ORLANDO HEALTH®

Dyslipidemia management in 2017

No disclosures

Outline

- ACC / ESC / AACE
- Risk assessment
- Testing and Treatment targets
- Management
- Monitoring / Statins
- Non statin medications
- 2017 ACC Update


BANG HEAD HERE

Case # 1

- 63 y/o male comes to your clinic to establish care
- Has not seen a doctor in 15 years
- Does not take meds /Active smoker
- Works at one of our theme parks (walks)
- Father died of MI at 55
- Has no symptoms
- Vitals – 148/90, 70, 18
- Labs TC 150, Trig 94, LDL 94, HDL 34

Question: **Next step?**

1. Suggest a DASH diet
2. Recommend smoking cessation
3. Recommend regular physical exercise
4. Perform risk assessment using a CV risk assessment tool
5. All of the above

Risk assessment

4 Statin Benefit Groups

- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease

†Requires risk discussion between clinician and patient before statin initiation

‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

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)

*10-year ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke

Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - CAC score ≥300 Agaston units
  - ABI <0.9
- Statin use still requires discussion between clinician and patient

Risk categories (1)

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≤10%.

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Risk categories (2)

High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

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Table 5
Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age[a-d]	Obesity, abdominal obesity[c,d]	⇧Lipoprotein (a)
⇧ Total serum cholesterol level[a,b,d]	Family history of hyperlipidemia[d]	⇧ Clotting factors
⇧ Non–HDL-C[d]	⇧ Small, dense LDL-C[d]	⇧ Inflammation markers (hsCRP; Lp-PLA_2)
⇧ LDL-C[a,d]	⇧ Apo B[d]	⇧Homocysteine levels
Low HDL-C[a,d,e]	⇧LDL particle concentration	Apo E4 isoform
Diabetes mellitus[a-d]	Fasting/post-prandial hypertriglyceridemia[d]	⇧ Uric acid
Hypertension[a-d]	PCOS[d]	⇧ TG-rich remnants
Chronic kidney disease 3,4[h]	Dyslipidemic triad[f]	
Cigarette smoking[a-d]		
Family history of ASCVD[a,d,g]		

Case # 2

- 56 y/o African – American gentleman comes to the clinic for lab results. Based on AHA /ACC risk calculator his 10 year risk for CV events is 9.6%. Before you start a statin medication which labs are recommended

Question:

1. Repeat fasting lipid panel
2. LFT
3. CPK
4. LFT and CPK
5. All of the above

Testing

Lipid analyses

Recommendations	Class	Level
LDL-C has to be used as the primary lipid analysis.	I	C
HDL-C is recommended to be analysed before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
When available, apoB should be an alternative to non-HDL-C.	IIa	C
Lp(a) should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD.	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C

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Individuals who should be considered for lipoprotein(a) screening

Individuals with:
• Premature CVD.
• Familial hypercholesterolaemia.
• A family history of premature CVD and/or elevated Lp(a).
• Recurrent CVD despite optimal lipid-lowering treatment.
• ≥5% 10-year risk of fatal CVD according to SCORE.

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Possible causes of hypertriglyceridaemia (1)

Genetic predisposition.
Obesity.
Type 2 diabetes.
Alcohol consumption.
Diet high in simple carbohydrates.
Renal disease.
Hypothyroidism.
Pregnancy (physiological triglyceride concentrations double during the third trimester).

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Possible causes of hypertriglyceridaemia (2)

Paraproteinaemia and auto-immune disorders such as systemic lupus erythematosus.

Multiple medications including:

- Corticosteroids.
- Oestrogens, especially those taken orally.
- Tamoxifen.
- Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides.
- Isotretinoin.
- Bile acid-binding resins.
- Ciclosporin.
- Antiretroviral regimens (protease inhibitors).
- Psychotropic medications: phenothiazines, second generation antipsychotics.

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Lipid analyses as treatment targets

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

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Case # 3

- 64 y/o gentleman had an NSTEMI 3 weeks prior to office visit. He had a STENT to LAD He is currently doing well with no symptoms. Your Lipid profile done in office 2 months prior to his event shows an LDL of 146. His current medications include

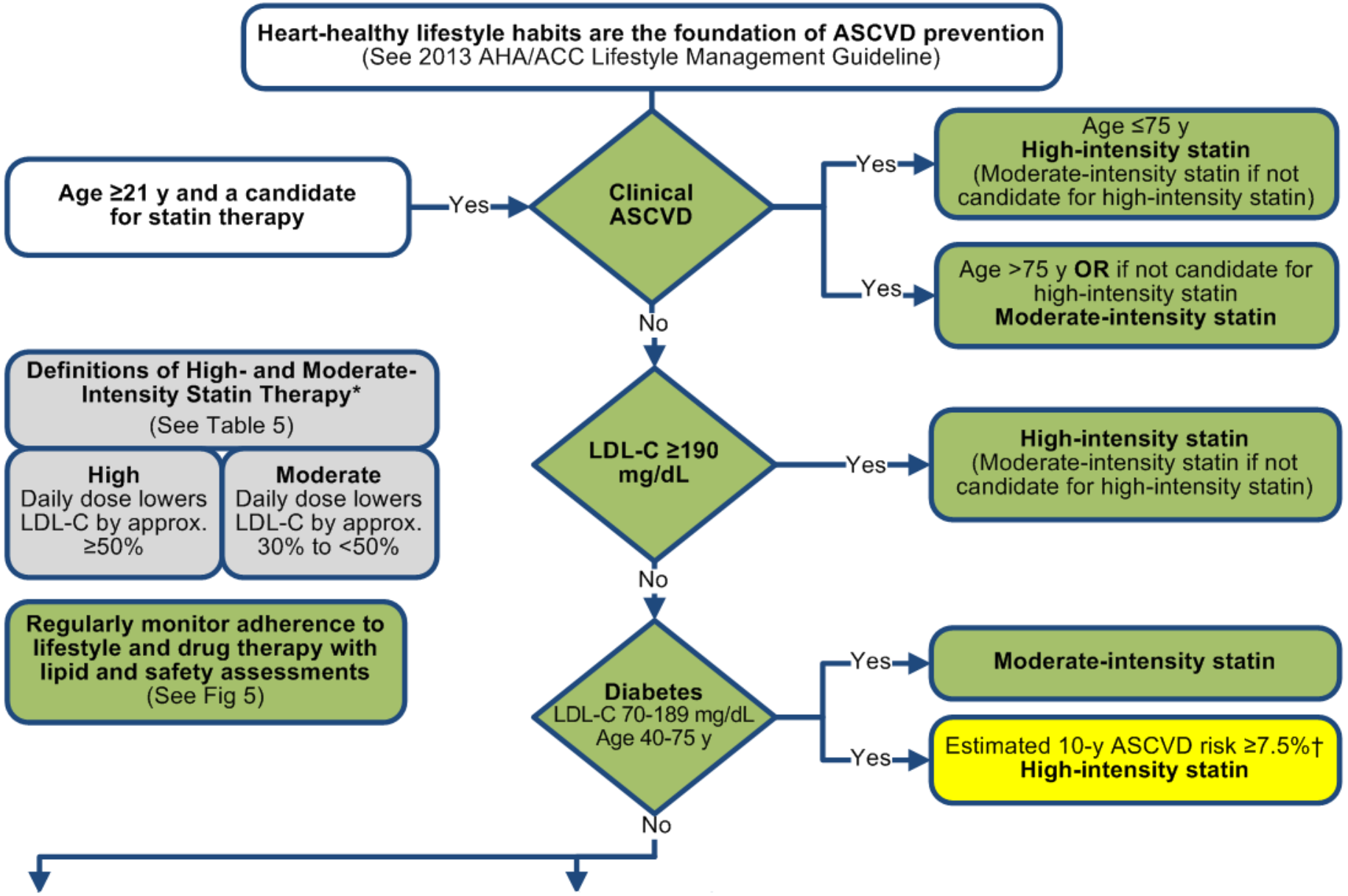
  ASA 81 mg, Plavix 75 mg, Atorvastatin 40 mg, Lisinopril 20 mg

Question: In addressing his Lipids …

1. Check his Lipid panel in 2 months and adjust Statin dose as tolerated and needed
2. Increase Atorvastatin to 80 mg
3. Keep the same dose of Atorvastatin since he is doing well on current dose
4. Add Ezetimibe

Treatment targets

Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)



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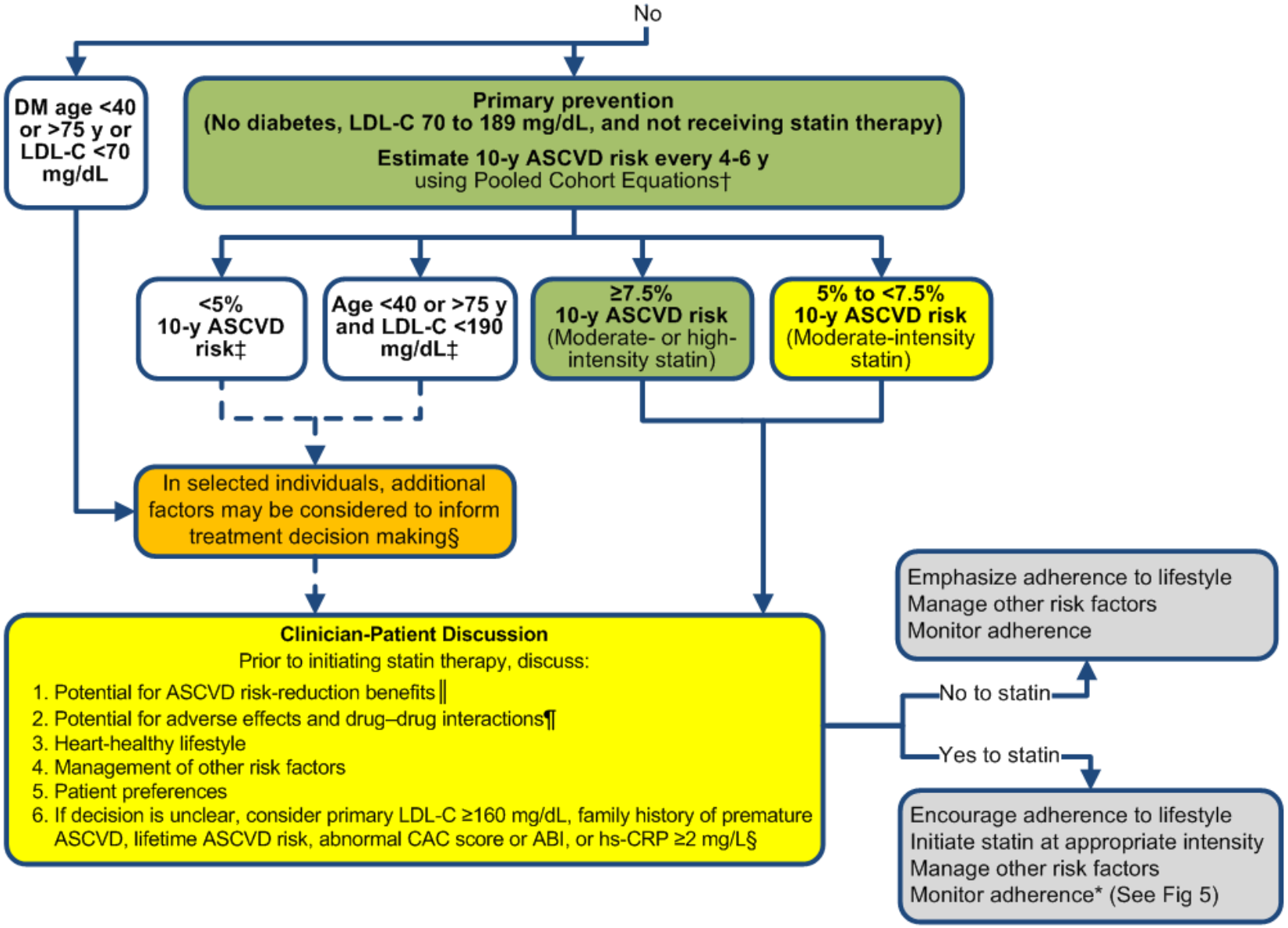

Treatment targets and goals for cardiovascular disease prevention (2)

Lipid LDL-C is the primary target	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<8.6 mmol/L).

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Treatment goals for low-density lipoprotein-cholesterol

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

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Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Management

Impact of specific lifestyle changes on lipid levels (1)

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TC and LDL-C levels		
Reduce dietary trans fat	+++	A
Reduce dietary saturated fat	+++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice supplements	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B
Use soy protein products	+/-	B

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Impact of specific lifestyle changes on lipid levels (2)

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TG-rich lipoprotein levels		
Reduce excessive body weight	+++	A
Reduce alcohol intake	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrate	++	A
Use supplements of n-3 polyunsaturated fat	++	A
Reduce intake of mono- and disaccharides	++	B
Replace saturated fat with mono- or polyunsaturated fat	+	B

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Impact of specific lifestyle changes on lipid levels (3)

	Magnitude of the effect	Level of evidence
Lifestyle interventions to increase HDL-C levels		
Reduce dietary trans fat	+++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A
Modest consumption in those who take alcohol may be continued	++	B
Quit smoking	+	B
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+/-	C
Reduce intake of mono- and disaccharides	+/-	C

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Dietary recommendations to lower low-density lipoprotein-cholesterol (1)

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream
Legumes	Lentils, beans, fava beans, peas, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks

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Dietary recommendations to lower low-density lipoprotein-cholesterol (2)

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skim milk and yogurt	Low fat milk, low fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yogurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

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Pharmacological treatment of hypercholesterolaemia

Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

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Intensity of Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <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*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Monitoring

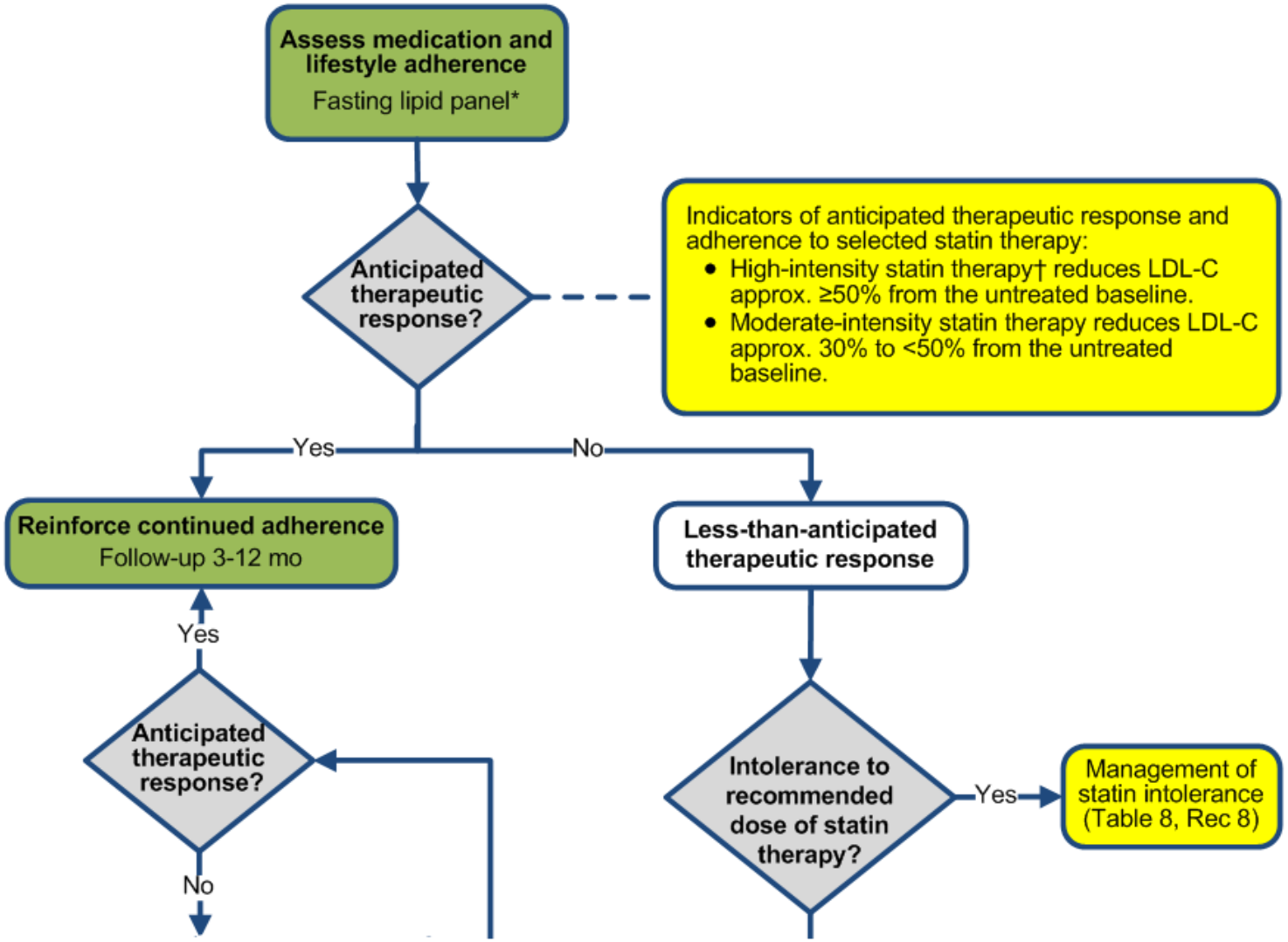
Case # 4

- A 53 y/o gentleman is establishing care with you since he has moved to Orlando recently. His PMH includes dyslipidemia. He is on 40 mg of Simvastatin and he reports that his cholesterol is doing very good on current dose. His BP in the clinic today is 140/90 mm Hg. He reports that his BP has been trending high over last 2 years. His recent work physical also revealed a BP of 156/92 mm Hg. You want to start him on a BP medication

Question: **Which of the following BP medications is preferred?**

1. Amlodipine
2. Lisinopril
3. Chlorthalidone
4. Lisinopril or Chlorthalidone
5. Diltiazem

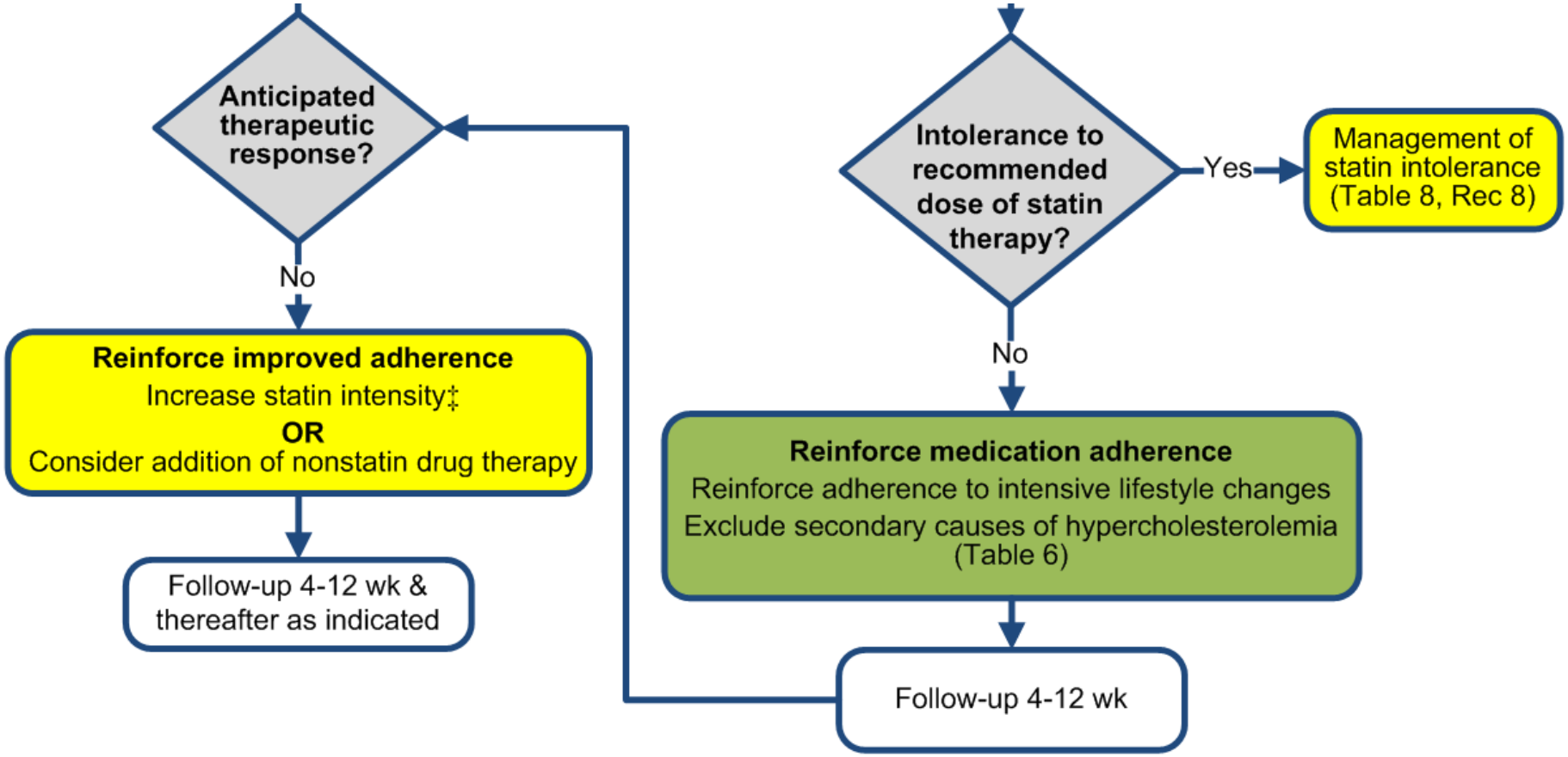
Statin Therapy: Monitoring Response-Adherence



*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.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.

Monitoring Response-Adherence (cont.)



‡See guideline text

Monitoring lipids and enzymes in patients on lipid-lowering therapy (1)

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 (±4) weeks after starting treatment. • 8 (±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).
Monitoring liver and muscle enzymes
How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs? • Before treatment. • Once 8–12 weeks after starting a drug treatment or after dose increase. • Routine control of ALT thereafter is not recommended during lipid-lowering treatment.

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Monitoring lipids and enzymes in patients on lipid-lowering therapy (2)

Monitoring liver and muscle enzymes (Cont'd)

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT <3x ULN:
- Continue therapy.
- Recheck liver enzymes in 4–6 weeks.

If value rises to ≥3x ULN
- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

How often should CK be measured in patients taking lipid-lowering drugs?

Pre-treatment
- Before starting therapy.
- If baseline CK is 4x ULN, do not start drug therapy; recheck.

Monitoring
- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease or sport athletes.

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Monitoring lipids and enzymes in patients on lipid-lowering therapy (3)

Monitoring liver and muscle enzymes (Cont'd)

What if CK becomes elevated in a person taking lipid-lowering drugs?
Re-evaluate indication for statin treatment.

If ≥4 x ULN:
- If CK >10x ULN: stop treatment, check renal function and monitor CK every 2 weeks.
- If CK <10x ULN: if no symptoms, continue lipid lowering therapy while monitoring CK.
- If CK <10x ULN: if symptoms present, stop statin and monitor normalization of CK, before re-challenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

If <4 x ULN:
- If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
- If muscle symptoms, monitor symptoms and CK regularly.
- If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
- Consider re-challenge with the same or another statin.
- Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy.

For details on CK elevation and treatment of muscular symptoms during statin treatment see algorithm in supplementary.

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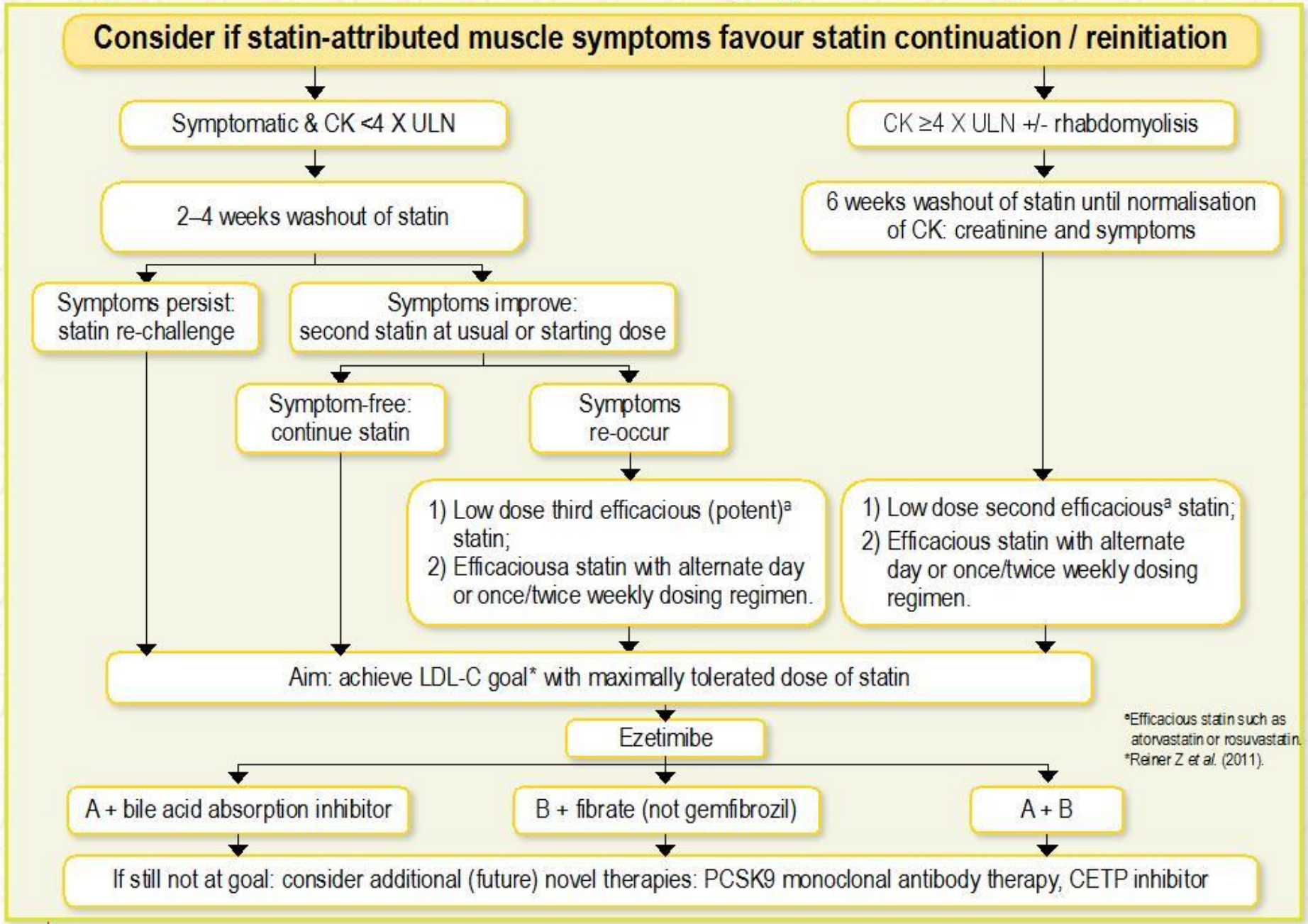
Algorithm for treatment of muscular symptoms during statin treatment



Statin intolerance

- Age >80 years, Female sex, Low BMI
  - African American men
- Vigorous activity
- Family history of statin intolerance /Myopathy
- Osteoarthritis
- Fibromyalgia
- Musculoskeletal deformities
- Excess alcohol
- Major surgery, trauma, infection

Drugs potentially interacting with statins metabolized by CYP3A4 loading to increased risk of myopathy and rhabdomyolysis

Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil

Adapted from Egan and Colman and Wiklund et al.

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Simvastatin

- Patients taking Amiodarone, Verapamil or Diltiazem

  The dose of Simvastatin should not exceed 10 mg/day

- Patients taking Amlodipine or Ranolazine

  The dose of Simvastatin should not exceed 20 mg/day

Statin- Important points

- Hepatic metabolism – Pravastatin, Rosuvastatin, Pitavastatin
- Mild elevation in LFT – no indication of worsening

  Diabetes Mellitus (NNT -225 pts over 4 years)- dose /potency related

  Proteinuria (Rosuvastatin) – Tubular reabsorption

  Dementia

  Hepatic steatosis

  Cancer

  Venous thromboembolism

  PCOS

Non statin medications

Ezetimibe

Study Design

IMPROVE-IT

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

↓

N=18,144

Standard Medical & Interventional Therapy

↓ ↓

Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

↓ ↓

Duration: Minimum 2 ½-year follow-up **(5314 events)**

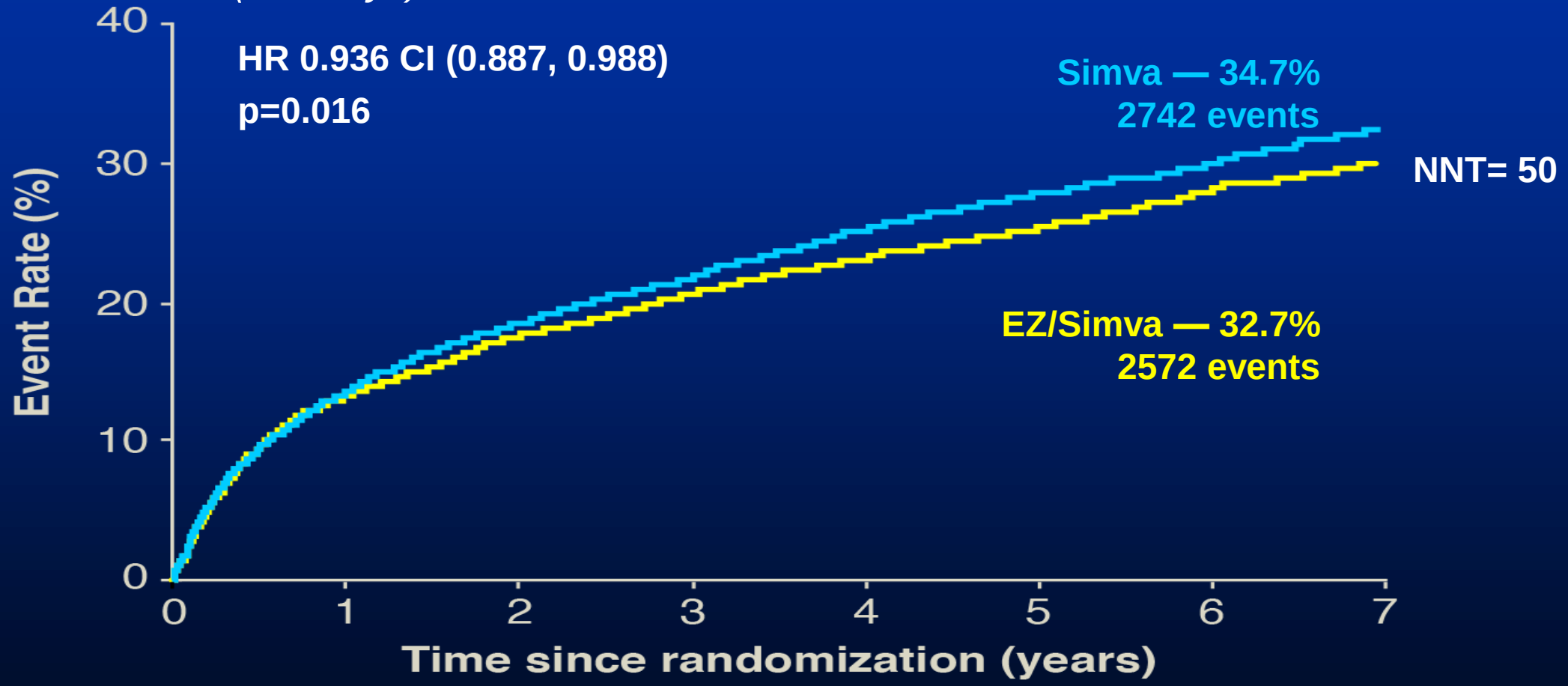
↓

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



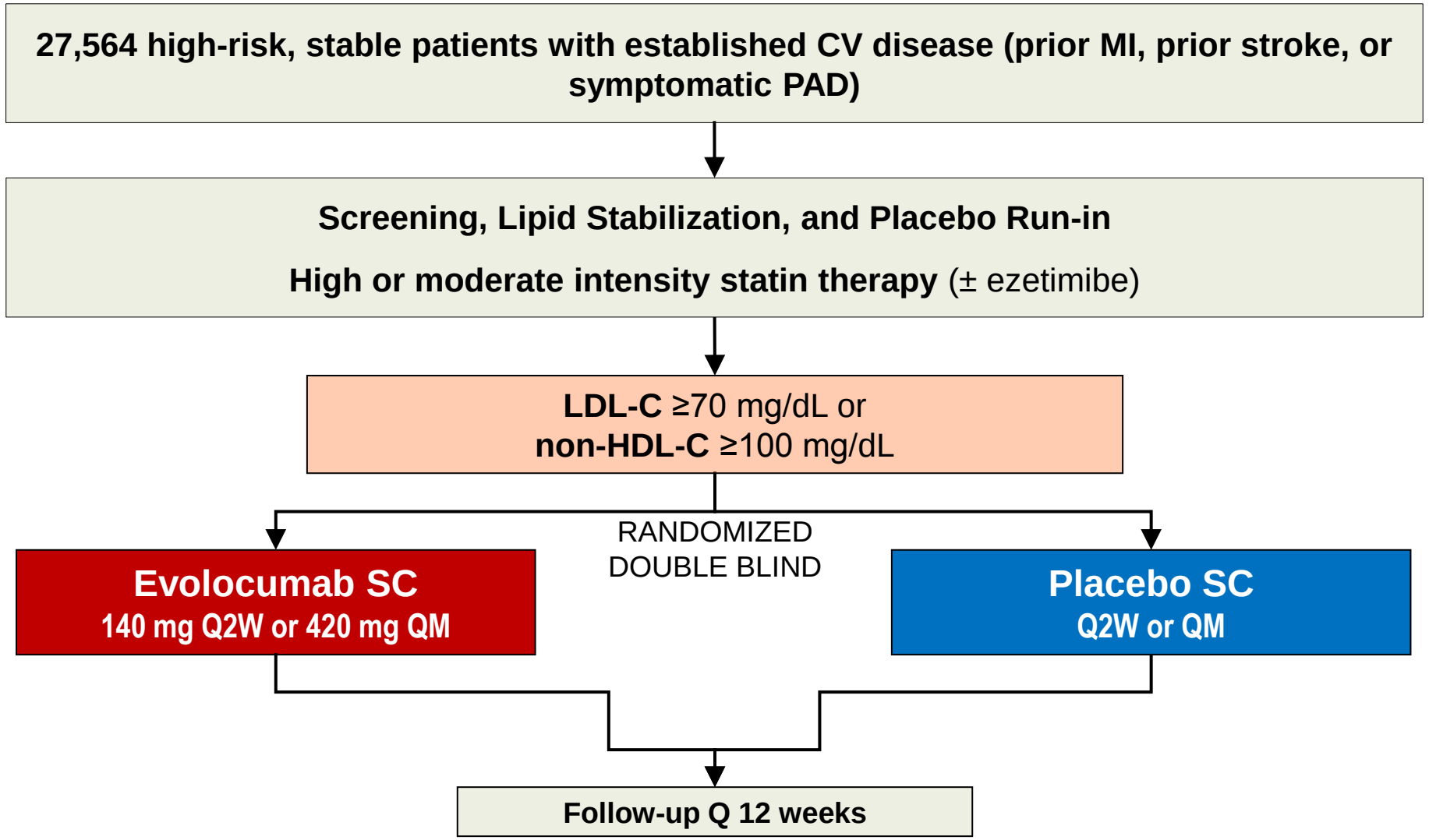
7-year event rates

Cannon CP, Blazing MA, Giugliano RP, et. al. *N Engl J Med* 2015; Epub before print.

PCSK9 -Inhibitors

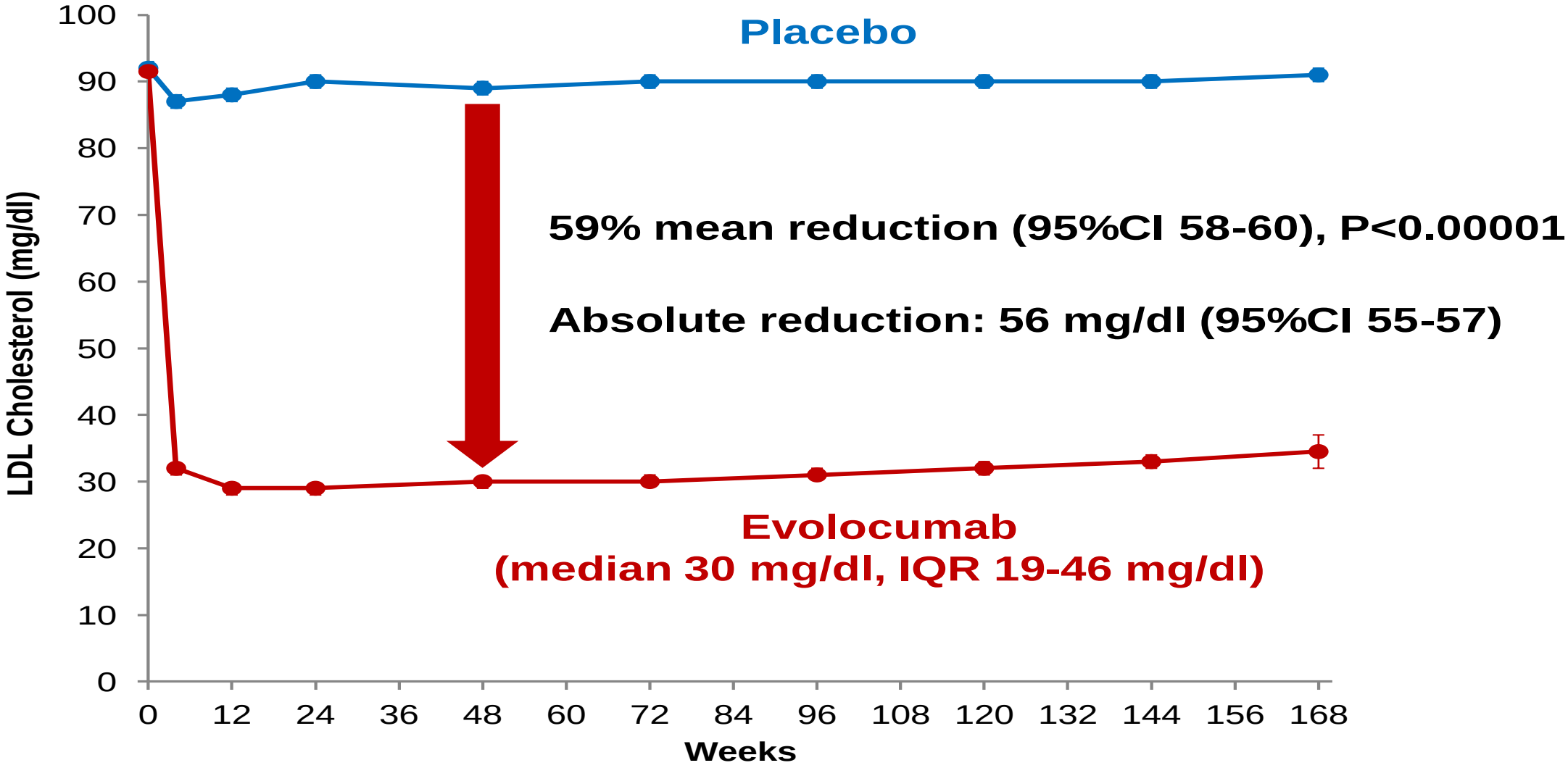
- Evolucumab (Repatha)
- Alirocumab (Praluent)
- Bococizumab

Trial Design

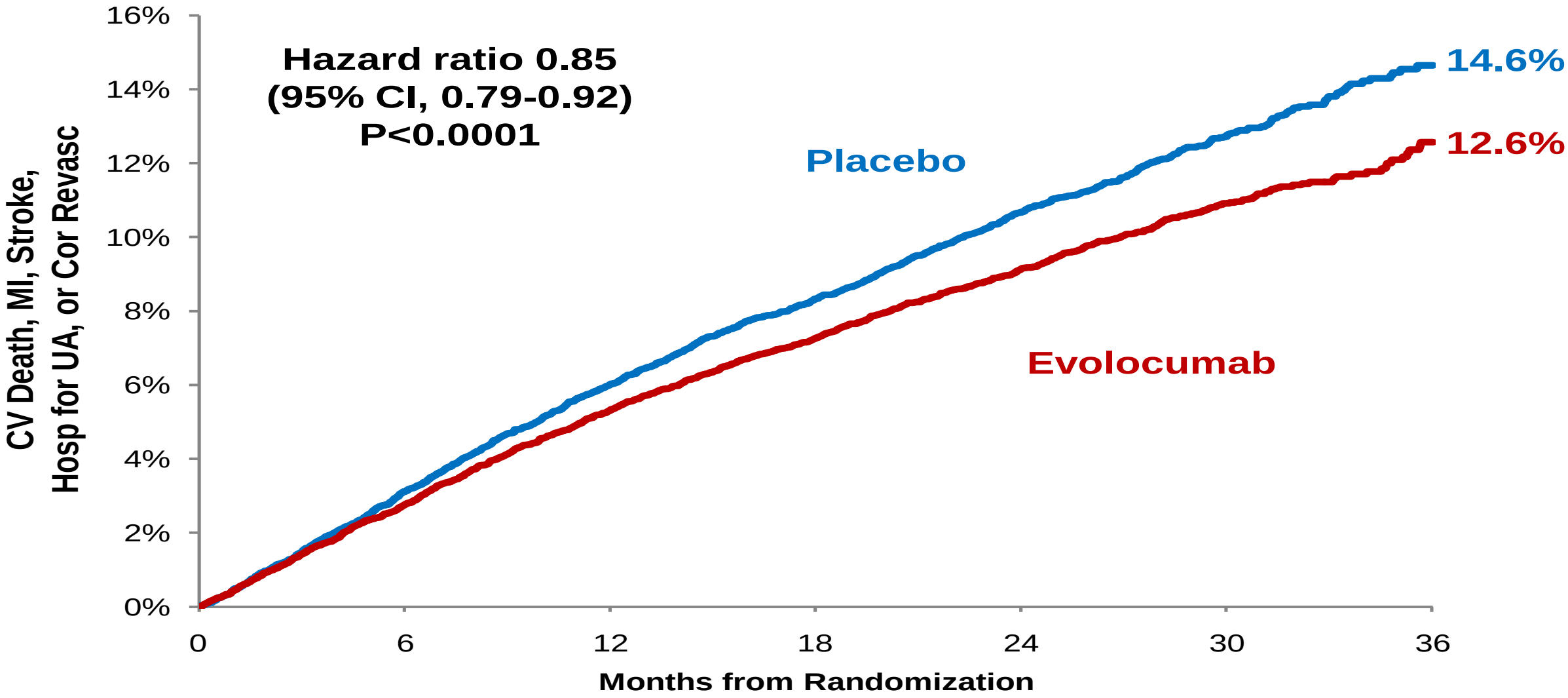


Sabatine MS et al. *Am Heart J* 2016;173:94-101

LDL Cholesterol



Primary Endpoint



2017 Update

Key points

- Clinical ASCVD – LDL goal 50% reduction and LDL < 70
- Reasonable to add either Ezetimibe or PCSK9 inhibitor

  <25% vs. >25%

FDA approval

- Alirocumab - HeFH, Clinical ASCVD
- Evolocumab - HeFH, Clinical ASCVD, HoFH

Ezetimibe (49)	■ **Mechanism of action:** Inhibits Niemann-Pick C1 like 1 (NPC1L1) protein; reduces cholesterol absorption in small intestine. ■ **FDA-approved indication(s):** As adjunct to diet to: 1) ↓ TC, LDL-C, Apo B, non-HDL-C in patients with primary hyperlipidemia, alone or in combination with a statin; 2) ↓ TC, LDL-C, Apo B, non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; 3) ↓ TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin; 4) ↓ sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia). ■ **Dose:** 10 mg PO daily, with or without food. Take either ≥2 hours before or ≥4 hours after BAS if used in combination. ■ **Mean % reduction in LDL-C (per PI):** Monotherapy—18%; combination therapy with statin (incremental reduction)—25% ■ **Adverse effects:** Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea. ■ **Drug-drug interactions:** cyclosporine, fibrates, BAS ■ **CV outcomes trials:** IMPROVE-IT (6) (The addition of ezetimibe to moderate-intensity statin in patients with recent ACS resulted in incremental lowering of LDL-C and reduced primary composite endpoint of CV death, nonfatal MI, UA requiring re-hospitalization, coronary revascularization [≥30 days after randomization], or nonfatal stroke. The median follow-up was 6 years.); SHARP (46) (Simvastatin plus ezetimibe reduced LDL-C and reduced primary endpoint of first major ASCVD event [nonfatal MI or CHD death, non-hemorrhagic stroke, or any arterial revascularization procedure] compared to placebo over a median f/u of 4.9 years). ■ **Prescribing considerations:** Generally well tolerated. Generic available.

PCSK9 inhibitors (50,51)	■ **Mechanism of action:** Human monoclonal antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL. ■ **FDA-approved indication(s):** Alirocumab and evolocumab: Adjunct to diet and maximally tolerated statin therapy to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction. Evolocumab: Adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who need more LDL-C reduction. ■ **Dose and route of administration:** Alirocumab—initiate 75 mg subcutaneously (SQ) every 2 weeks. If more LDL reduction needed, may ↑ dose to 150 mg every 2 weeks. Alternative starting dose is 300 mg SQ every 4 weeks. Evolocumab—in primary hypercholesterolemia with established clinical ASCVD or HeFH, give 140 mg SQ every 2 weeks or 420 mg SQ once monthly in abdomen, thigh, or upper arm. In HoFH, give 420 mg SQ once monthly. To administer 420 mg, give 3 (140 mg) injections consecutively within 30 minutes. ■ **Mean % LDL-C reduction (per PI):** Alirocumab—when added to maximally tolerated statin therapy, alirocumab 75 mg and 150 SQ every 2 weeks ↓ LDL-C by an additional 45% and 58%, respectively. When added to maximally tolerated statin therapy evolocumab 140 mg every 2 weeks and 420 mg SQ every 4 weeks, ↓ LDL-C by an additional 64% and 58%, respectively. ■ **Adverse effects:** Alirocumab—nasopharyngitis, injection site reactions, influenza. Evolocumab—nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. No evidence of increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS (7,52). ■ **Drug-drug interactions:** No clinically significant drug-drug interactions identified for alirocumab or evolocumab. ■ **CV outcomes trials:** Alirocumab—ODYSSEY Outcomes (4) (18,600 post-ACS [4–52 weeks] patients on evidence-based statin therapy; Primary endpoint is CHD death, MI, ischemic stroke, or hospitalization for UA. Estimated study completion is December 2017). Evolocumab—FOURIER (7) (27,564 patients with prior MI, stroke, or PAD on atorvastatin ≥20 mg or equivalent; Demonstrated that addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization or hospi talization for UA). Bococizumab—SPIRE-1 and -2 (2) (27,438 patients at high risk of CV event with LDL-C 70–99 mg/dL [SPIRE-1] or ≥100 mg/dL [SPIRE-2] on lipid-lowering therapy; Studies terminated by sponsor at median follow-up 10 months). There was no benefit in the combined analysis with respect to the primary composite endpoint of CV death, MI, stroke, or urgent revascularization. ■ **Considerations in prescribing:** Cost, SQ administration, robust LDL-C reduction, CV outcomes trials not completed for alirocumab, burdensome prior authorization process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謝謝
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kia ora
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welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
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blagodaram
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grazzi
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хвала
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dankie
nanni
nandri
dhanyavad
mauruuru
thank you
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