Statins

Introduction

- What is the role of statin therapy in the management of dyslipidemia and prevention of CVD?
- What are starting statin doses, dosage ranges, metabolic effects, and main considerations?
- How should statin treatment be monitored?
- What is the major evidence supporting the use of statin therapy?

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Statin Therapy in the Management of Dyslipidemia and Prevention of CVD

- In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals.[1]
- On the basis of morbidity and mortality outcome trials, statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals.[2]
- For clinical decision-making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2D associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction.[3]
- Certain benefits associated with statin therapy may not be due to their LDL-C-lowering effect, but rather associated with pleiotropic benefits, such as reduced inflammation in the vasculature, kidney, and bone.[4]

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes.

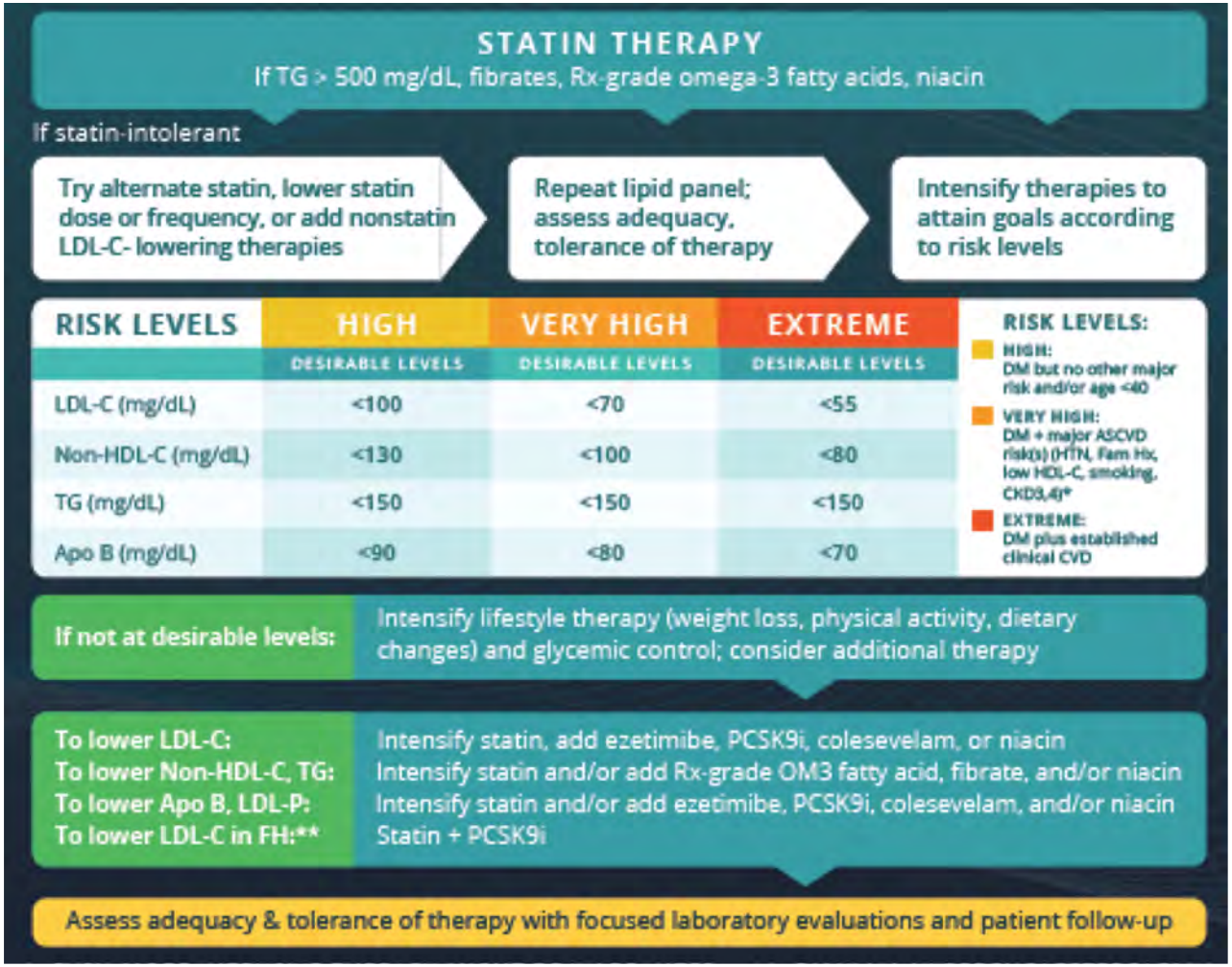
1-3 Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87
4 McFarlane SI, et al. *J Clin Endocrinol Metab.* (2002) 87(4):1451–1458.

Statin Therapy in the AACE ASCVD Risk Factor Modification Algorithm

**Even more intensive therapy might be warranted.

Apo B = apolipoprotein B;
ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease;
DM = diabetes mellitus; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol
HTN = hypertension; Hx = history;
LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; OM3 = omega-3;
PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor;
Rx = prescription; TG = triglyceride

Garber AJ, et al. *Endocr Pract*. (2018) 24(1):91–120.



Statins, ASCVD Risk Categories, and LDL-C Treatment Goals

- In high-risk individuals, further LDL-C lowering beyond established targets with statins results in additional ASCVD event reduction and may be considered in:
  - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or with T2D plus ≥1 additional risk factor should be treated with statins to target a reduced LDL-C goal of <70 mg/dL
  - Extreme-risk individuals should be treated with statins to a LDL-C treatment goal of <55 mg/dL
- Combination therapy with lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually statin) does not achieve therapeutic goal.

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Metabolic Effects of Statin Therapy

Statin Therapy

- Inhibits HMG-CoA reductase, a key rate-limiting enzyme in hepatic cholesterol synthesis
  - Triggers increased expression of hepatic LDL receptors and increased LDL-C clearance
- Decreases plasma LDL-C in a dose-dependent fashion by 20%-55%
- Exerts modest lowering effects on VLDL-C, IDL-C, and TG (10%-30%)
- Raises HDL-C by 2%-10%
- Improves LDL subfraction profiles (atorvastatin and rosuvastatin)
  - Larger clinical trials necessary to confirm effect of statins on LDL particle size and density

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; IDL = intermediate-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Representative Statin Effects on Lipids After 6 Weeks of Treatment in Men and Women With LDL-C ≥160 mg/dL and ≤250 mg/dL (N=2431)

- The lipid-lowering effects of statins in these studies are representative of other controlled trials, with one exception: pravastatin had a slightly greater TG-lowering effect in the CARE, WOSCOPS, and LIPID trials.
- Lovastatin and fluvastatin data are from the 8-week CURVES trial, a comparison of the effects of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin in patients with LDL-C 192-244 mg/dL (N=534); these data do not represent head-to-head analyses.

Statin	Dosage range, daily (mg/dL)	TC	LDL-C	HDL-C	TG
Lovastatin	20-80	↓ 21 to ↓ 36	↓ 29 to ↓ 48	↑ 4.6 to ↑ 8.0	↓ 12 to ↓ 13
Pravastatin	10-40	↓ 15 to ↓ 22	↓ 20 to ↓30	↑ 3.2 to ↑ 5.6	↑ 8 to ↓ 13
Simvastatin	10-80[a]	↓ 20 to ↓ 33	↓ 28 to ↓ 46	↑ 5.2 to ↑ 6.8	↓ 12 to ↓ 18
Fluvastatin	20-40	↓ 13 to ↓ 19	↓ 17 to ↓ 23	↑ 0.9 to ↓ 3.0	↓ 5 to ↓ 13
Atorvastatin	10-80	↓ 27 to ↓ 39	↓ 37 to ↓ 51	↑ 2.1 to ↑ 5.7	↓ 20 to ↓ 28
Rosuvastatin	10-40	↓ 33 to ↓ 40	↓ 45 to ↓ 55	↑ 7.7 to ↑ 9.6	↓ 20 to ↓ 26

[a] Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

CARE=Cholesterol and Recurrent Events; CURVES=Comparative Dose Efficacy of Atorvastatin, Simvastatin, Pravastatin, Lovastatin, and Fluvastatin; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; LIPID=Long-Term Intervention With Pravastatin in Ischemic Disease; TC=total cholesterol; TG=triglycerides; WOSCOPS=West of Scotland Coronary Prevention Study.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87

Statin Starting Doses and Dosage Ranges

Statin	Recommended Starting Daily Dose	Dosage Range
Lovastatin[1]	20 mg	10-80 mg
Pravastatin[2]	40 mg	10-80 mg
Simvastatin[3]	20-40 mg	5-80 mg[a]
Fluvastatin[4]	40 mg	20-80 mg
Atorvastatin[5]	10-20 mg	10-80 mg
Rosuvastatin[6]	10 mg[b]	5-40 mg
Pitavastatin[7]	2 mg	2-4 mg

[a] Simvastatin 80 mg not approved for therapy unless individual has been on treatment for >1 year without myopathy; Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

[b] Consider 5 mg starting dose in Asian patients; Crestor (rosuvastatin calcium) [PI]; 2010.

[1] Mevacor (lovastatin) [PI]; 2012. [2]Pravachol (pravastatin sodium) [PI]; 2016. [3]Zocor (simvastatin) [PI]; 2018. [4]Lescol (fluvastatin sodium) [PI]; 2017. [5]Lipitor (atorvastatin calcium) [PI]; 2017. [6]Crestor (rosuvastatin calcium) [PI]; 2010. [7]Livalo (pitavastatin) [PI]; 2016.

Main Considerations

- Conduct liver function testing prior to therapy and as clinically indicated thereafter.
- Myalgias and muscle weakness present in some individuals.
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, such as cyclosporine, warfarin, and protease inhibitors, and multiple other medications
- Myopathy/rhabdomyolysis in rare cases; increased risk with co-administration of some drugs (see product label)
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for ≥12 months without muscle toxicity.
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine.
- Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups.

New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with metabolic syndrome, may be less common with pravastatin and possibly pitavastatin, and occurs to a lesser extent overall than the associated decrease in ASCVD.

ASCVD = atherosclerotic cardiovascular disease;
MetS = metabolic syndrome.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Monitoring Statin Therapy

- Reassess individuals' lipid status 6 weeks after therapy initiation and again at 6-week intervals until treatment goal is achieved.
- While on stable lipid therapy:
  - Individuals should be tested at 6- to 12-month intervals.
  - The specific testing interval should depend on individual adherence to therapy and lipid profile consistency
  - If adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment.

ASCVD = atherosclerotic cardiovascular disease.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Monitoring Statin Therapy

- More frequent lipid status evaluation is recommended in the following situations:
  - Deterioration of diabetes control
  - Use of a new drug known to affect lipid levels
  - Progression of atherosclerotic disease
  - Considerable weight gain
  - Unexpected adverse change in any lipid parameter
  - Development of a new ASCVD risk factor
  - Convincing new clinical trial evidence or guidelines that suggest stricter lipid goals
- CK levels should be assessed and statins discontinued if patients report clinically significant myalgias or muscle weakness on statin therapy.

ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Establishing the Efficacy, Safety, and Benefits of Statin Therapy

Statins: The evidence

Primary ASCVD Prevention With Statin Therapy

Numerous large clinical trials have established the efficacy and safety of statin therapy, and the cardiovascular benefits of LDL-C reduction with statin therapy in both primary and secondary prevention.

Trial	Agent	Inclusion criteria (mg/dL)			Mean baseline values (mg/dL)	Mean achieved values (mg/dL)	Relative risk reduction	Experimental event rate %[a,c]	Control event rate %	Absolute risk reduction %	NNT
		TG	HDL-C	LDL-C	LDL-C	LDL-C					
Primary prevention											
WOSCOPS 0% Female	Pravastatin, 40 mg vs. PBO	---	---	155-232	192	159	30%	5.5% at 5.0 y	7.9%	2.4%	42
AFCAPS 15% Female	Lovastatin, 20-40 mg vs. PBO	≤400	<45 M <47 F	130-190	150	115	40%	4.0% at 5.2 y	6.8%	1.2%	83
ASCOT-LLA 19% Female	Atorvastatin, 10 mg vs. PBO	<400	---	TC <250	134	90	37%	1.9% at 3.3 y	3.0%	1.1%	91
CARDS 32% Female	Atorvastatin, 10 mg vs. PBO	<600	---	≤160	118	82	35%	3.0% at 4.0 y	4.6%	1.6%	63
JUPITER[b] 38% Female	Rosuvastatin, 20 mg vs. PBO	<500	---	<130[e]	108[d]	55[d]	44%	1.6% at 1.9 y[b,e]	2.8% at 1.9 y[b,e]	---	95[f]

AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HDL-C = high-density lipoprotein cholesterol; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; NNT = number needed to treat; PBO = placebo; TG = triglycerides; WOSCOPS = West of Scotland Coronary Prevention Study.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Secondary ASCVD Prevention With Statin Therapy

Trial	Agent	Inclusion criteria (mg/dL)			Mean baseline values (mg/dL)	Mean achieved values (mg/dL)	Relative risk reduction	Experimental event rate %[a,c]	Control event rate %	Absolute risk reduction %	NNT
		TG	HDL-C	LDL-C	LDL-C	LDL-C					
4S 19% Female	Simvastatin, 20-40 mg vs. PBO	≤225	---	TC = 215-315	190	124	35%	8.2% at 5.4 y	11.5%	9.2%	11
CARE 14% Female	Pravastatin, 40 mg vs. PBO	<350	---	115-74	139	98	23%	10.2% at 5.0 y	13.2%	3.0%	33
LIPID 17% Female	Pravastatin, 40 mg vs. PBO	<445	---	TC = 155-271	150	112	23%	12.3% at 6.1 y	15.9%	3.6%	28
HPS 25% Female	Simvastatin, 40 mg vs. PBO	---	---	TC ≥135	129	90	26%	8.7% at 5.0 y	11.8%	3.1%	32
TNT 19% Female	Atorvastatin, 80 mg vs. atorvastatin, 10 mg	≤600	---	<130	98	77 on atorvastatin, 80 mg; 101 on atorvastatin, 10 mg	21% in favor of atorvastatin, 80 mg	6.9% at 4.9 y	8.7%	1.8%	56
PROVE IT – TIMI 22% Female	Atorvastatin, 80 mg vs. pravastatin, 40 mg	---	---	TC ≤240 or TC ≤200 on therapy	106 (median)	62 on atorvastatin, 80 mg; 95 on pravastatin, 40 mg	17% in favor of atorvastatin	8.3% at 2 y	10.0% at 2 y	1.7%	59
A to Z 25% Female	Simvastatin, 40/80 mg vs. PBO/ simvastatin, 20 mg	---	---	TC ≤250[a]	112	66 on simvastatin, 40/80 mg; 81 on PBO/ simvastatin, 20 mg	11% in favor of simvastatin, 40/80 mg	14.4% at 2 y	16.7% at 2 y	---	77[b]

4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events Trial; HDL-C = high-density lipoprotein cholesterol; HPS = Heart Protection Study; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; NNT = number needed to treat; PBO = placebo; PROVE IT–TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction; TG = triglycerides; TNT = Treating to New Targets.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Secondary ASCVD Prevention With Statin Therapy

Trial	Agent	Inclusion criteria (mg/dL)			Mean baseline values (mg/dL)	Mean achieved values (mg/dL)	Relative risk reduction	Experimental event rate %[a,e]	Control event rate %	Absolute risk reduction %	NNT
		TG	HDL-C	LDL-C	LDL-C	LDL-C					
IDEAL 19% Female	Atorvastatin, 40-80 mg vs. simvastatin, 20-40 mg	≤600	---	---	121.5	80 on atorvastatin, 40-80 mg; 100 on simvastatin, 20-40 mg	12% in favor of atorvastatin	9.9% at 4.8 y	11.2% at 4.8 y	1.2%	77
AIM-HIGH 15% female	Simvastatin + niacin, 1,500-2,000 mg vs. simvastatin + PBO[i] *	150-400 mg/dL	<40 mg/dL for men; <50 mg/dL for women	<180 mg/dL	74	65	–1%[j]	16.4	16.2	–0.2[j]	–5[j]
IMPROVE-IT 24% female	Simvastatin, 40 mg + ezetimibe, 10 mg vs. simvastatin, 40 mg + PBO	≤350	---	≥50 and ≤125 or ≥50 and ≤100 on therapy	93.8	53.2	5.8%[j]	32.7	34.7	2.0%	50[j]
HPS2-THRIVE 17.3% female	In combination with simvastatin or simvastatin + ezetimibe, extended-release niacin, 2 g + laropiprant, 40 mg vs. PBO	None[k]	None[k]	None[k]	63	Mean –10 mg/dL change	3.7%[j]	13.2	13.7	0.5%[j]	200[j]

***AIM-HIGH PBO included 50 mg niacin to mask blinded treatment to patients and study personnel.**

AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides; HDL-C = high-density lipoprotein cholesterol; HPS2 THRIVE = Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; IDEAL = Incremental Decrease in Endpoints Through Aggressive Lipid lowering; IMPROVE-IT = IMProved Reduction of Outcomes, Vytorin Efficacy International Trial; LDL-C = low-density lipoprotein cholesterol; NNT = number needed to treat; PBO = placebo; TG = triglycerides.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)

Randomized, double-blind, placebo-controlled study of statin therapy (rosuvastatin 20 mg) in patients (N=17,802) with moderate to low LDL-C (<130 mg/dL) and elevated hsCRP (≥2.0 mg/L)
Median follow-up, 1.9 years; maximal follow-up, 5 years

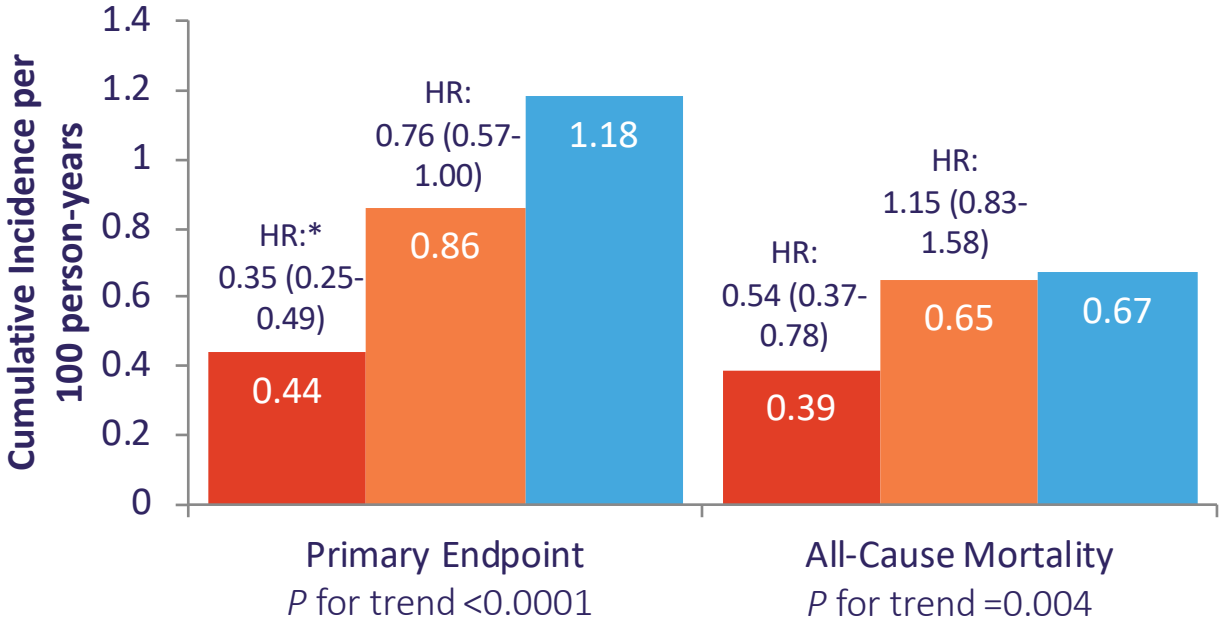
- Primary endpoint: first occurrence of MACE (nonfatal MI, nonfatal CVA, hospitalization for unstable angina, arterial revascularization, or CV death)
- Trial was suspended due to unequivocal evidence of reduced CV morbidity and mortality in the statin group vs placebo
- At 12 months, median LDL-C, TG, and hsCRP levels were 50%, 17%, and 37% lower, respectively, in the rosuvastatin vs placebo groups
- Relative MACE hazard reduction of 44% in the rosuvastatin group (95% CI, 0.46-0.69; *P*<0.00001)

CV = cardiovascular; CVA = cerebrovascular attack; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = myocardial infarction; TG = triglycerides.

Ridker PM, et al. *N Engl J Med*. (2008) 359(21):2195-207.

JUPITER: Lower Risk of CV Events With LDL-C <50 mg/dL

- Rosuvastatin participants achieving LDL-C <50 mg/dL had lower risk of CV events without increased AEs.
- Rates of myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes were not significantly different among rosuvastatin participants with/without LDL-C <50 mg/dL.



* All hazard ratios are vs placebo

	Rosuva, <50 mg/dL n=4154	Rosuva, not <50 mg/dL n=4000	Placebo n=8150
Median LDL-C, mg/dL	44	70	110

AE = adverse event; CV = cardiovascular; DM = diabetes mellitus; HR = hazard ratio; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; rosuva = rosuvastatin.

Hsia J, et al. *JACC.* (2011) 57(16):1666-1675.

Cholesterol Treatment Trialists' Collaboration: Benefit of LDL-C Lowering with Statin Therapy

A 2010 meta-analysis of major vascular events (coronary death, MI, coronary revascularization, and ischemic stroke) in RCTs with ≥1,000 patients and ≥2 years of more- vs less-intensive statin therapy, and/or statin vs control (N=169,138); 5 years' follow-up

- Confirmed benefit of LDL-C lowering with statin therapy
- **A 1 mmol/L (38.7 mg/dL) reduction in LDL-C resulted in:**
  - 22% decrease in major vascular events (nonfatal MI or ASCVD death)
  - 25% reduction in coronary revascularizations
  - 16% reduction in CVA

ASCVD = atherosclerotic cardiovascular disease; CVA = cerebrovascular event;
LDL-C = low-density lipoprotein cholesterol;
MI = myocardial infarction; RCT = randomized-controlled trial.

Lancet. (2010) 376:1670-81.

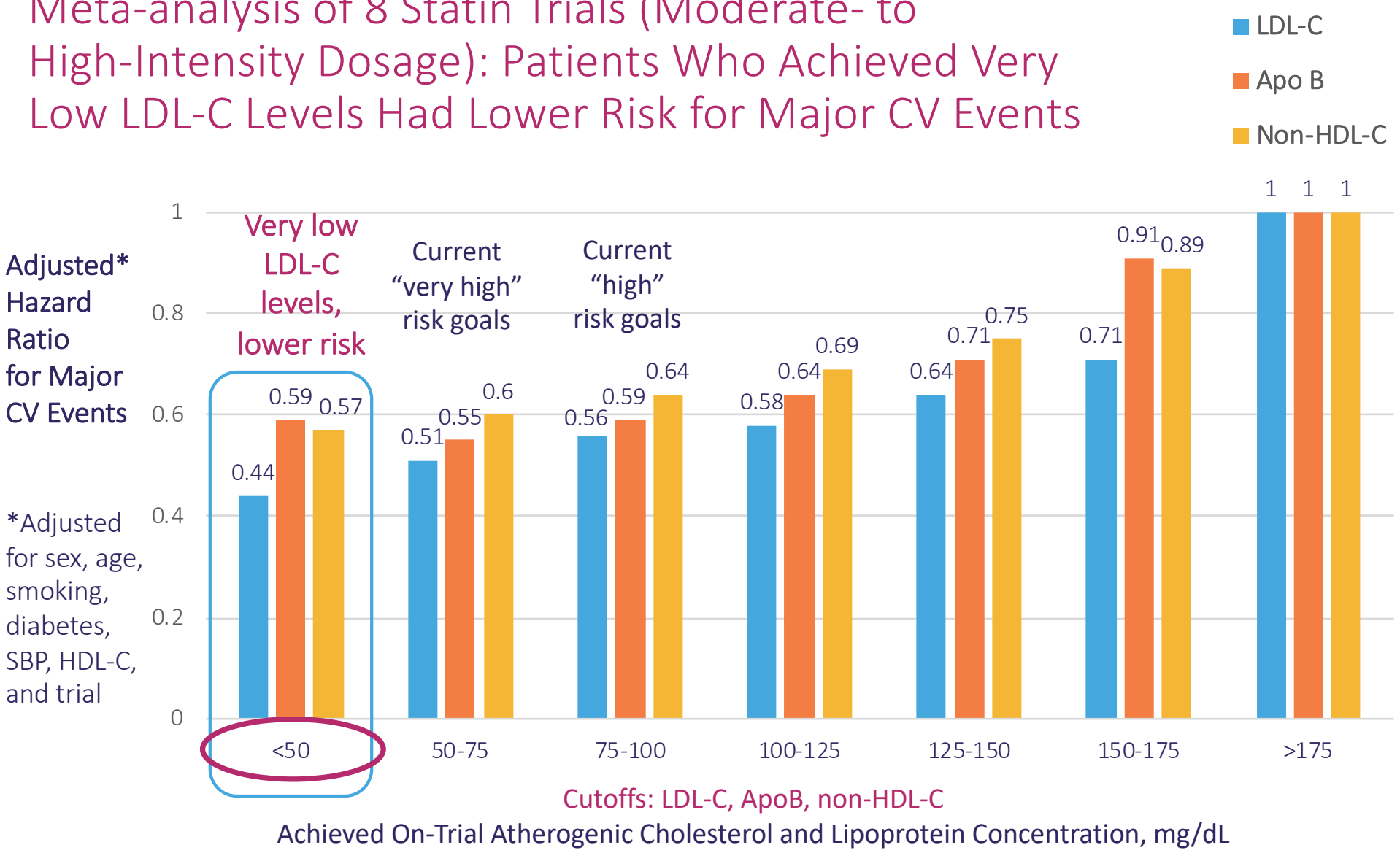
Cholesterol Treatment Trialists' Collaboration: Benefit of Intensive LDL-C Lowering

- Compared to standard regimens, more intensive statin therapy showed a significant 15% further reduction in major vascular events.[1]
- Data suggest that reducing LDL-C by 2-3 mmol/L (~77 to 116 mg/dL) would reduce the risk of major vascular events by 40%-50%.[2]
- The primary goal for individuals at high risk of occlusive vascular events should be to achieve the largest possible LDL-C reduction without increasing myopathy risk, rather than setting an LDL-C target goal.[3]

LDL-C = low-density lipoprotein cholesterol; RR = relative risk.

[1 & 3] Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[2] *Lancet*. (2010) 376:1670-81.

Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosage): Patients Who Achieved Very Low LDL-C Levels Had Lower Risk for Major CV Events



Apo = apolipoprotein; CV = cerebrovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Boekholdt SM, et al. *J Am Coll Cardiol*. (2014) 64(5):485-494.

Imaging Studies Assessing the Impact of Statin Therapy on Coronary Atherosclerosis Regression and Progression

Statins: Imaging Studies

Imaging Studies on the Effect of Statin Therapy on Coronary Atherosclerosis

Several studies have applied imaging techniques to assess the effect of statin therapy on coronary atherosclerosis regression and progression.

- **MARS**: In lesions with ≥50% stenosis at baseline, lovastatin 80 mg/day resulted in a significant mean reduction of 4.1% vs 0.9% with placebo (P=0.005).[1]
- **REVERSAL**: Intravascular ultrasonography showed that intensive therapy (atorvastatin, 80 mg daily) resulted in a significantly lower progression rate of both atheroma volume and % atheroma volume compared with moderate therapy (pravastatin, 40 mg daily).[2]
- **ASTEROID:** Rosuvastatin (40 mg daily for 24 months) resulted in a mean atheroma volume reduction of 0.98% and a mean change in atheroma volume of 6.1 mm^3 in the most diseased 10-mm^3 segment.[3]
- **HATS:** The combination of simvastatin (titrated to 13±6 mg per day) and niacin decreased proximal stenosis by 0.4% vs an increase of 3.9% with placebo.[4]

ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; HATS = HDL-Atherosclerosis Treatment Study; HDL = high-density lipoprotein; MARS = Monitored Atherosclerosis Regression Study; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering.

[1-3] Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[4] Brown BG, et al. *N Engl J Med.* (2001) 345(22):1583–1592.

Major Statin Imaging Studies (1/4)

Trial	Agent	Primary endpoint parameter	Patients, n		F/U, y	Mean baseline lipid values, mg/dL			Mean achieved lipid values, mg/dL			Mean experimental % change, primary endpoint		Mean control % change, primary endpoint	
			M	F		LDL-C	HDL-C	TG	LDL-C	HDL-C	TG	Overall	Most diseased sub-segment	Overall	Most diseased sub-segment
STATINS															
MARS	Lovastatin, 80 mg (experimental) vs. PBO (control)	Percent diameter stenosis measured by QCA	247	23	2.2	157[a]	43	159	86[a]	46	120	1.6	–4.1[b]	2.2	–0.9[b]
HATS (imaging arm)	Simvastatin + niacin (experimental) vs. PBO (control)[c,d]	Percent diameter stenosis measured by QCA	139	21	3.2	125	31	212	75	40	126	0.4	–5.8[b]	3.9	0.1[b]
REVERSAL	Atorvastatin, 80 mg (experimental) vs. pravastatin, 40 mg (control)	Atheroma volume measured by coronary IVUS	362	140	1.5	150	42	197	79 on atorvastatin, 80 mg; 110 on pravastatin, 40 mg	43 on atorvastatin, 80 mg; 45 on pravastatin, 40 mg	148 on atorvastatin, 80 mg; 166 on pravastatin, 40 mg	4.1	–4.2[d]	5.4	–1.7[e]

F = female; F/U = follow-up; HATS = HDL-Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; IVUS = intravascular ultrasonography; LDL-C = low-density lipoprotein cholesterol; M = male; MARS = Monitored Atherosclerosis Regression Study; PBO = placebo; QCA = quantitative coronary angiography; REVERSAL = Reversing Atherosclerosis with Aggressive Lipid Lowering; TG = triglycerides.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Major Statin Imaging Studies (2/4)

Trial	Agent	Primary endpoint parameter	Patients, n		F/U, y	Mean baseline lipid values, mg/dL			Mean achieved lipid values, mg/dL			Mean experimental % change, primary endpoint		Mean control % change, primary endpoint	
			M	F		LDL-C	HDL-C	TG	LDL-C	HDL-C	TG	Overall	Most diseased sub-segment	Overall	Most diseased sub-segment
STATINS															
ASTEROID	RRosuvastatin, 40 mg no control group	Atheroma volume measured by coronary IVUS	245	104	2	130	43	152	61	49	121	–0.98	–8.5	NA	NA
Schmermund	Atorvastatin, 80 mg (experimental) vs. atorvastatin, 10 mg (control)	Coronary artery calcification measured by EBCT	149	217	1	155[f,g]	50[f,g]	208[f,g]	87 on atorvastatin, 80 mg; 109 on atorvastatin, 10 mg	53 on atorvastatin, 80 mg; 54 on atorvastatin, 10 mg	137 on atorvastatin, 80 mg; 151 on atorvastatin, 10 mg	27	NA	25	NA
ENHANCE	Simvastatin, 80 mg + ezetimibe, 10 mg (experimental) vs. simvastatin, 80 mg + placebo (control)	Carotid-artery intima-media thickness measured by carotid ultrasound	370	350	2	319 (simvastatin/ ezetimibe); 317.8 (simvastatin)	46.7 (simvastatin/ ezetimibe); 47.4 (simvastatin)	157 (simvastatin/ ezetimibe); 160 (simvastatin)[h]	141.3 (simvastatin/ ezetimibe); 192.7 (simvastatin)	50.9 (simvastatin/ ezetimibe); 50.7 (simvastatin)	108 (simvastatin/ ezetimibe);120 (simvastatin)[h]	0.0111[i]	NA	0.0058[i]	NA

ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; EBCT = electron-beam computed tomography; ENHANCE = Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; F = female; F/U = follow-up; HDL-C = high-density lipoprotein cholesterol; IVUS = intravascular ultrasonography; LDL-C = low-density lipoprotein cholesterol; M = male; TG = triglycerides.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Major Statin Imaging Studies (3/4)

Trial	Agent	Primary endpoint parameter	Patients, n		F/U, y	Mean baseline lipid values, mg/dL			Mean achieved lipid values, mg/dL			Mean experimental % change, primary endpoint		Mean control % change, primary endpoint	
			M	F		LDL-C	HDL-C	TG	LDL-C	HDL-C	TG	Overall	Most diseased sub-segment	Overall	Most diseased sub-segment
STATINS															
METEOR	Rosuvastatin, 40 mg (experimental) vs. PBO (control)	Carotid-artery intima-media thickness measured by carotid ultrasound	588	396	2	155 (rosuvastatin); 154 (PBO)	50 (rosuvastatin); 49 (PBO)	126 (rosuvastatin); 134 (PBO)	78	53	98	–0.0014[i]	NA	0.0131[i]	NA
Niacin, colestipol and/or combination ARBITER-3	Extended-release niacin added to statin therapy	Mean carotid-artery intima-media change measured by ultrasound following up to 24 months of niacin use	120	10	1 or 2	90.5	39.2	180.4	79.2 (1 year niacin use); 78.4 (2 years niacin use)	48.5 (1 year niacin use); 48.6 (2 years niacin use)	120.5 (both 1 and 2 years niacin use)	–0.027 (12 months); –0.041 (24 months)	NA	NA	NA
CLAS	Niacin + colestipol	Change in Global Coronary Change score based on combined coronary, femoral, and carotid angiograms	162	0	2	171.0	44.6	151.0	97.0	60.8	110	0.3[i]	NA	0.8[i]	NA

ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CLAS = Cholesterol Lowering Atherosclerosis Study; F=female; F/U = follow-up; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; M = male; METEOR = Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin; PBO = placebo; TG = triglycerides.

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Major Statin Imaging Studies (4/4)

Trial	Agent	Primary endpoint parameter	Patients, n		F/U, y	Mean baseline lipid values, mg/dL			Mean achieved lipid values, mg/dL			Mean experimental % change, primary endpoint		Mean control % change, primary endpoint	
			M	F		LDL-C	HDL-C	TG	LDL-C	HDL-C	TG	Overall	Most diseased sub-segment	Overall	Most diseased sub-segment
STATINS															
FATS	Colestipol 30 g; + niacin 4 g; Colestipol 30 g + lovastatin 40 mg	Percentage change in disease severity (proximal coronary artery lesion stenosis), measured by arteriography	146	0	2.5	189.9 (niacin + colestipol); 196.1 (lovastatin + colestipol)	39.0 (niacin + colestipol); 35.1 (lovastatin + colestipol)	193.8 (niacin + colestipol); 200.9 (lovastatin + colestipol)	128.9 (niacin + colestipol); 106.9 (lovastatin + colestipol)	54.8 (niacin + colestipol); 40.9 (lovastatin + colestipol)	137.2 (niacin + colestipol); 183.2 (lovastatin + colestipol)	–1.1% (niacin + colestipol); –0.3% (lovastatin + colestipol)	–6.4% (niacin + colestipol); –2.6% (lovastatin + colestipol)	2.0%	1.1%
PCSK9 inhibitors GLAGOV	Evolocumab, 420 mg (experimental) vs. PBO (control)	Nominal change in % atheroma volume, measured by intravascular ultrasound	699	269	6.5	92.6 (evolocumab); 92.4 (PBO)	46.7 (evolocumab; 45.4 (PBO)	117 (evolocumab); 124.5 (PBO)	36.6 (evolocumab)	51.0 (evolocumab)	105.1 (evolocumab)	–0.95	NA	+0.05	NA

FATS = Familial Atherosclerosis Treatment Study; F = female; F/U = follow-up; GLAGOV = Global Assessment of Plaque Regression with a PCSK9 Antibody; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; M = male; PBO = placebo; TG = triglycerides.

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Statin Combination Therapy

Statin Combination Therapy

- Combination therapy of lipid-lowering agents should be considered when LDL-C/non-HDL-C levels are markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

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Conclusion

- Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals.
- Statins decrease plasma LDL-C in a dose-dependent fashion by 20%-55%.
- Numerous clinical trials and imaging studies confirm the CV benefits of statin therapy.
- Statin therapy should be monitored at 6-12 weeks and then periodically thereafter.
- The benefits of intensive statin therapy for ASCVD risk reduction outweigh the associated increased risk of new-onset T2D.
- Combination therapy should be considered when statin monotherapy does not achieve therapeutic targets.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular;
LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes.