations for Patient-centered



Assessing response to therapy...

2013 ACC/AHA Blood Cholesterol

Heart healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

Age ≤ 75 y
High-intensity statin

Has patient achieved expected % *LDL-C* reduction?

LDL-C by approx. $\geq 50\%$ | LDL-C by approx. 30% to $<50\%$

Diabetes Type 1 or 2 Age 40-75 y

Yes → Moderate-intensity statin

Yes → Estimated 10-y ASCVD risk $\geq 7.5\%$ * High-intensity statin

- Atorvastatin 40-80 mg
- Rosuvastatin 20*-40** mg
- 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
- Simvastatin 10 mg
- Pravastatin 10*-20* mg
- Lovastatin 20* mg
- Fluvastatin 20**-40** mg
- Pitavastatin 1** mg

J Am Coll Cardiol. 2014;63:2889-2934



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2013 ACC/AHA Cholesterol Guidelines

Recommendations on Use of Non-Statins

- Clinicians treating high risk patients who have a
 - *Less than anticipated response to statins*
 - *Unable to tolerate a less than recommended intensity of a statin*
 - *Completely statin intolerant*
- When to add non-statin therapy?
- Stay tuned...more to come!

J Am Coll Cardiol 2013;2889-934.



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Safety and efficacy of lower levels of LDL-C...

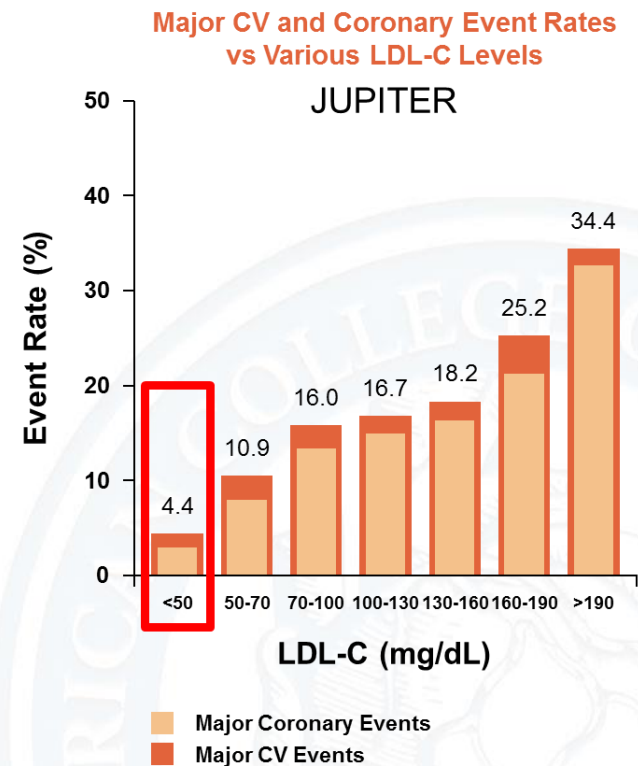
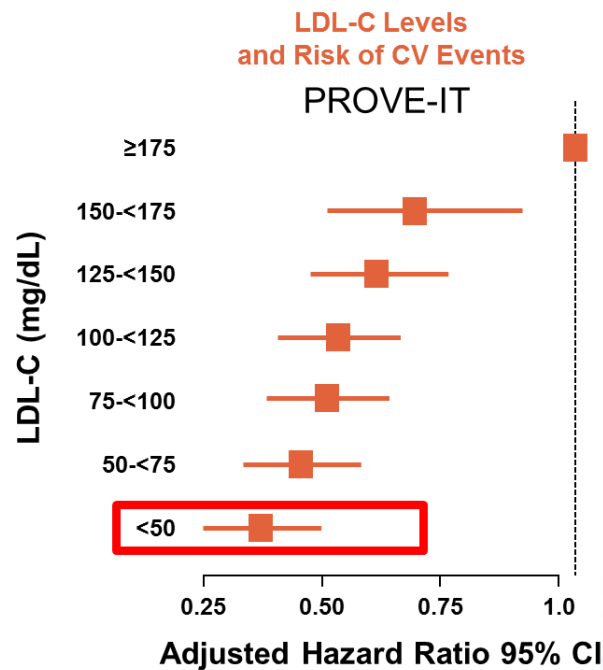


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Very low levels of LDL-C...

LDL-C Levels and Event Rates



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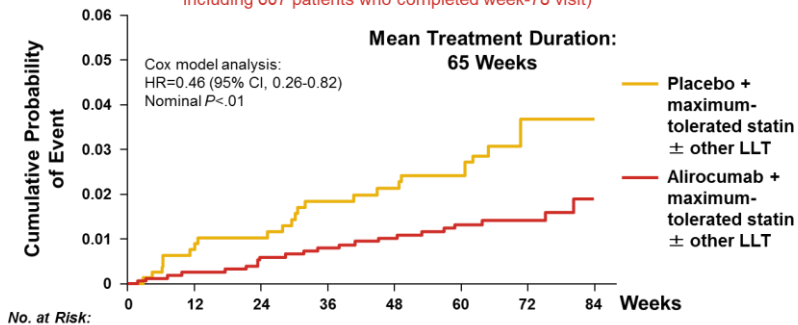
Very low levels of LDL-C...

Post Hoc Adjudicated CV TEAEs*

Safety Analysis (at least 52 weeks for all patients in on-going study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

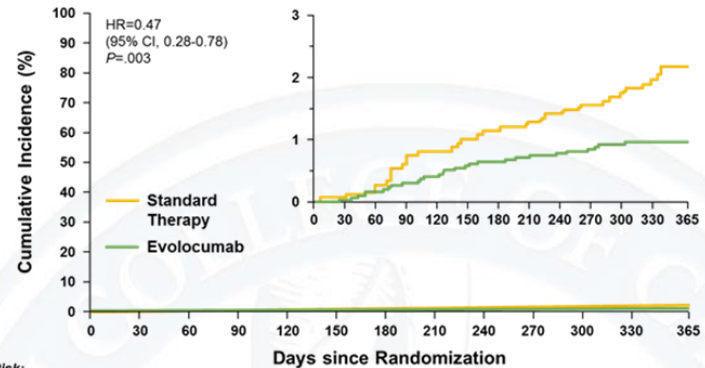
Safety analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed week-78 visit)



No. at Risk:

	0	12	24	36	48	60	72	84
Placebo	788	776	731	703	682	667	321	127
Alirocumab	1550	1534	1446	1393	1352	1335	642	252

Efficacy and Safety of Evolocumab in Reducing Lipids and CV Events: Cumulative Incidence of CV Events



No. at Risk:

	0	30	60	90	120	150	180	210	240	270	300	330	365
Standard Therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843

Sabatine MS, et al. NEJM 2015;372:1500-9

*Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization.

Robinson JG, et al. ESC hotline session; Barcelona, August 31, 2014.



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Putting it all together...



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What we know...

- LDL-C is causally related to ASCVD.
- Statin medications are first-line therapy for LDL-C lowering and ASCVD risk reduction.
- Lowering LDL-C with statin therapy, ezetimibe, and *possibly* PCSK9 inhibitors is associated with ASCVD risk reduction.
- It is important to monitor response to therapy.



What we know...

- There is considerable inter-individual variability in response to lipid-lowering therapy.
- High-risk patients with inadequate response to maximally-tolerated statin may be candidates for combination therapy.
- Lifestyle therapy is the foundation of all approaches to the management of dyslipidemia for ASDVD risk reduction.



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What we await...

- How low should we go?
- What is the benefit/risk of very low levels of atherogenic lipoproteins?
- Is lowering of atherogenic lipoproteins with PCSK9 inhibitors associated with reduction in ASCVD events?
 - *What is the role of the only remaining CETP inhibitor (anacetrapib/REVEAL) in clinical studies in ASCVD risk reduction?*
 - *Will we ever understand and/or modify HDL-C to reduce ASCVD risk?*



EXPERT CONSENSUS DECISION PATHWAY

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk



A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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2016 Expert Consensus Decision Pathway

Rationale

- Provide more specific guidance on the adequacy of statin therapy and whether or when to use non-statin therapies if response to statins is deemed inadequate or less than anticipated
- Extend beyond 2013 evidence base to incorporate recent trial data and address current gaps in care for LDL-C lowering to reduce ASCVD risk
 - HPS2-THRIVE
 - IMPROVE-IT
- Consider use of drugs FDA-approved after publication of 2013 guideline (alirocumab, evolocumab)



2016 Expert Consensus Decision Pathway

Questions Addressed

1. In what ***patient populations*** should non-statin therapies be considered?
2. In what ***situations*** should non-statin therapies be considered?
 - When is the *amount of LDL-C lowering* less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?
3. If non-statin therapies are to be added, ***which agents*** or therapies should be considered and in ***what order***?



2016 Expert Consensus Decision Pathway

Assessing response to therapy...

- **Thresholds for consideration of net benefit**
 - Maximally-tolerated statin therapy
 - **Percent** LDL-C reduction: Achieve $\geq 50\%$ LDL-C reduction on high-intensity statin, or $\geq 30\%$ to $< 50\%$ reduction for moderate-intensity statin
 - May consider **absolute** LDL-C levels (or non-HDL-C in patients with DM) as factors
 - WG emphasizes that these are not firm triggers (not “goals”) for adding medication but factors that may be considered within the broader context of an individual patient’s clinical situation



2016 Expert Consensus Decision Pathway

Assumptions and Definitions

- Other important factors to consider in shared decision making
 - Available scientific evidence for safety and tolerability
 - Potential for drug-drug interactions
 - Efficacy of additional LDL-C lowering
 - Cost
 - Convenience and medication storage
 - Pill burden
 - Route of administration
 - Potential to jeopardize adherence to evidence-based therapies
 - Patient preferences



2016 Expert Consensus Decision Pathway

Non-statin Therapies Considered

- Ezetimibe
- Bile-acid sequestrants (BAS)
- PCSK9 inhibitors
 - Alirocumab, evolocumab
- Mipomersen
- Lomitapide
- LDL apheresis
- Niacin NOT routinely recommended



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2016 Expert Consensus Decision Pathway

Patient Populations Addressed

PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS

Adults ≥ 21 years of age with clinical ASCVD, on statin for secondary prevention

Adults ≥ 21 years of age with LDL-C ≥ 190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention

Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention

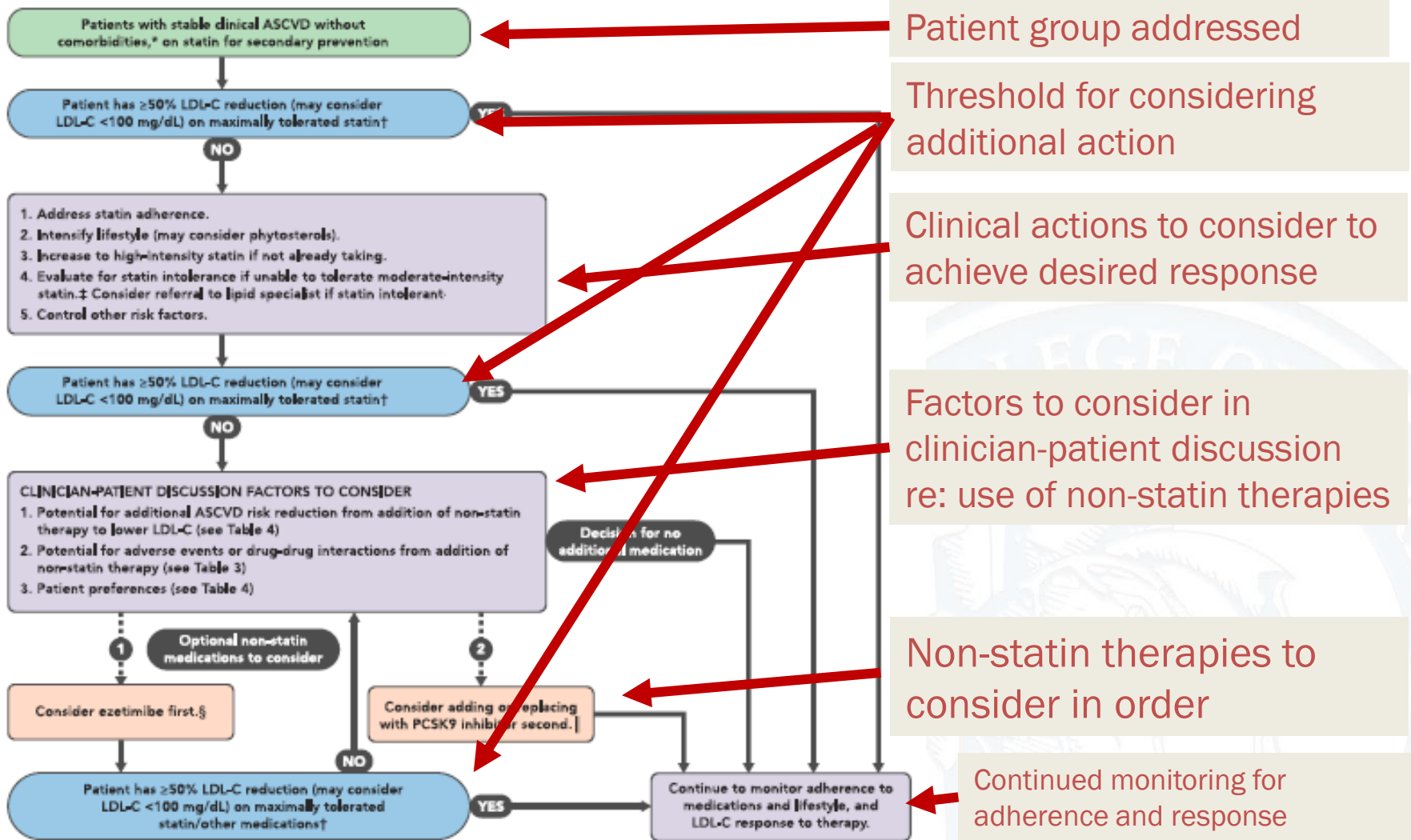
Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of $\geq 7.5\%$, on statin for primary prevention



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Decision Pathway Algorithms

General



Patient group addressed

Threshold for considering additional action

Clinical actions to consider to achieve desired response

Factors to consider in clinician-patient discussion re: use of non-statin therapies

Non-statin therapies to consider in order

Continued monitoring for adherence and response

Patients with Stable Clinical ASCVD without Comorbidities -2

Patient has $\geq 50\%$ LDL-C reduction (may consider LDL-C < 100 mg/dL) on maximally tolerated statin†

YES

- On maximally tolerated statin
- If $\leq 50\%$ LDL-C reduction
- May consider LDL-C > 100 mg/dL
- Ezetimibe* first, then may consider PCSK9i

*May consider BAS if TG < 300 mg/dL

NO

Patient has $\geq 50\%$ LDL-C reduction (may consider LDL-C < 100 mg/dL) on maximally tolerated statin/other medications†

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

Patients with Clinical ASCVD and with Comorbidities

(DM, recent acute ASCVD event, ASCVD event while on statin, baseline LDL-C ≥ 190 mg/dl, uncontrolled major RFs, elevated Lp(a), CKD)

- Same initial clinical steps
- If $\leq 50\%$ LDL-C reduction
- May consider LDL-C **>70** mg/dL or non-HDL-C >100 in pts with DM
- Ezetimibe* first, then may consider PCSK9i

*May consider BAS if TG <300 mg/dL

Patient has $\geq 50\%$ LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

Patients with Clinical ASCVD and with Baseline LDL-C ≥ 190 mg/dL

Patient has $\geq 50\%$ LDL-C reduction

- Same initial clinical steps
- Strong recommendation for referral to lipid specialist*
- If $\leq 50\%$ LDL-C reduction
- May consider LDL-C **>70** mg/dL
- Ezetimibe **OR** PCSK9i may be considered first

* May consider mipomersen, lomitapide, LDL apheresis in HoFH

NO

Referral to lipid specialist and RDN recommended

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.



Patients without Clinical ASCVD and with Baseline LDL-C ≥ 190 mg/dL

Patient has $\geq 50\%$ LDL-C reduction (may consider

- Same initial clinical steps
- Strong recommendation for referral to lipid specialist*
- If $\leq 50\%$ LDL-C reduction
- May consider LDL-C **>100** mg/dL
- Ezetimibe **OR** PCSK9i may be considered first

* May consider mipomersen, lomitapide, LDL apheresis in HoFH

Patient has $\geq 50\%$ LDL-C reduction (may consider LDL-C < 100 mg/dL) on maximally tolerated statin/other medication†

YES

NO

Referral to lipid specialist recommended

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.



Patients 40-75 yo without Clinical ASCVD and with DM

- Same initial clinical steps
- On moderate- or high-intensity statin
- Increase to high-intensity statin if needed
- If less than expected % LDL-C reduction
- May consider **LDL-C >100 mg/dL or non-HDL-C >130 mg/dL**
- Ezetimibe or BAS* may be considered in higher-risk pts
- PCSK9i **not** currently indicated

*If TG <300 mg/dL

Patients 40-75 yo without Clinical ASCVD and with 10-year ASCVD Risk $\geq 7.5\%$

Patient has 30-49% LDL-C reduction (may consider

YES, and without

- Same initial clinical steps
- Consideration of high-risk markers*
- On moderate- or high-intensity statin
- Increase to high-intensity statin if needed
- If less than expected % LDL-C reduction
- May consider LDL-C >100 mg/dL
- Ezetimibe or BAS[†] may be considered in higher-risk patients
- PCSK9i **not** currently indicated

*Risk $\geq 20\%$, LDL-C ≥ 160 mg/dL, uncontrolled RFs, family history, elevated Lp(a), accelerated subclinical dz, elevated hs-CRP, CKD, HIV or other inflammatory disorders

[†]If TG < 300 mg/dL

Consider ezetimibe first;
BAS second-line.§

Continue to monitor adherence to
medications and lifestyle, and
LDL-C response to therapy.

2016 Expert Consensus Decision Pathway Summary: Patient Populations Addressed

PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS

Adults ≥ 21 years of age with clinical ASCVD, on statin for secondary prevention

- Ezetimibe first
- PCSK9i may then be added or replace ezetimibe
- LDL-C ≥ 190 mg/dl either agent first

Adults ≥ 21 years of age with LDL-C ≥ 190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention

- Ezetimibe OR PCSK9i may be considered first

Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention

- Ezetimibe may be considered
- PCSK9i not recommended in primary prevention patients with DM

Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of $\geq 7.5\%$, on statin for primary prevention

- Ezetimibe may be considered
- PCSK9i are not recommended



2016 Expert Consensus Decision Pathway

Take Home Points

- Follow evidence-based 2013 ACC/AHA Cholesterol Guidelines for use of lipid-lowering therapies to reduce ASCVD risk
- Engage in shared decision making to consider potential benefits and harms of non-statin therapies
- Consider specific non-statin therapies only in higher-risk pts who have inadequate response to statin or statin intolerance
- Individualize care for other patient groups



Conclusions...



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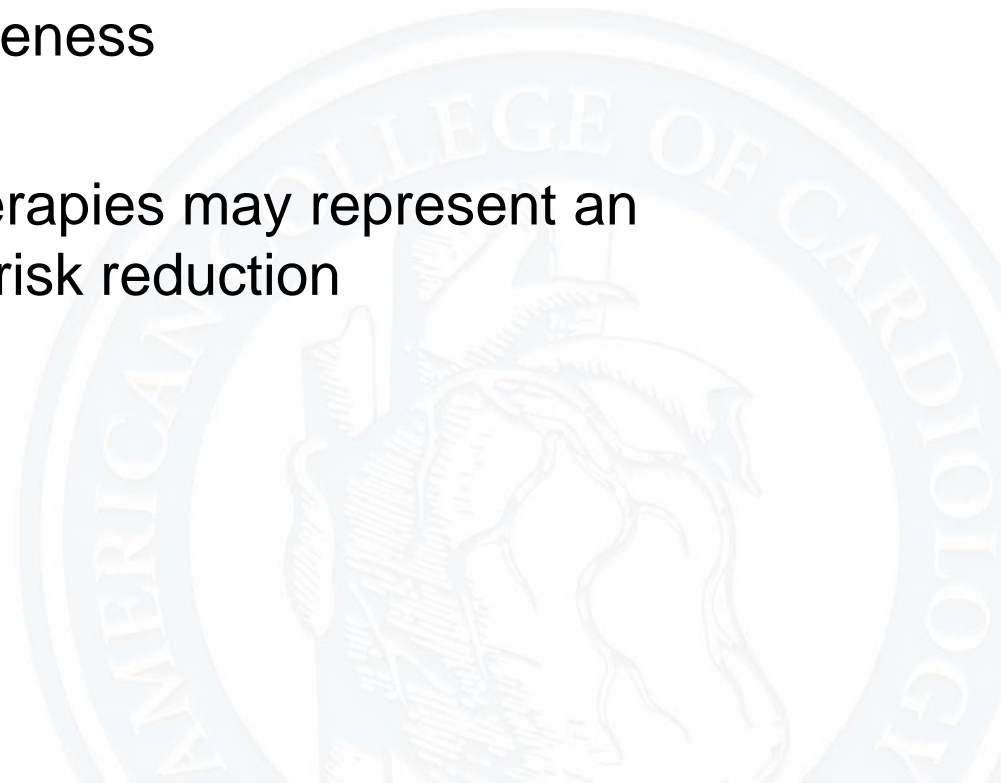


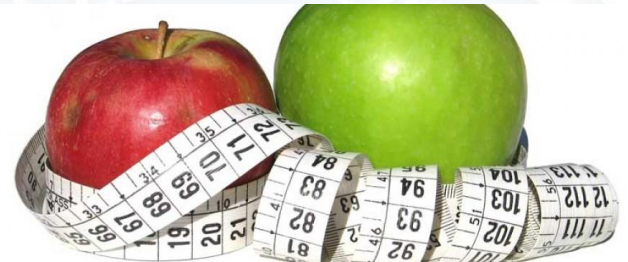
Conclusions

- LDL-C remains a central factor in ASCVD
-
- High-risk patients remain untreated to LDL-C goals for many reasons, including statin intolerance and intra-individual variability in statin responsiveness
- Alternative LDL-lowering therapies may represent an additional option to ASCVD risk reduction



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