Update of High-intensity Statins in ASCVD prevention

Implication from 2018 ACC/AHA Guideline

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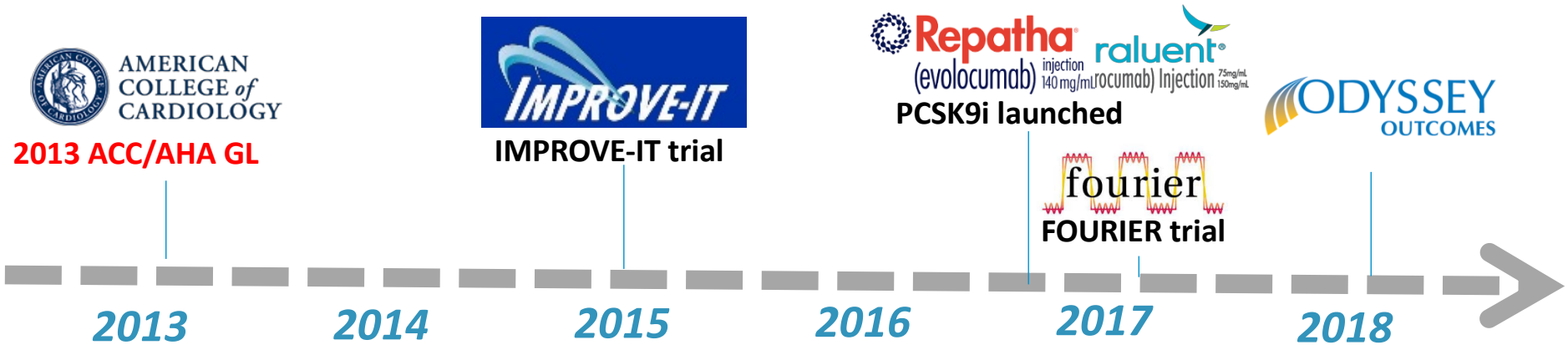
Why the update?

- Since 2013, new clinical evidence has emerged demonstrating the benefits of adding non-statin drugs to statin therapy in reducing ACSVD risk.



The 2018 guideline provides updated guidance for the management of dyslipidaemia with non-statin agents while continuing to emphasize the importance of a healthy lifestyle and the benefits of statin therapy.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

2018 guideline update

- The "2018 Guidelines on the Management of Blood Cholesterol" was presented by the ACC/AHA on November 10, at the 2018 AHA Annual Scientific Sessions in Chicago, Illinois.

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Circulation

The new guidelines are simultaneous published in Circulation and Journal of the American College of Cardiology

The 2018 ACC/AHA guideline is approved and endorsed by 10 other professional medical societies:

AACVPR American Association of Cardiovascular and Pulmonary Rehabilitation

AAPA

ABC Association of Black Cardiologists, Inc. Saving the Hearts and Minds of a Diverse America

ACPM American College of Preventive Medicine

American Diabetes Association.

AGS Geriatrics Healthcare Professionals

APhA

ASPC The American Society for Preventive Cardiology

nla NATIONAL LIPID ASSOCIATION

PCNA PREVENTIVE CARDIOVASCULAR NURSES ASSOCIATION

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Principle in 2018 guideline for ASCVD risk reduction is unchanged from 2013[1,2]

LDL-C is the primary target and "lower is better"

Lipid disorder (LDL-C↑, HDL↓, TG↑)

Major ASCVD contributing risk factors

- Hypertension
- Metabolic syndrome
- Smoking/ inactive lifestyle
- High CRP/ CKD
- DM
- Obesity

Increased CVD risk

Risk-enhancing factors

LDL-C measurements are important for initial ASCVD risk assessment and monitoring adherence and response to LDL-C lowering medications and lifestyle therapies.

A reduction in LDL-C levels of 1% gives an approximate 1% reduction in ASCVD risk.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; COR: Class of Recommendation; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LOE: Level of evidence; LDL-C: low-density lipoprotein cholesterol; TG, triglycerides.

1.Stone NJ et al. J Am Coll Cardiol. 2014 Jul 7; 63:2889-934; 2.Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Lipid lowering pharmacotherapies in the 2018 ACC/AHA guideline

First line therapy: Statins

ACC/AHA divides statin therapies into 3 intensity categories:

	High Intensity	Moderate intensity	Low intensity
Average LDL-C reducing effect	**≥ 50%**	**30%-49%**	**< 30%**
Daily doses	**Atorvastatin 40-80 mg** **Rosuvastatin 20 mg (40 mg)** *Rosuvastatin is only approved at 20 mg in Taiwan unless for familial hypercholesterolemia*	**Atorvastatin 10-20 mg** **Rosuvastatin 5-10 mg** Simvastatin 20-40 mg **Pravastatin 40-80 mg** Lovastatin 40-80 mg Pitavastatin 1-4 mg **Fluvastatin** 40 mg BID/**80 mg** *Rosuvastatin 5mg starting dose is recommended in Asians with caution taken when titrating*	Simvastatin 10 mg **Pravastatin 10-20 mg** Lovastatin 20 mg Fluvastatin 20-40 mg

Boldface *type indicates statins that can be given at anytime of day.*
Normal-face text indicates statins that should be administered in the evening to achieve maximum LDL-C reduction.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CTT: Cholesterol Treatment Trialists; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, hemoglobin A1C; LDL-C: low-density lipoprotein cholesterol.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Second line therapy: Ezetimibe

- **Indicated for combination therapy with statins in patients with elevated LDL-C despite maximally tolerated statin therapy or whom experience statin-associated side effects.**[1]

Treatment regime	LDL-C lowering effects[2]
Ezetimibe Monotherapy (12W)	
Ezetimibe 10 mg	↓ LDL-C 13%-20%
Ezetimibe + Statin vs. Statin Monotherapy (12W)	
Ezetimibe 10 mg + Atorvastatin 10-80 mg	↓ LDL-C 53%-61%
Atorvastatin 10-80 mg	↓ LDL-C 37%-54%
Ezetimibe 10 mg + Simvastatin 10-80 mg	↓ LDL-C 46%-58%
Simvastatin 10-80 mg	↓ LDL-C 27%-45%
Ezetimibe 10 mg + Pravastatin 10-40 mg	↓ LDL-C 34%-42%
Pravastatin 10-80 mg	↓ LDL-C 21%-31%
Ezetimibe 10 mg + Lovastatin 10-40 mg	↓ LDL-C 34%-46%
Lovastatin 10-80 mg	↓ LDL-C 20%-30%

IMPROVE-IT demonstrated ezetimibe add-on to statin therapy can lower LDL-C by about 24% and further reduce the absolute risk of ASCVD by 2%.[3]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol.

1.Grundy SM et al. J AM Coll Cardiol. 2018 Nov 10. Epub ahead of print
2.ZETIA Prescribing Information. Accessed date: 13 Dec 2018
3.Cannon CP et al. N Engl J Med. 2015 Jun 18. 373(25): 2397-97

Second/third line therapy: PCSK9i

- **Indicated as add-on therapy for patients with significant ASCVD risk or with FH after maximal statin therapy ± ezetimbe.[1]**

Treatment	LDL-C reducing effect	ASCVD risk reduction
Alirocumab: 75 mg Q2W / 300 mg Q4W + **Statin:** Maximum tolerated dose ± other lipid-lowering therapy	↓ LDL-C 54.7% vs. placebo[2]	15% risk reduction in major adverse cardiac events compared with placebo*[2]
Evolocumab: 140 mg Q2W / 520 mg once monthly + **Statin:** Maximum tolerated dose ± other lipid-lowering therapy	↓ LDL-C 59% vs. placebo[3]	15% risk reduction of composite of CHD death, non-fatal MI, ischemic stroke, or UA requiring hospitalization[3]

*composite of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or diagnosis of unstable angina

Cons: (1) Requires subcutaneous injection; (2) Limited long-term safety data; (3) High cost

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C: low-density lipoprotein cholesterol; MI, myocardial infarction; UA, unstable angina; Q2(4)W, every 2(4) weeks.

1.Grundy SM et al. J AM Coll Cardiol. 2018 Nov 10. Epub ahead of print
2.Schwartz GG et al. N Engl J Med. 2018 Nov 29. 379(22): 2097-2107
3.Sabatine MS et al. N Engl J Med. 2017 May 4. 376(28): 1713-1722

Other LDL-C lowering/triglyceride lowering agents

	Agents	Clinical consideration
Bile acid-sequestrants[1]	• **Cholestyramine** • **Colesvelam** • **Colestipol**	• Lowers LDL-C 15%-30% • Add-on to statin therapy or use in patients with statin-associated side effects supported by RCT • Avoided if TG ≥ 300 mg/dL • Associated with GI side effects
Fibrates[1,2]	• **Gemfibrozil** • **Fenofibrate** • **Fenofibric acid**	• Lowers TG 20-35% • Add-on to statin therapy for LDL-C reduction not supported by RCTs • Increases myositis and myalgia risk with concomitant statin therapy
Niacins[1,2]	• **Nicotinic acid**	• Lowers TG 20-30%; LDL-C 10-25% • Add-on to statin therapy for LDL-C reduction not supported by RCTs
Omega-3 fatty acids[2]	• **Omega-3 fatty acid ethyl esters (Ethyl eicosapentaenoic acid)**	• Lowers TG 27-45% • Effect of cardiovascular morbidity and mortality unknown in patients with severe hypertriglyceridemia

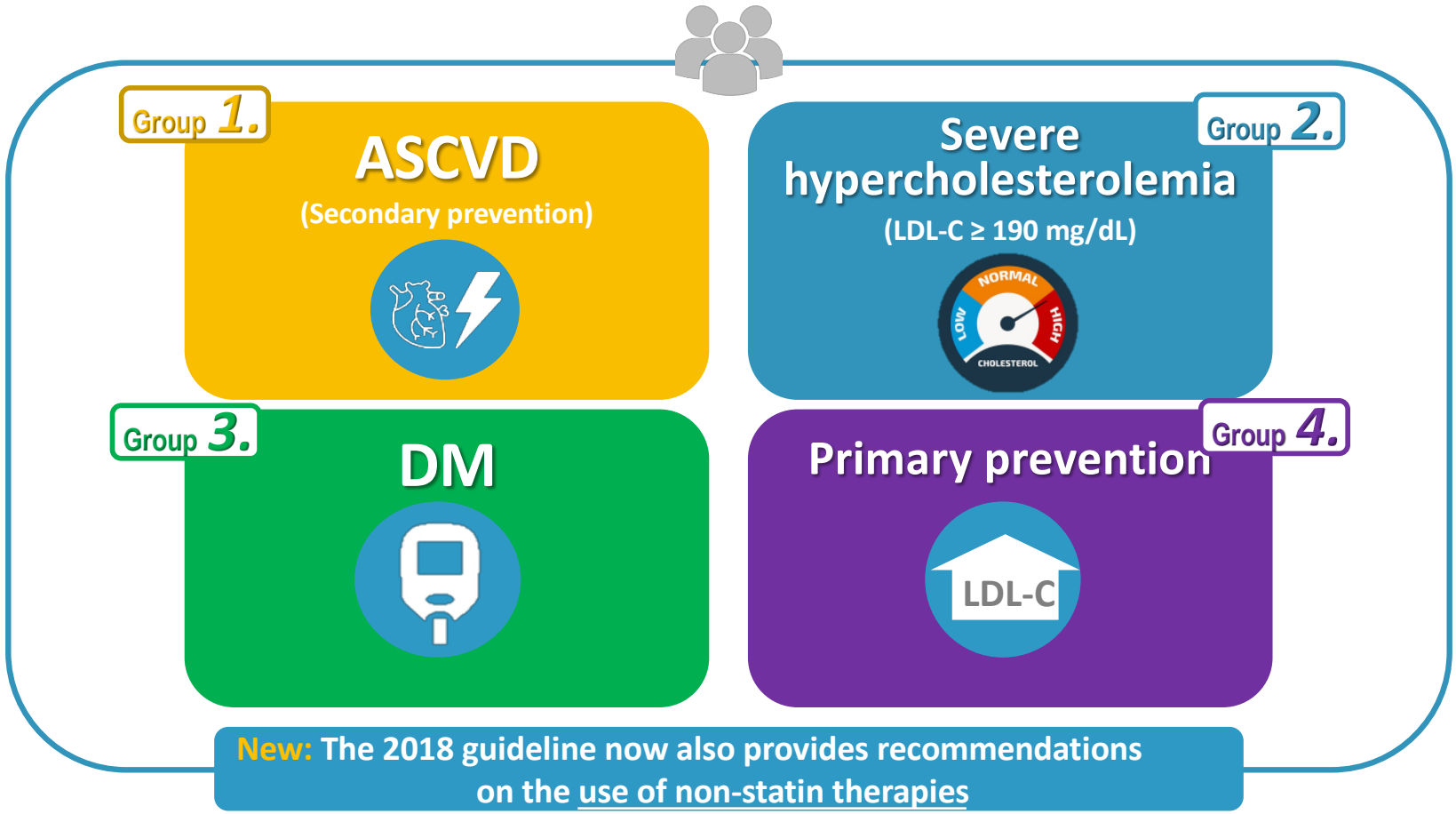
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; GI, gastrointestinal; LDL-C: low-density lipoprotein cholesterol; RCT, randomized clinical trial; T2DM, type 2 diabetes; TG, triglycerides.

1.Grundy SM et al. J AM Coll Cardiol. 2018 Nov 10. Epub ahead of print
2.Jellinger PS et al. Endocr Pract. 2017 Apr. 23(Suppl 2): 1-87

Updated treatment algorithms (2018 vs. 2013)

Patient management groups

Consistent with 2013 guideline: 4 patient groups who may significantly benefit from ASCVD risk reduction with statin therapy are endorsed.



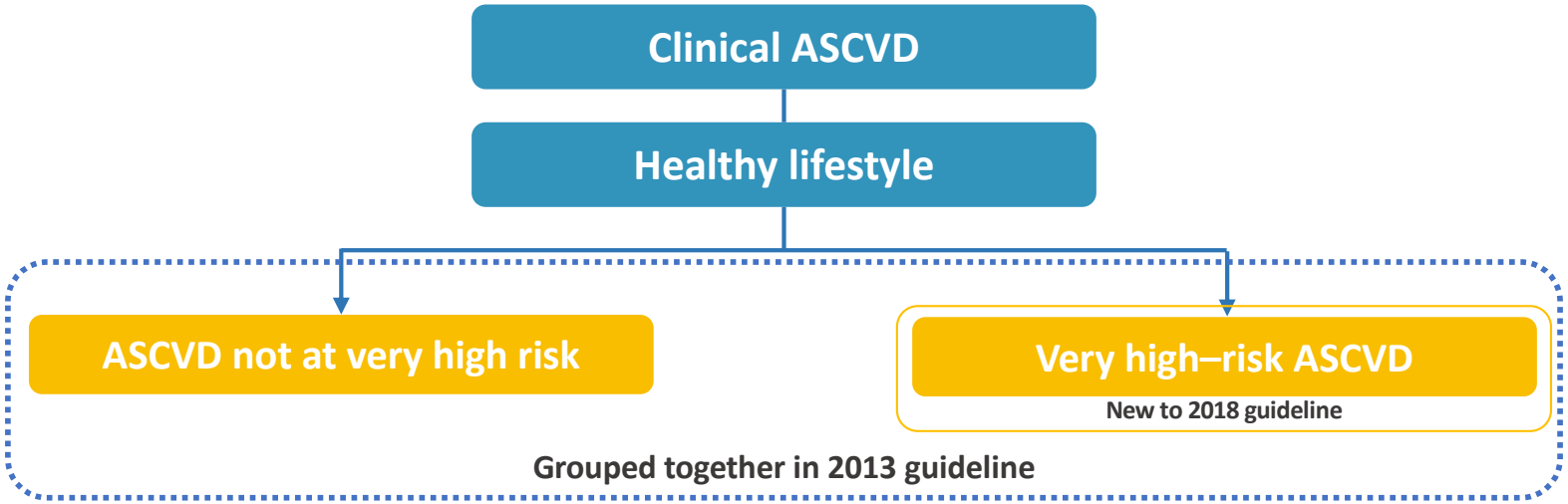
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease ; DM, diabetes mellitus.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Secondary Prevention

Group 1. ASCVD Secondary prevention

New to 2018 guideline: ASCVD patients are now classified into at "very high" or "not very high" risk sub-groups.



Who are the very high risk patients?

Patients with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Major ASCVD events
- Recent ACS (0-12 M)
- History of MI (>12 M)
- History of ischemic stroke
- Symptomatic PAD

High-risk conditions
- Age ≥ 65
- Heterozygous FH
- DM
- Hypertension
- CKD
- Currently Smoking
- Persistent elevated LDL-C
- Congestive HF
- Prior CABG or PCI intervention outside of major ASCVD events

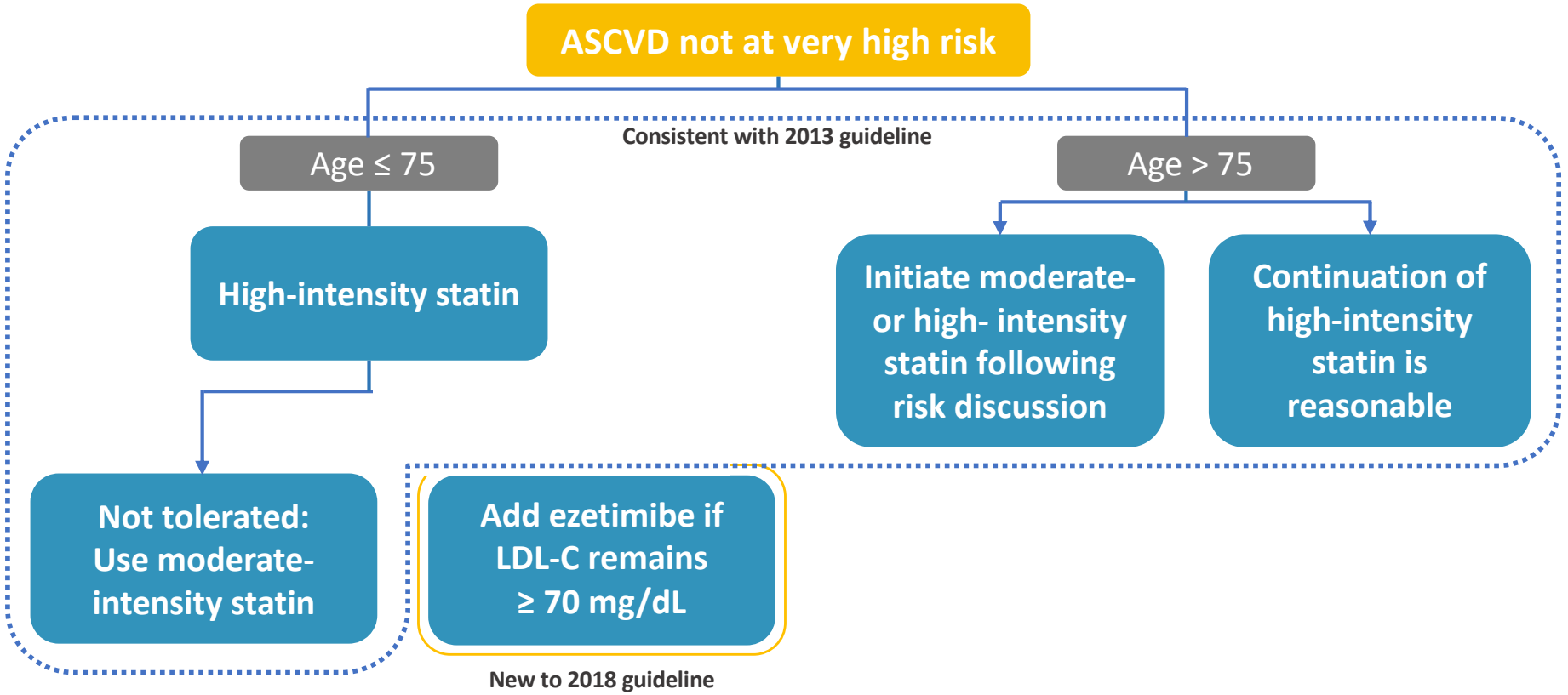
Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft, CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention, UA, unstable angina.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Group 1. ASCVD Secondary prevention

Secondary Prevention:
ASCVD patients not at very high risk

New to 2018 guideline: Consider Ezetimibe as add-on therapy to high-intensity statin therapy for secondary prevention in ASCVD patients ≤ 75 years.



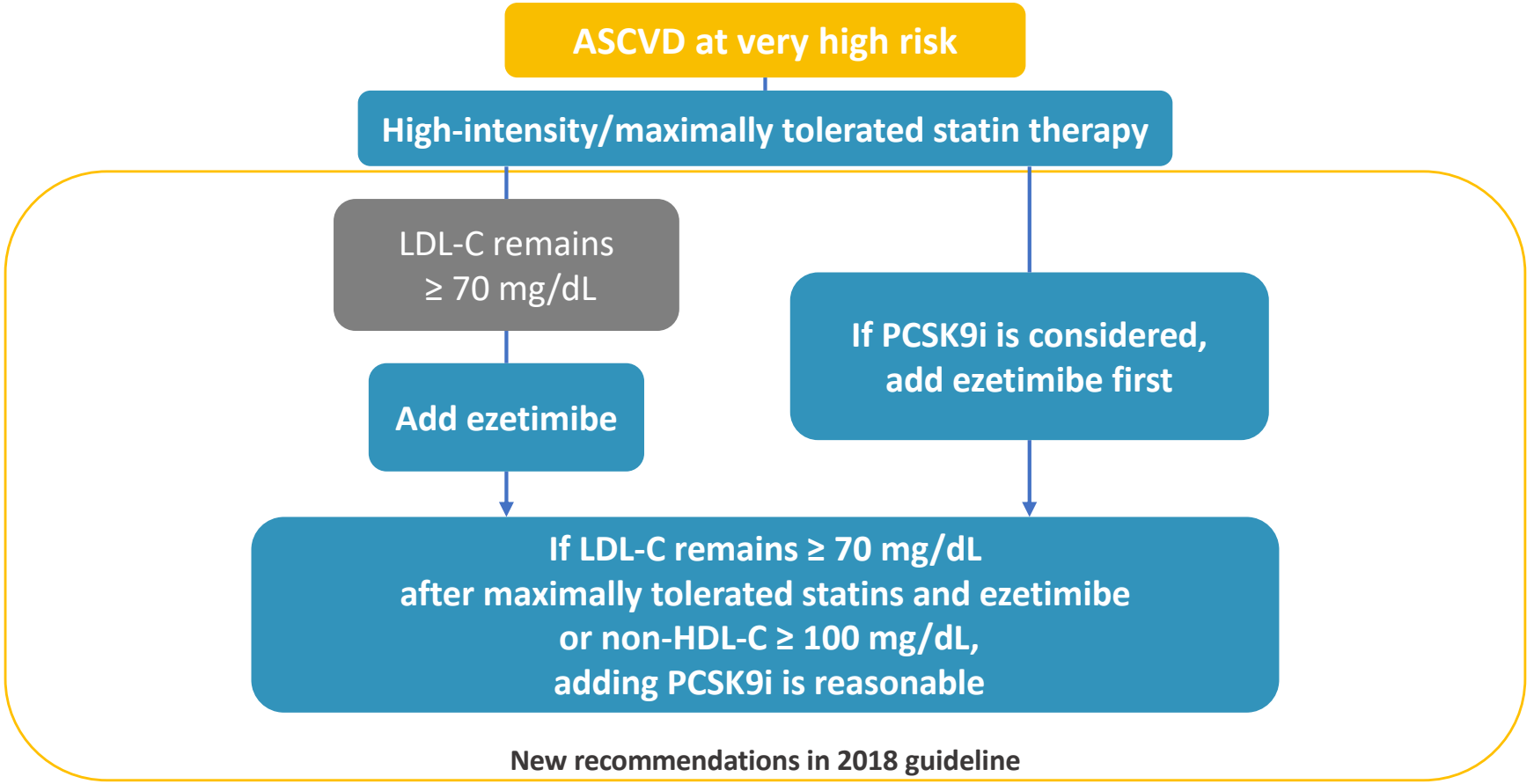
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Group 1. ASCVD Secondary prevention

Secondary Prevention:
ASCVD patients at very high risk

New in 2018 guideline: Consider ezetimibe followed by PCSK9i add-on therapy when LDL-C reduction remains sub-optimal despite maximally tolerated statin therapy.



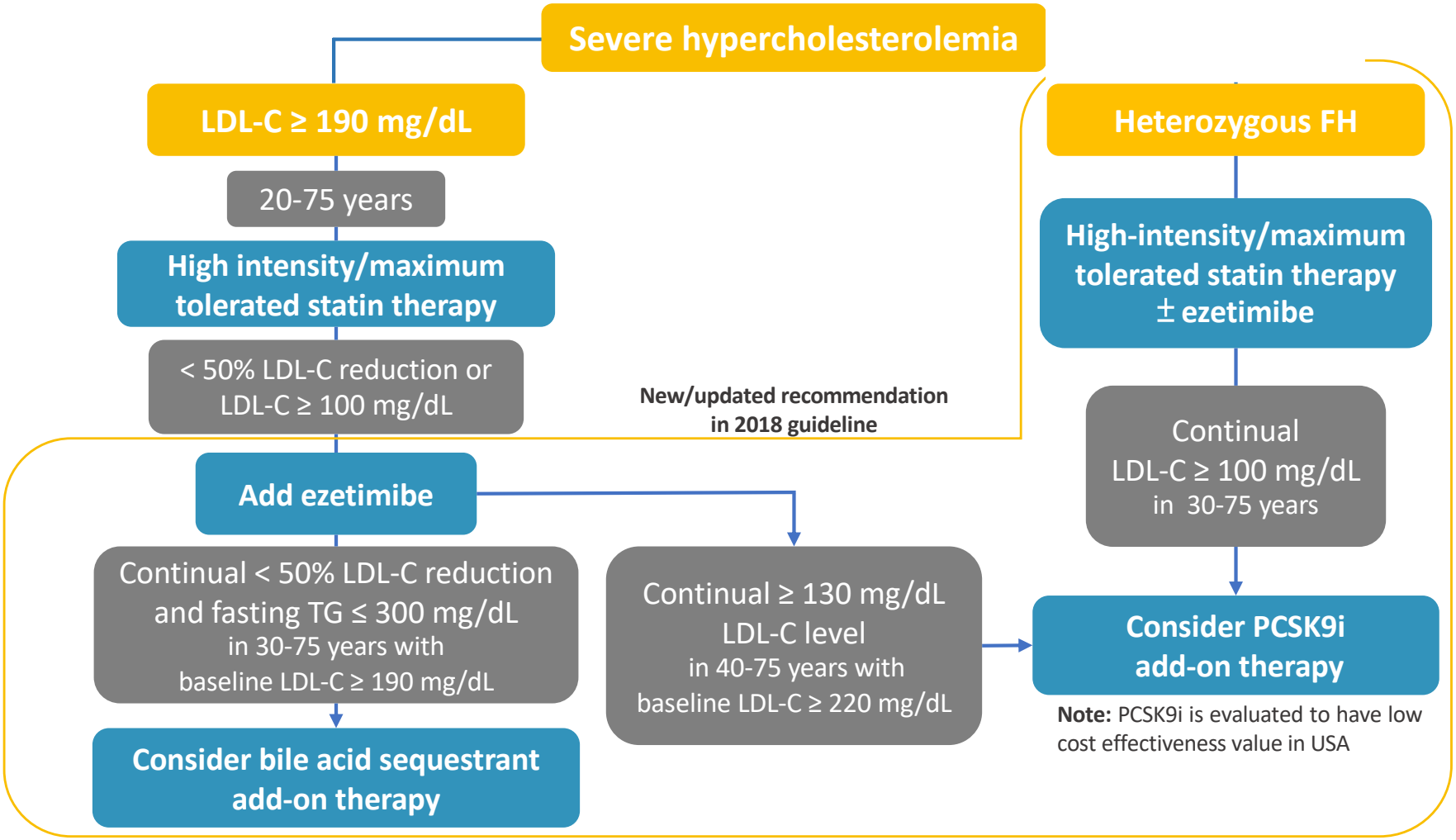
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Patients with high lifetime ASCVD risk:
Severe hypercholesterolemia

Group 2. LDL-C ≥ 190 mg/dL

New to 2018 guideline: Consider ezetimibe followed by PCSK9i add-on therapy if statin therapy not tolerated or maximum tolerated statin therapy in select patients.



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; TG, triglycerides.

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Patients with high lifetime ASCVD risk:
Diabetes Mellitus

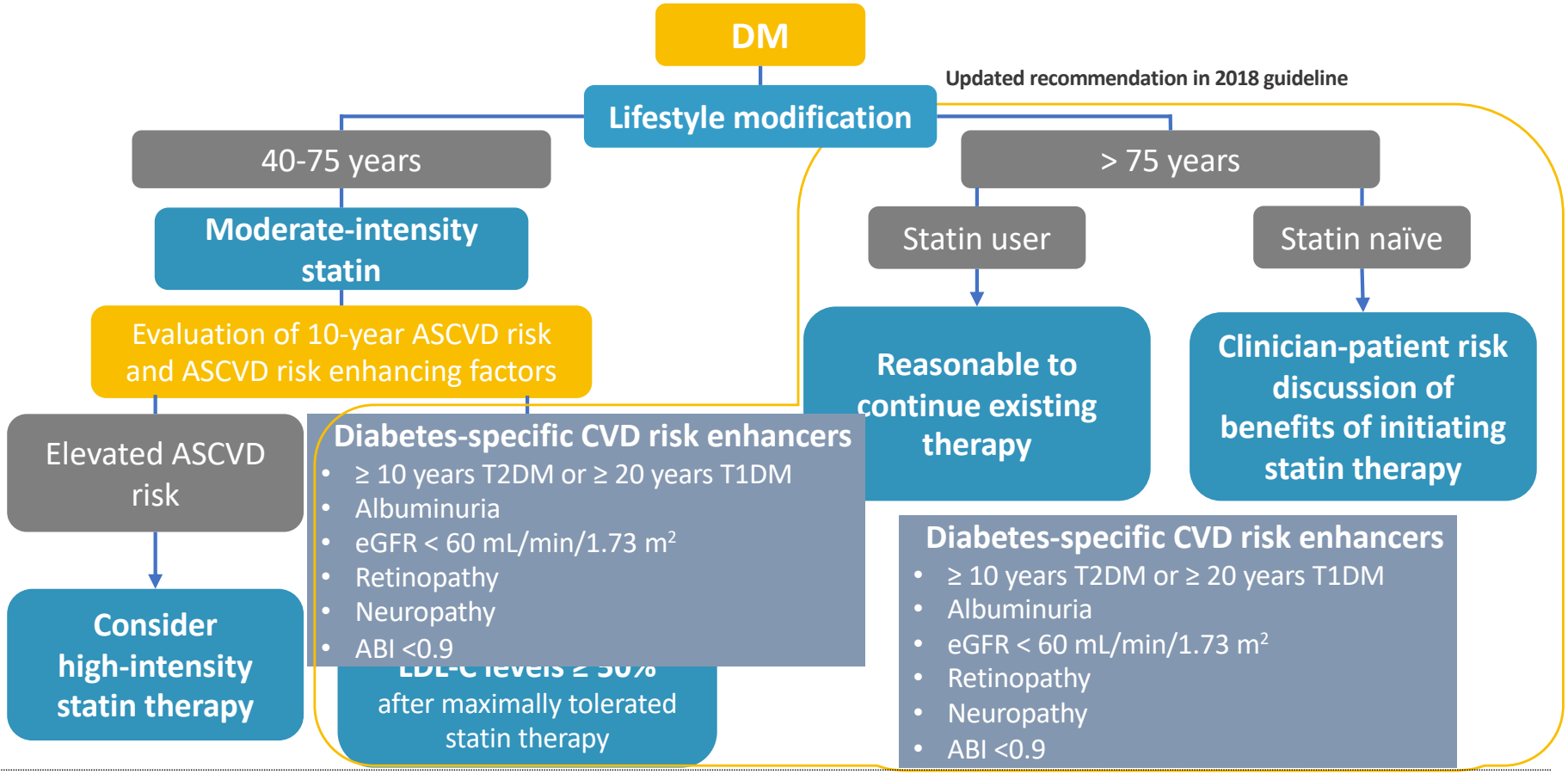
Group 3. DM

Consistent with 2013 guideline:

- Moderate-intensity statin therapy for adults of 40-75 year of ages without ASCVD risk estimation.

New to 2018 guideline:

- New statin recommendations for > 75 years of age.
- Consider ezetimibe in DM patients who fail to achieve ≥ 50% LDL-C reduction on maximally tolerated statin therapy.



Abbreviations: ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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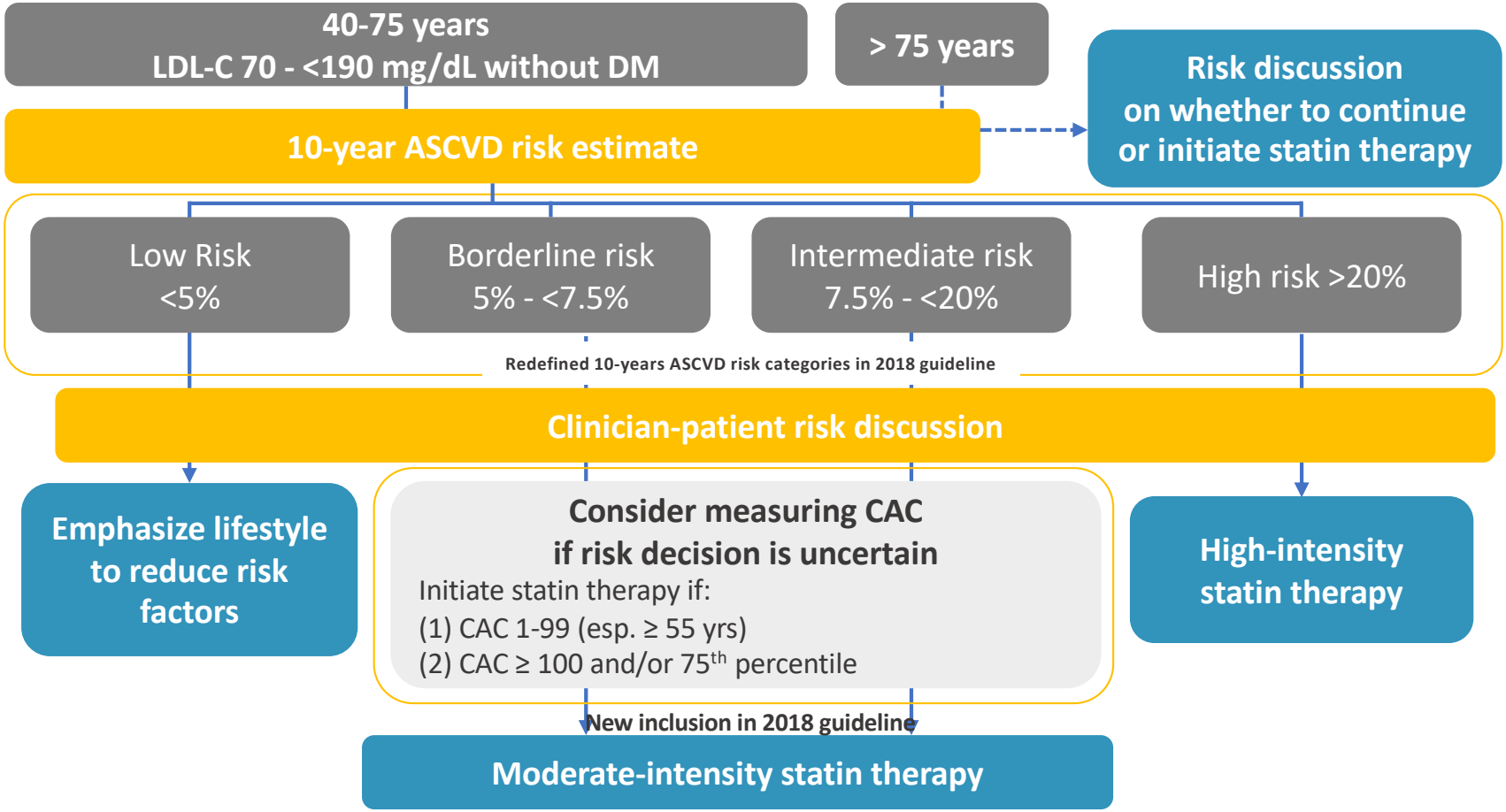
Primary prevention (I)

Group 4. Primary Prevention

New in 2018 guideline:

- 10-year ASCVD risk should be estimated using the pooled cohort equations.
- Clinician-patient risk discussion importance emphasized after ASCVD risk calculation.



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

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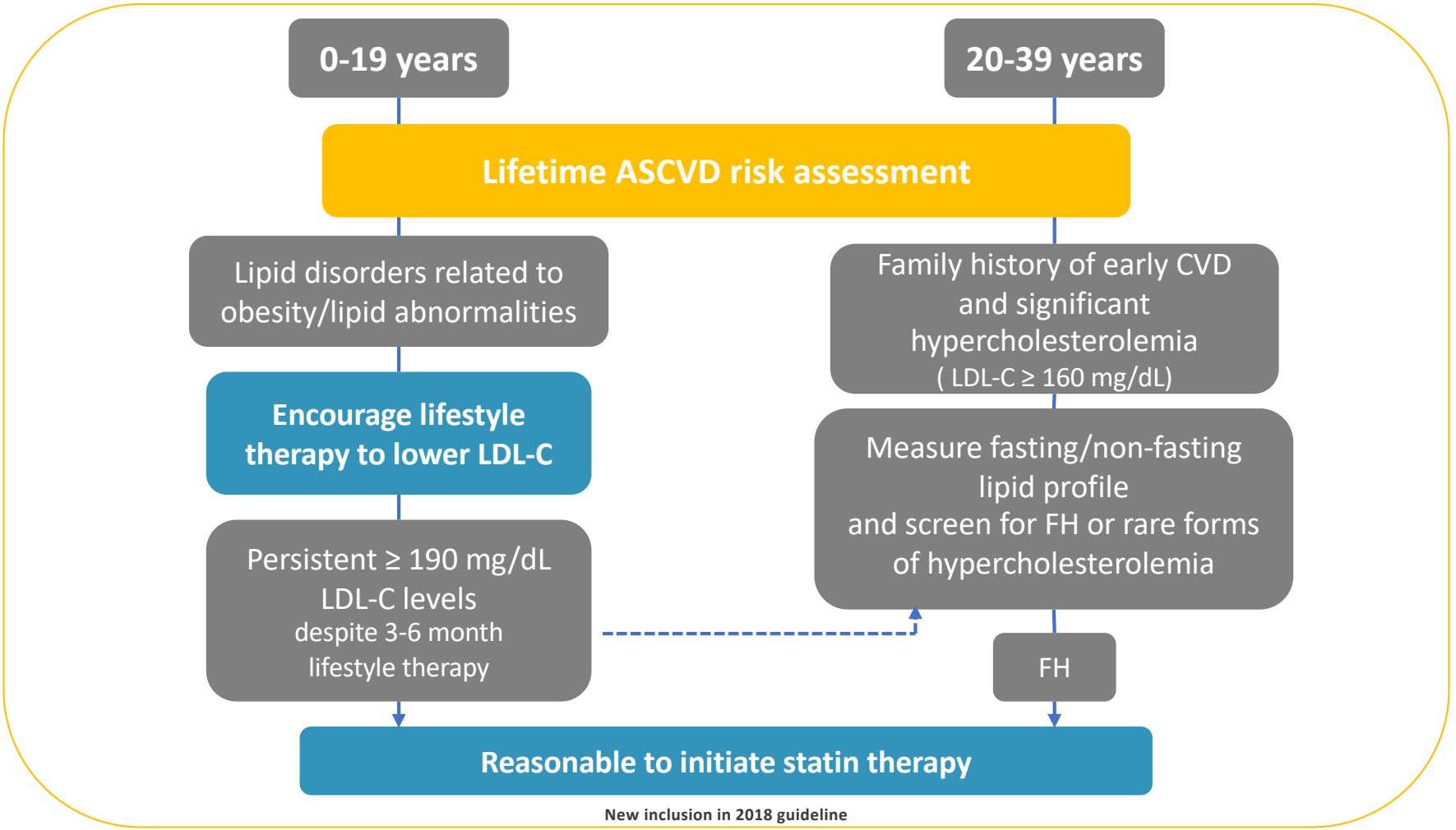
Primary prevention (II)

Group 4. Primary Prevention

New to 2018 guideline: Guidance is now provided for early ASCVD primary prevention.



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

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Risk Assessment (I)

Updated: 10-year ASCVD risk assessment should be followed by a clinician-patient discussion of the presence of risk-enhancing factor and review of racial/ethnic features to guide risk classification and treatment decisions.

Risk-Enhancing Factors

- **Family history of premature ASCVD** (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL; non–HDL-C 190–219 mg/dL)*
- **Metabolic syndrome** (increased waist circumference, elevated TG [>175 mg/dL], elevated BP, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **CKD** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (e.g., South Asian ancestry)

* Optimally, 3 determinations

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; AIDS, acquired immune deficiency syndrome; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis ; TG, triglycerides.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Risk Assessment (II)

Updated: 10-year ASCVD risk assessment should be followed by a clinician-patient discussion of the presence of risk-enhancing factor and review of racial/ethnic features to guide risk classification and treatment decisions.

Risk-Enhancing Factors

- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥ 175 mg/dL);
  - If measured.
- **Elevated hsCRP** (≥ 2.0 mg/L)
- **Elevated Lp(a):**
  - A relative indication for its measurement is family history of premature ASCVD.
  - An Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
- **Elevated apoB** ≥ 130 mg/dL: A relative indication for its measurement would be TG ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to LDL-C >160 mg/dL and constitutes a risk-enhancing factor
- **ABI** < 0.9

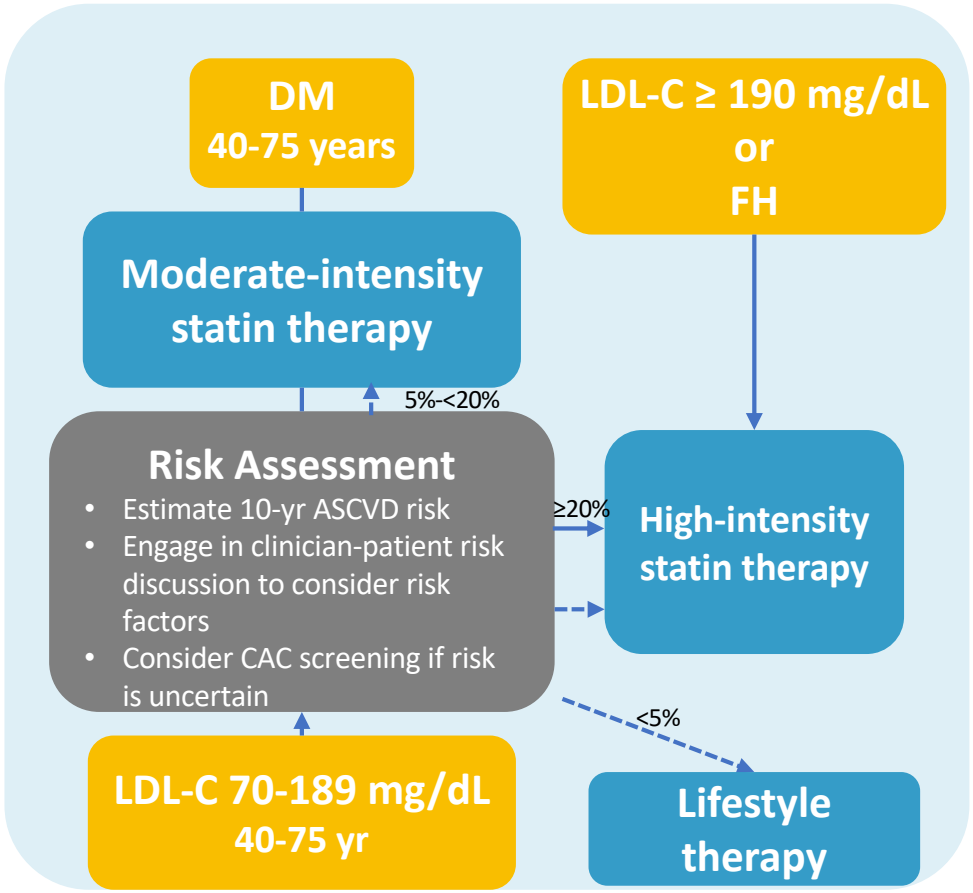
* Optimally, 3 determinations

Abbreviations: ABI, ankle-branchial index; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); hsCRP, high-sensitivity C-reactive protein; TG, triglyceride.

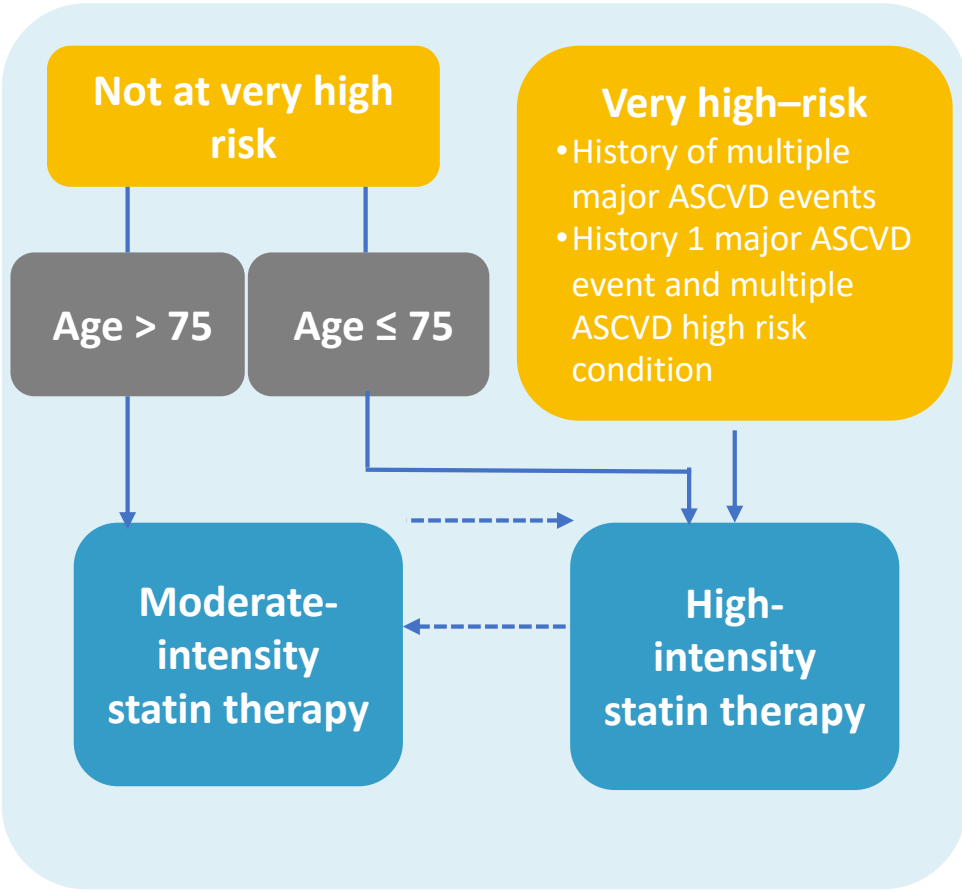
Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Treatment algorithm summary:
Use the right statin intensity for the right patients

Patients with no prior clinical ASCVD



Patients with history/current clinical ASCVD



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Treatment algorithm summary:
Add-on non-statin therapies in high-risk patients

Consider ezetimibe followed by PCSK9i add-on therapy when LDL-C reduction remains sub-optimal despite maximally tolerated statin therapy.

Ezetimibe

Clinical ASCVD patients
- **On maximally tolerated statin therapy**
- LDL-C < 50% reduction and/or
- LDL-C ≥ 100 mg/dL

LDL-C ≥ 190 mg/mL patients
- 20-75 yrs
- **On maximally tolerated statin therapy**
- LDL-C < 50% reduction and/or
- LDL-C ≥ 100 mg/dL

DM patients
- 20-75 yrs
- **On maximally tolerated statin therapy**
- LDL-C < 50% reduction and/or
- LDL-C ≥ 100 mg/dL

Primary prevention
- Evidence is not available

PCSK9i

Clinical ASCVD patients
- LDL-C ≥ 70 mg/dL

LDL-C ≥ 190 mg/mL patients

30-75 yrs with FH
- LDL-C ≥ 100 mg/dL

40-75 yrs
- LDL-C ≥ 130 mg/dL
- Baseline LDL-C ≥ 220 mg/dL

DM patients
- Evidence is not available

Primary prevention
- Evidence is not available

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

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Statins,
how safe are they?

Statin-associated side-effects

Updated in 2018 GL: The term "statin-associated side effects" is used in favor of "statin intolerance".

Statin-associated side effects	Frequency	Predisposing factors
Myalgia (CK Normal)	Clinical studies: 1-5% Observation studies/ Clinical setting: 5-10%	Age, female sex, low BMI, high-risk medications*, comorbidities#, Asian ancestry, excess alcohol, high levels of physical activity, and trauma
Myositis/myopathy (CK> ULN) with symptoms or objective weakness	Rare	-
Rhabdomyolysis	Rare	-
Statin-associated autoimmune myopathy	Rare	-
New-onset DM	Depends on population; more frequent if DM risk factors are present	DM risk factors: BMI ≥ 30, FBG ≥ 100 mg/dL; metabolic syndrome, HbA_{1c} ≥ 6%
Transaminase elevation 3 x ULN	Infrequent	-
Hepatic failure	Rare	-

*High-risk medications: CYP3A4 inhibitors, OATP1B1 inhibitors. #Comorbidities: HIV, renal, liver, thyroid, preexisting myopathy.

Abbreviations: BMI, body mass index; CK, creatine kinases; DM, diabetes mellitus; FBG, fasting blood sugar; HIV, human immunodeficiency virus; ULN, upper limit of normal.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Statin prescription considerations

Prescription considerations

Atorvastatin[1] 10-80 mg	• Generally demonstrated to have comparable efficacy and safety to placebo in clinical trials in many patient populations. • No dose relationship in non-fatal serious adverse events (all-causality and treatment-related) in atorvastatin-treated patients.
Rosuvastatin[2] 5-40 mg	• 2-fold increase in drug exposure in Asian patients. • No indication for concomitant use with bile acid sequestrants provided on the label. • Dose adjustment required in patients with severe renal impairment (CCr ≤ 30 mL/min).
Simvastatin[3] 10-40 mg	• Dose-related risk of myopathy in Chinese patients treated concurrently with niacin-containing products. • Should be administered in the evening to achieve maximum LDL-C reduction. • Dose should start at 5 mg/day in patients with severe renal impairment (CCr ≤ 30 mL/min). • Limited to 40 mg maximum dose in 2011.
Pravastatin[4] 10-80 mg	• 10 mg starting dose recommended in patients with severe renal impairment (CCr ≤ 30 mL/min).
Lovastatin[5] 40-80 mg	• Should be administered in the evening to achieve maximum LDL-C reduction. • Dose increase above 20 mg should be implemented with caution in patients with severe renal impairment (CCr ≤ 30 mL/min).
Pitavastatin[6] 1-4 mg	• Pitavastatin limited to 1 mg/daily to max 2 mg daily for patients with moderate to severe renal impairment.

Abbreviations: CCr, creatine clearance; LDL-C, low-density lipoprotein cholesterol.

1. Newman CB, et al. Am J Cardiol 2006 Jan 1.97(1):61–67
2. CRESTOR Prescribing Information. Accessed date: 13 Dec 2018
3. ZOCOR Prescribing Information. Accessed date: 13 Dec 2018
4. PRAVACHOL Prescribing Information. Accessed date: 13 Dec 2018
5. MEVACOR Prescribing Information. Accessed date: 13 Dec 2018
6. LIVALO Prescribing Information. Accessed date: 13 Dec 2018

Atorvastatin: an established safety profile across treatment groups

Group 1. Secondary prevention

- **TNT:** AEs were comparable between low and high doses of atorvastatin in patients with stable CHD and diabetes.[1]
- **SPARCL:** Rates of SAEs and discontinuation due to AEs were comparable between atorvastatin and placebo.[2]

Group 3. Diabetes

- **CARDS:** No difference in the overall frequency of AEs between atorvastatin and placebo in patients with T2DM and ≥1 risk factor.[3]

Group 4. Primary prevention

- **ASCOT-LLA**: Rates of SAEs and liver-enzyme abnormalities did not differ between the atorvastatin and placebo-treated groups.[4]
- In a retrospective analysis of pooled data from 49 clinical trials, which included patients over the age of 65, atorvastatin 80 mg had a similar safety profile to atorvastatin 10 mg.[5]

Abbreviations: AEs, adverse events; SAEs: serious adverse events; CHD, coronary heart disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; T2DM, type 2 diabetes mellitus.

1. LaRosa JC et al. Am J Cardiol 2007 Sep 1. 100(5):747–752
2. Amarenco P et al. N Engl J Med 2006 Aug 10. 355(6):549–559
3. Colhoun HM et al. Lancet 2004 Aug 21. 364(9435):685–696
4. Sever PS et al. Lancet 2003 Apr 5. 361(9364):1149–1158
5. Newman CB et al. Am J Cardiol 2006 Jan 1. 97(1):61–67

Atorvastatin in Asians

Pooled analysis of Asian data in 52 short-term and 6 long term atorvastatin clinical trails has shown:

- Incidence of all-causality AEs and SAEs are similar or lower than that observed with other statins or placebo in non-Asian patients.
- No direct relationship exist between atorvastatin dose and incidences of musculoskeletal AEs in Asians.
- Myalgia rate in Asians are low/comparable to the wider atorvastatin clinical trail population.
- Incidences of ALT or AST > 3×ULN were comparable to wider atorvastatin clinical trail population.
- No cases of rhabdomyolysis were observed among the atorvastatin-treated Asian population.

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase, SAE, serious adverse event; ULN, upper limit of normal

Chan JCN et al. Cardiovasc Ther. 2016 Dec. 34(6):431-440

Guideline comparisons

2013 ACC/AHA vs. 2018 ACC/AHA

	2013 ACC/AHA[1]	2018 ACC/AHA[2]
Statin treatment groups	1. Clinical ASCVD 2. Severe hypercholesterolemia (LDL-C ≥ 190 mg/dL) 3. Diabetes mellitus with LDL-C ≥ 70 mg/dL, 4. Age 40–75 yr with LDL-C 70–189 mg/dL and 10-y ASCVD risk ≥7.5%	**Includes additional statements for statin therapy considerations in children/adolescents** Age ≥ 10 y with persistent LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with likely FH, statin therapy is reasonable
LDL-C threshold	**No Threshold**	**LDL-C ≥ 70 mg/dL as threshold for non-statin drug considerations in ASCVD patients**
Recommendation for non-statin agents	**No non-statin agent specifically called out for use in ASCVD risk management** Non-statins recommended for individuals with higher ASCVD risk with less-than-anticipated response to statin or statin candidates who are completely statin intolerant	**Non-statin add-on recommendations after maximally tolerated statin therapy** **ASCVD not at very high risk:** *Age ≤ 75:* Add ezetimibe if LDL-C reduction < 50% or ≥70 mg/dL **At high ASCVD risk:** LDL-C reduction < 50% or ≥ 70 mg/dL, add ezetimibe LDL-C remains ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL after ezetimibe, add PCSK9i **Age 20-75 with baseline LDL-C ≥ 190 mg/dL:** Add ezetimibe if < 50% LDL-C reduction or LDL-C ≥ 100 mg/dL Add bile sequestrant if fasting TG ≤ 300 mg/dL **Age 30-75 with FH:** Add ezetimibe if < 50% LDL-C reduction or LDL-C ≥ 100 mg/dL Add PCSK9i if LDL-C remains ≥ 130 mg/dL
Risk assessment	**Uses the PCE to calculate 10-yr ASCVD risk and considers additional risk factors to assist in treatment decision** **Risk factors:** • Primary LDL–C ≥ 160 mg/dL • Family history of premature ASCVD • Hs-CRP ≥ 2 mg/L • CAC score ≥ 300 Angaston units or ≥ 75th percentile for age/sex/ethnicity • ABI < 0.9 • High lifetime risk of ASCVD	**New categorization of PCE risk scores** Low risk < 5%, Borderline risk (5% - <7.5%) Intermediate risk 7.5% - < 20% High risk (≥ 20%) **Indicates CAC testing if risk uncertain** **Emphasizes on considering ASCVD risk associated with different race/ethnicity as factors that can influence estimated ASCVD risk, intensity of treatment or even lipid drug use**

Abbreviations: ABI, ankle branchial index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCE, pooled cohort equations; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; TG, triglycerides.

1. Stone NJ, et al. J Am Coll Cardiol. 2014 Jul 7. 63:2889-934; 2. Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

2017 TLG vs. 2018 ACC/AHA

	2017 TLG[1]	2018 ACC/AHA[2]
ASCVD risk control algorithm	**"Target driven"** **LDL-C reduction to treatment targets using maximally tolerated evidence-based therapies**	**"Statin intensity driven"** **LDL-C percentage reduction using maximally tolerated evidence-based therapies**
Secondary prevention	**No DM**: LDL-C < 70 mg/dL **DM:** LDL-C < 55 mg/dL Ezetimibe + PCSK9i can be considered in ASCVD patients to reach LDL-C target	**High intensity statin therapy** **Not at very high ASCVD risk:** Age ≤ 75: Add ezetimibe if LDL-C reduction < 50% or ≥ 70 mg/dL Age > 75: Moderate-high intensity statin **At high ASCVD risk:** LDL-C reduction < 50% or ≥ 70 mg/dL; add ezetimibe LDL-C remains ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL after ezetimibe; add PCSK9i
LDL-C ≥ 190 mg/dL (including FH)	**No ASCVD:** LDL-C < 100 mg/dL (adults); LDL-C < 135 mg/dL (children) **ASCVD:** LDL < 70 mg/dL	**High-intensity statin therapy** **Add ezetimibe if < 50% LDL-C reduction or LDL-C ≥ 100 mg/dL** **Age 20-75 with baseline LDL-C ≥ 190 mg/dL:** Fasting TG ≤ 300 mg/dL; add bile acid sequestrant **Age 40-75 with baseline LDL-C ≥ 220 mg/dL:** On-treatment LDL-C ≥ 130 mg/dL; add PCSKS9i **Age 30-75 with FH:** LDL-C remains ≥ 100 mg/dL; add PCSK9i
DM	**DM:** LDL-C < 100 mg/dL **DM + ASCVD:** LDL-C < 70 mg/dL Ezetimibe + PCSK9i can be considered in DM patients to reach LDL-C target	**Moderate-intensity statin therapy** **Age 40-75:** *Multiple ASCVD risk factors*: High-intensity statin therapy *10-yr ASCVD >20%*: High-intensity statin therapy; if LDL-C reduction remains < 50%; add ezetimibe **Age > 75:** Benefit-risk discussion of statin therapy for new patients; continue for preexisting statin patients
Primary prevention	**N/A** Guideline focuses on providing guidance to patients at the highest risk of developing ASCVD	**10-yr ASCVD risk estimation using PCE followed by risk discussion;** **5% - <7.5% (borderline risk):** Moderate-intensity statin therapy risk-benefit discussion **7.5 - <20% (intermediate risk):** Moderate-intensity statin therapy risk-discussion **≥ 20% (High risk):** High-intensity statin therapy **CAC testing if risk uncertain**
CKD	GFR < 60 mL/min/1.73 m^2 and LDL-C ≥ 100 mg/dL; Initiate statin therapy	**Age 40-75 with LDL-C 70-189 mg/dL with 10-yr ASCVD risk ≥ 7.5%:** Moderate-intensity statin therapy ± ezetimibe

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; GFR, glomerular filtration rate, HDL-C; high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCE, pooled cohort equations; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; TG, triglycerides; TLG, Taiwan lipid guideline.

1. Li YH et al. J Formos Med Assoc. 2017 Apr. 116(4):217-248;2. Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

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REVIEW ARTICLE

2017 Taiwan lipid guidelines for high risk patients☆

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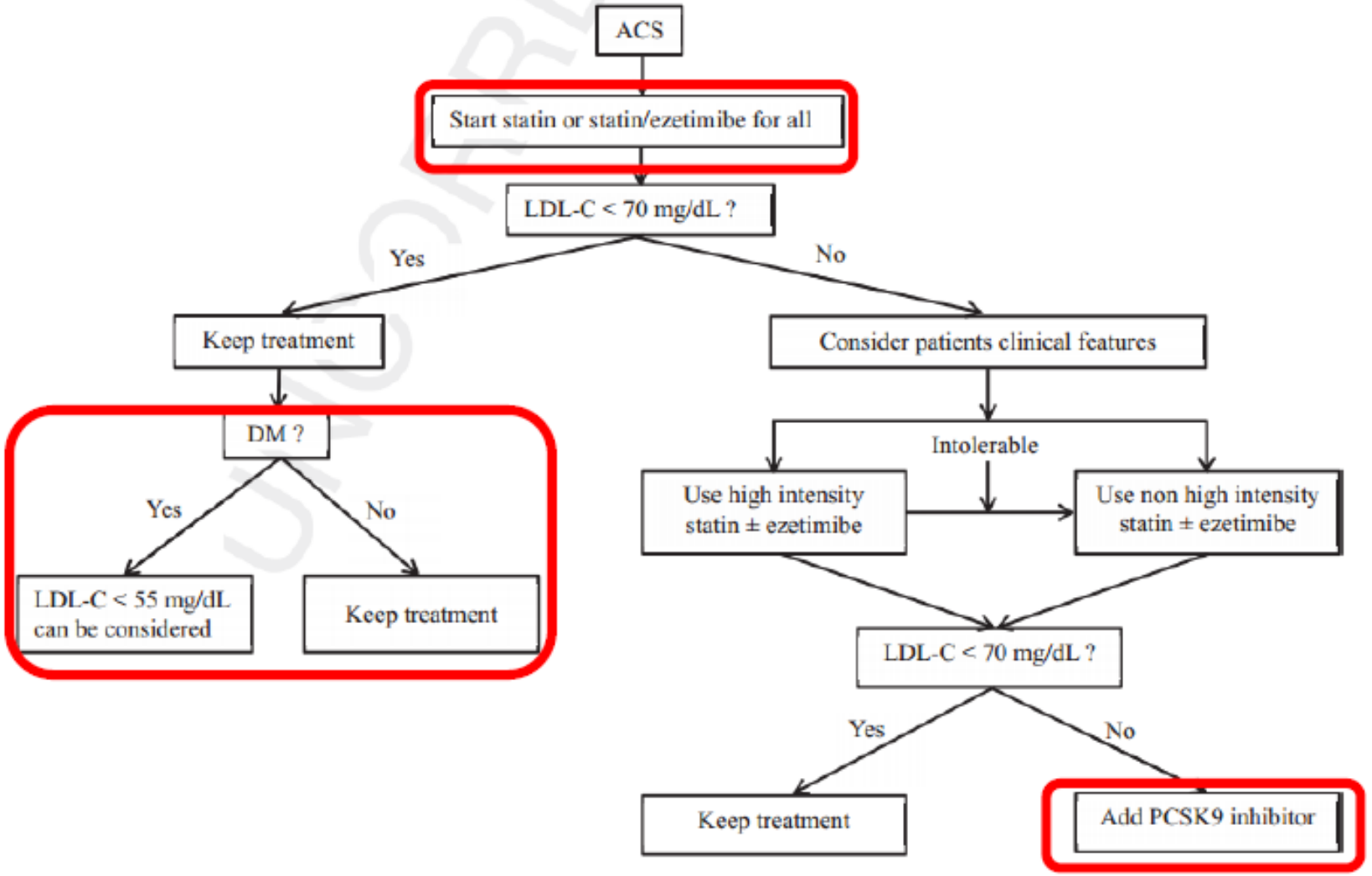
2017 Taiwan lipid guideline



Journal of the Formosan Medical Association(2017)116, 217-248

2017 Taiwan lipid guideline

Table 6 Intensity of statin therapy.

High-intensity statins daily dosage ↓ LDL-C ≥ 50%	Moderate-intensity daily statins dosage ↓ LDL-C 30% to <50%
Atorvastatin, 40–80 mg	Atorvastatin, 10–20 mg
Rosuvastatin, 20–40 mg[a]	Fluvastatin XL, 80 mg
	Lovastatin, 40 mg
	Pitavastatin, 2–4 mg
	Pravastatin, 40–80 mg
	Rosuvastatin, 5–10 mg
	Simvastatin, 20–40 mg

Rosuvastatin 40mg & is not indicated in Taiwan

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2017 Taiwan lipid guideline

Table 7 LDL-C targets in ACS, CAD, and PAD.

Disease category	LDL-C target
Primary target	
ACS	LDL-C < 70 mg/dL
ACS + DM	LDL-C < 55 mg/dL can be considered
Stable CAD	LDL < 70 mg/dL
PAD	LDL < 100 mg/dL
PAD + CAD	LDL < 70 mg/dL
Secondary target	
ACS, stable CAD, PAD with TG >200 mg/dL	Non-HDL-C < 100 mg/dL

ACS = acute coronary syndrome; CAD = coronary artery disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral arterial disease; TG = triglyceride.

Table 9 Lipid recommendations for diabetic patients.

Recommended Target	Individuals who should be targeted for lipid modification
LDL-C: - Without CVD: < 100 mg/dL - With CVD: < 70 mg/dL or 30–40% reduction	1. All diabetic patients aged ≥40 y 2. Diabetic patients aged <40 y who have overt ASCVD or ASCVD risk factors

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Summary: 2018 guideline changes

Secondary Prevention/Severe hypercholesterolemia

- Non-statin add-on therapy now recommended in very high-risk ASCVD with LDL-C ≥ 70 mg/dL as the threshold.
- Statin use is acceptable for young adults with severe hypercholesterolemia.

Diabetes

- High intensity statin therapy now indicated in patients "with multiple risk factors.
- Addition of ezetimibe now recommended in patients with 10-year ASCVD risk ≥ 20%.

Primary Prevention (40-75 y/o)

- Clinician-patient risk discussion on major risk and risk enhancing factors emphasized to help stratify patient risk and need for statin therapy.
- CAC test now recommended when ASCVD risk status is uncertain.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Grundy SM et al. J AM Coll Cardiol 2018 Nov 10. Epub ahead of print

Thanks for your attention!!