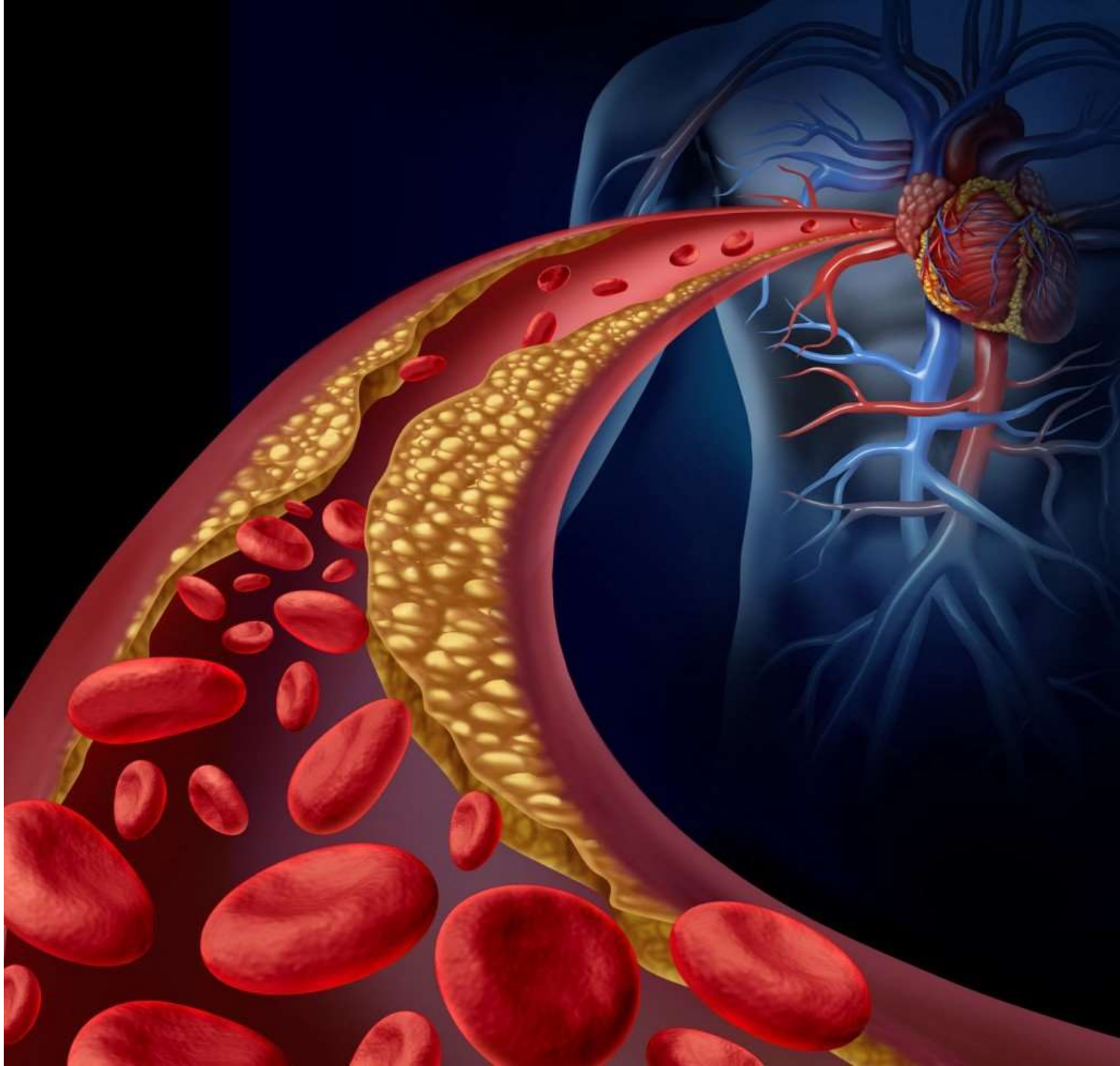
Management of Dyslipidemia:

Current paradigm and Optimizing lipid lowering therapy



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Burden of HLP

Cholesterol

The global prevalence ➡ 39%

Estimated to cause 2.6 million deaths

Major cause of ischemic heart disease & stroke

IR-1021-VLZ-6069-SP
Hypertension. 2020;75:1334–1357

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Cholesterol reduction leads to…

A 10% reduction in serum cholesterol in men aged 40:

Heart Disease 

↓ **50%**

Journey of HLP guidelines

2016 ESC/EAS
Guidelines for the management
of dyslipidemia

2019 ESC/EAS
Guidelines for the management
of dyslipidemia

2021 ESC
Guidelines on CVD
prevention

2016 2018 2019 2021

2018 ACC/AHA
Guideline on the Management
of Blood Cholesterol

Hypertension. 2020;75:1334–1357

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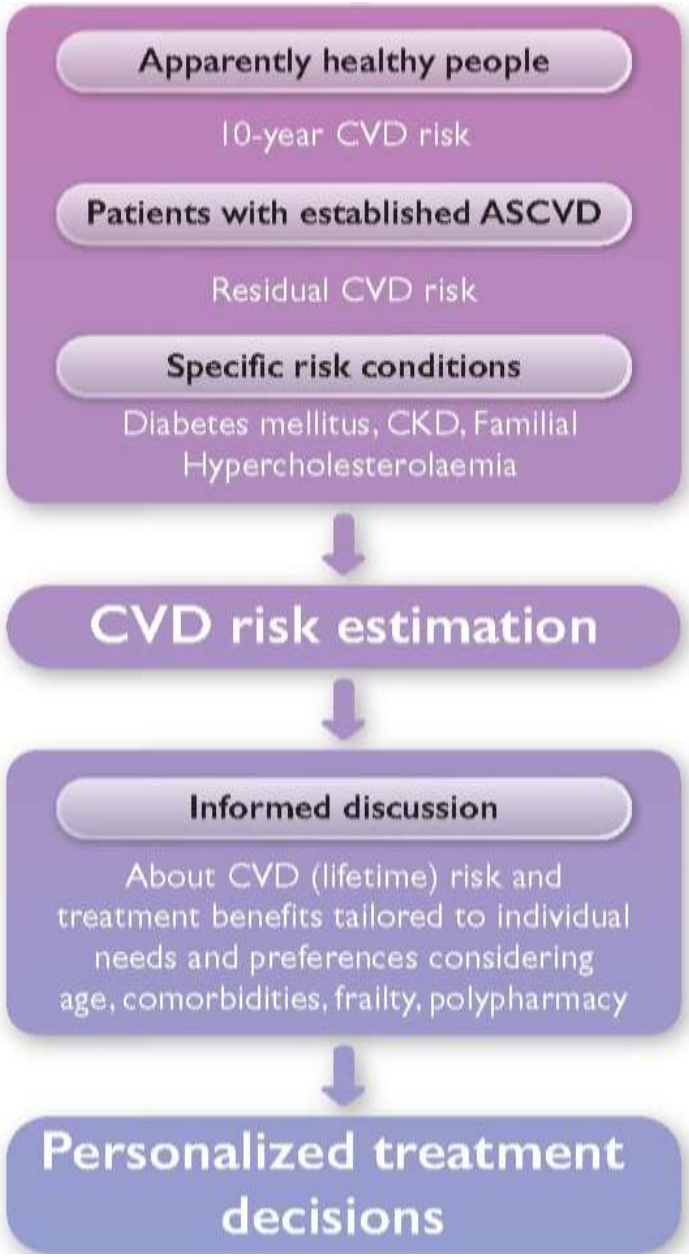
Prevention goals



Risk modifiers

- Psychosocial stress
- Ethnicity
- Imaging (e.g. coronary calcium scoring)

Comorbidity

- e.g. cancer, COPD, inflammatory disease, mental disorders, sex-specific conditions

ESC European Society of Cardiology

Eur Heart J. 2021;42(34):3227-3337.

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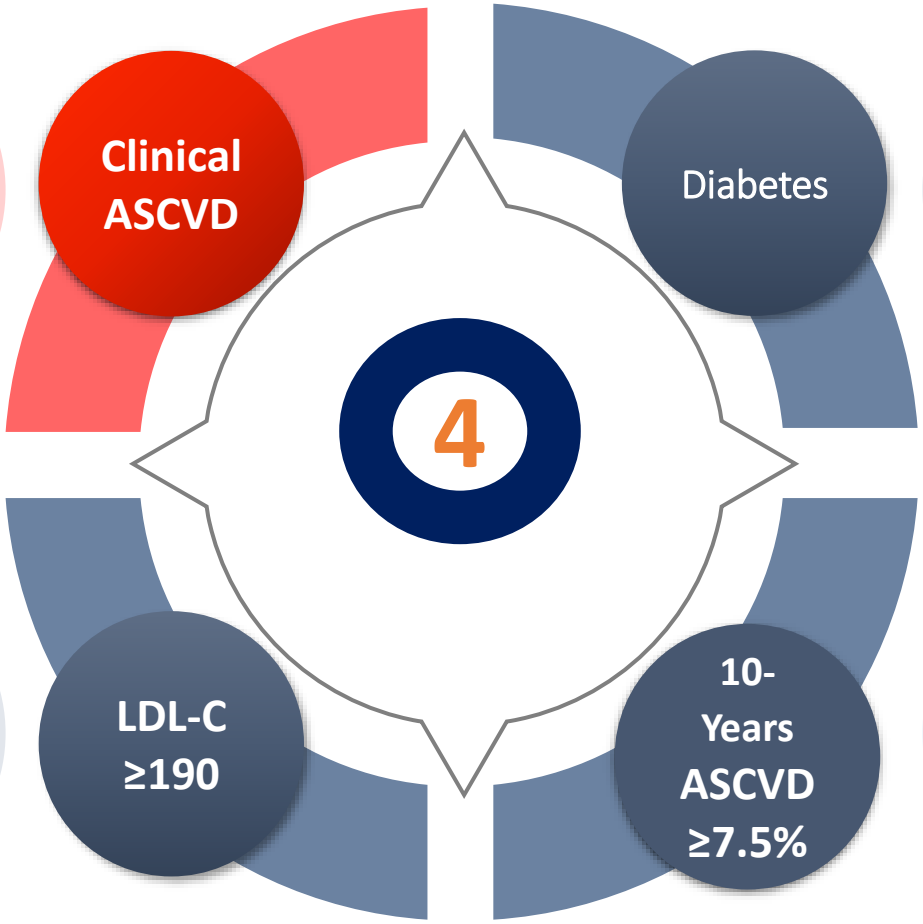
Statin Benefit Groups

Secondary Prevention
High-intensity statin therapy as first-line therapy in women and men ≤75 years of age who have clinical ASCVD.



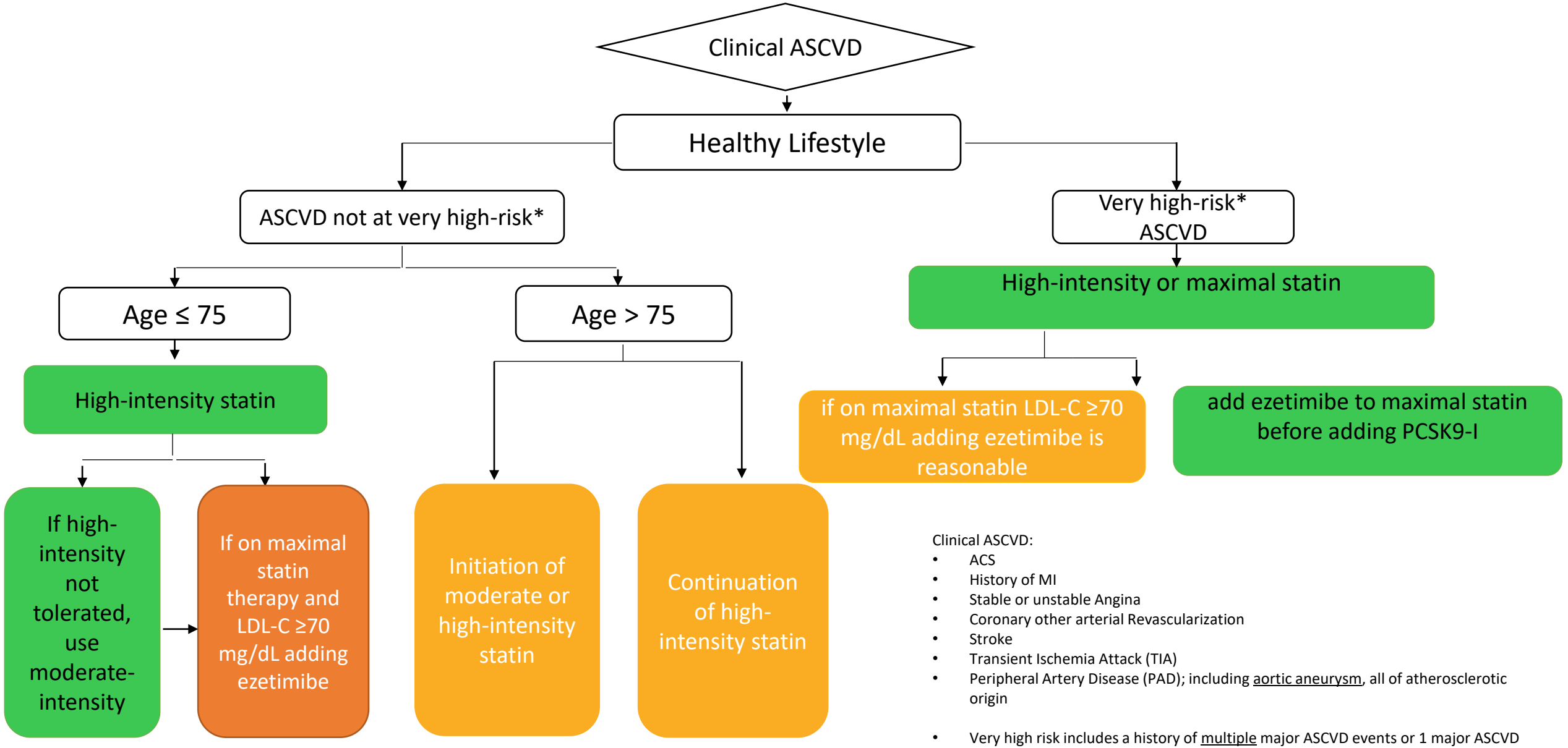
Primary Prevention
Moderate-intensity statin therapy for adults with diabetes.

Primary Prevention
Adults with LDL-C ≥190 mg/dL should be treated with statin therapy:
Use high-intensity statin therapy.

Primary Prevention
Adults with LDL-C 70–189 mg/dL with an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- intensity statin therapy.

Circulation. 2019;139(25):e1082-e1143.

The higher your risk of CVD, The more the benefits of statins



Clinical ASCVD:

- ACS
- History of MI
- Stable or unstable Angina
- Coronary other arterial Revascularization
- Stroke
- Transient Ischemia Attack (TIA)
- Peripheral Artery Disease (PAD); including aortic aneurysm, all of atherosclerotic origin

- Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high risk condition

JACC, 2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Primary Prevention of Clinical ASCVD

Primary prevention:
ASCVD risk assessment in each age group

- LDL≥190; No risk assessment; High intensity Statin
- DM and age 40-75 y: Moderate intensity Statin
- DM and age 40-75 y: risk assessment to consider high intensity Statin
- Age> 75
  Clinical assessment, Risk discussion

Age 0-19 Y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial hypercholesterolemia
→ Statin

Age 20-39 Y
Lifestyle to reduce ASCVD risk
Diagnosis of premature ASCVD and LDL≥ 160
→ Statin

Age 40-75 Y
LDL≥ 70-<190
Without DM
10-year ASCVD risk percent

- <5% "Low risk" → **Risk discussion: Emphasize Life style**
- 5%-<7.5% "Borderline risk" → **Risk discussion: If risk enhancers present Moderate intensity statin**
- ≥7.5%-<20% "Intermediate risk" → **Risk discussion: If risk enhancers present Moderate intensity statin**
- ≥ 20% "High risk" → **Risk discussion: High intensity statin**

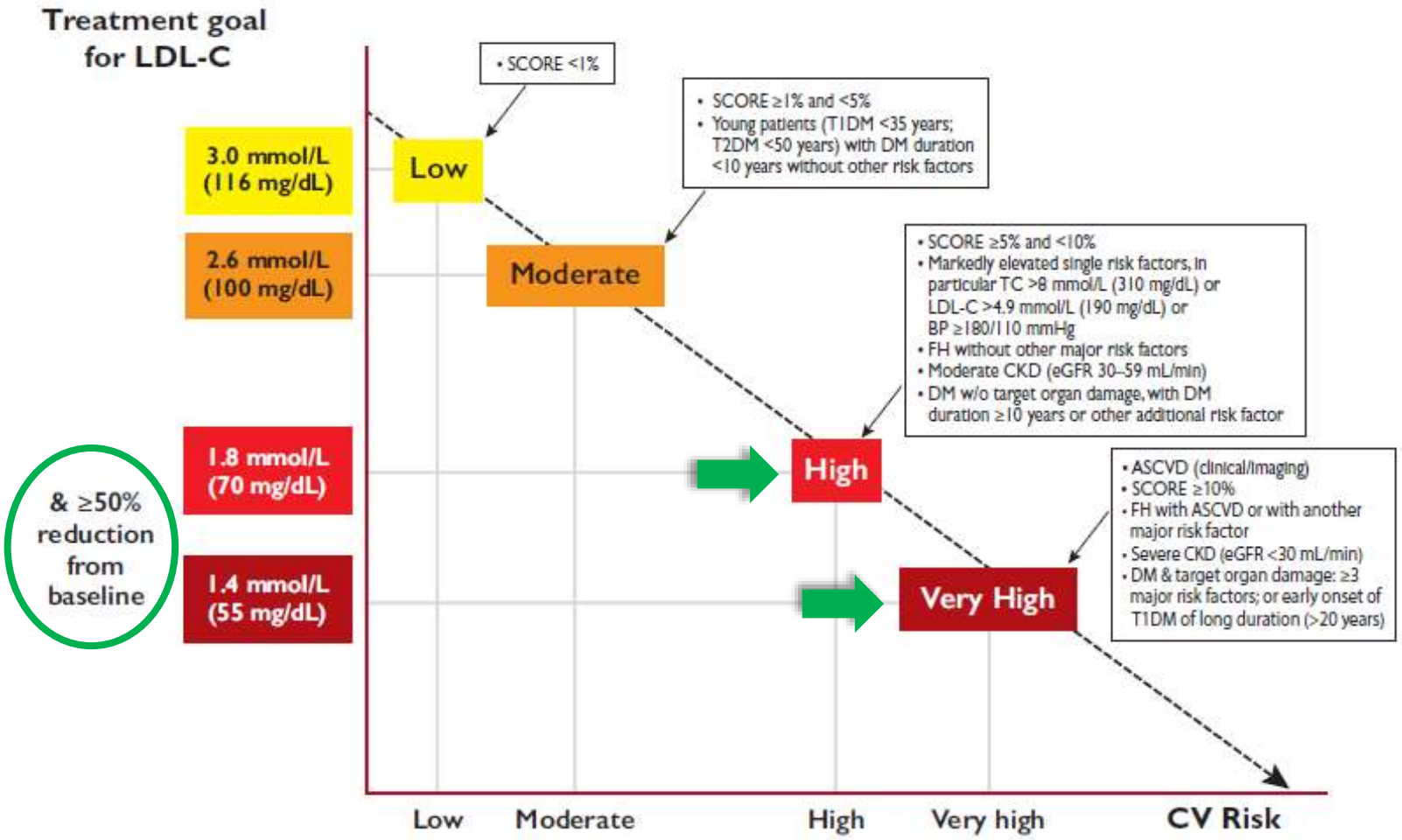
ASCVD risk enhancers:

- Family history of premature ASCVD
- Permanent LDL ≥ 160 mg/dl
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women; e.g. preeclampsia, premature menopause
- Inflammatory diseases e.g., rheumatoid arthritis, Psoriasis, HIV
- Ethnicity
- Persistent TG ≥ 175 mg/dl
- In selected individuals;
  hs-CRP ≥ 2 mg/l
  Lp(a) ≥ 50 mg/dl
  appoB ≥ 130 mg/dl
  ABI < 0.9

JACC, 2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Treatment goal for LDL-C

ESC European Society of Cardiology



IR-0122-RPX-6331-SP
Eur Heart J. 2020;41(1):111-188.

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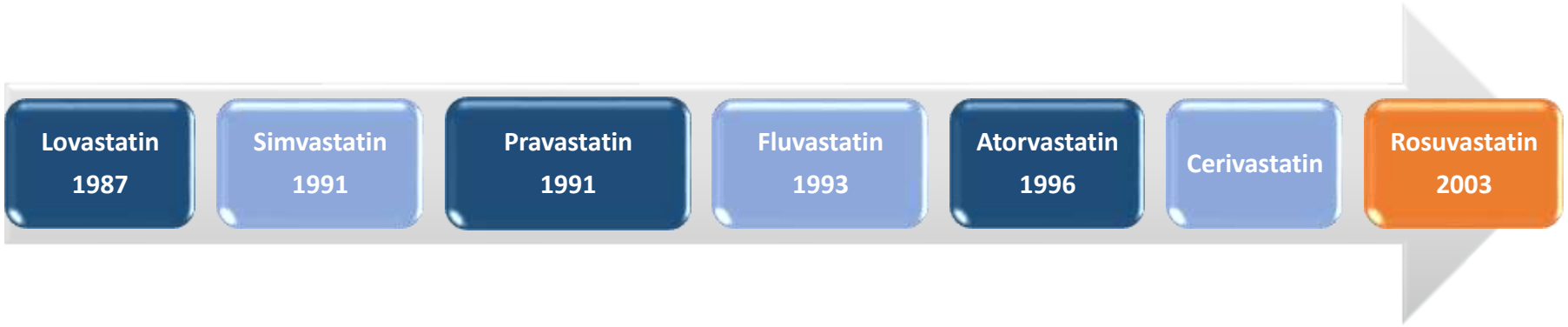
LOWER
IS
BETTER

Effects of Statins

LDL-C	Moderate intensity & High intensity 30-49% ≥50% ↓
TG	10-20% ↓
HDL-C	1-10% ↑
Major coronary events	23% ↓
Stroke	17% ↓
Total mortality	10% ↓

Eur Heart J.(2019) 00, 178.

Journey of Statins And Statin Eligibility



8%

1987

Statin eligibility

Over 50s

61%

2016

BMJ. 2019;367:l5674.

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Intensity of statin therapy

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg

IR-0122-RPX-6331-SP
Diabetes Care 2021; 44: S125-S150.

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Pharmacokinetic Parameters of Statins

- ✓ **Food intake has no effect on the bioavailability of rosuvastatin**
- ✓ **Longest activity among all statins**
- ✓ **Less drug interaction**
- ✓ **Good safety profile**

Parameters	Rosuvastatin	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Bioavailability (F), %	~10–20	12	24	< 5	17	< 5
Half-life (hours), mean	~19	14–21	< 1	3–4	1.8	3
Excretion, %						
Feces	90	> 98	90	83	70	60
Urine	10	< 2	5	10	20	13
Protein binding, %	88	≥ 90	98	95	50	95
CYP450 isoenzyme interactions	2C9, 2C19	3A4	2C9	3A4	None	3A4
Lipophilicity/hydrophilicity	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic

J Am Pharm Assoc. 2005;45:503–513.

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Monitoring in Response to LDL-C–Lowering Therapy

American College of Cardiology

American Heart Association

COR	LOE	Recommendations
I	A	1. Adherence to changes in lifestyle and effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety.

IR-0122-RPX-6331-SP
Circulation. 2019;139(25):e1082-e1143.

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 prompt 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?

• After starting treatment: 8 (±4) weeks.

• After adjustment of treatment: 8 (±4) weeks until the goal is achieved.

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

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

ACS = acute coronary syndrome

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 statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended.

ALT = alanine aminotransferase;

Monitoring liver and muscle enzymes

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

If ALT <3× ULN:

- Continue therapy.
- Recheck liver enzymes in 4-6 weeks.

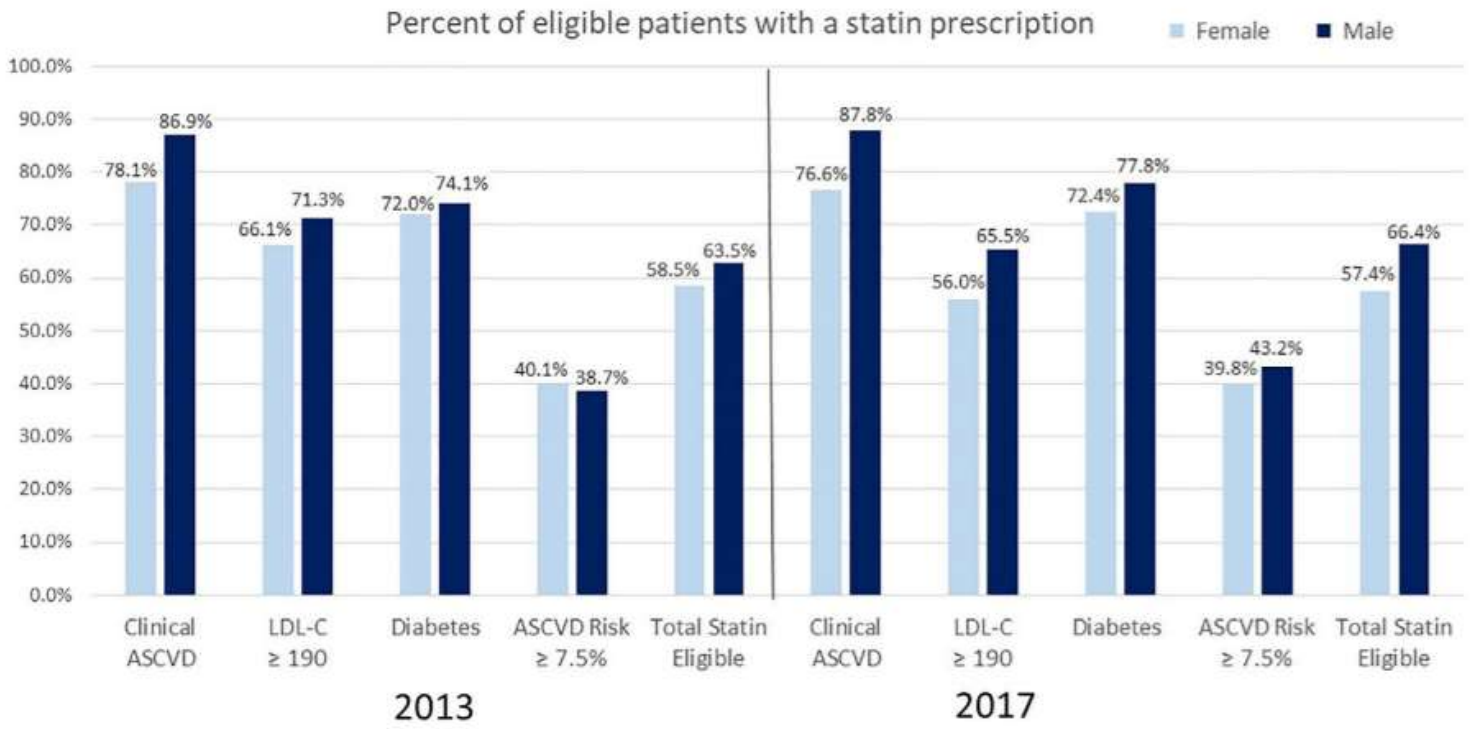
If ALT rises to >_3× ULN

- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 46 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

ALT = alanine aminotransferase; ULN = upper limit of normal.

Which Statin for Which Patient?

Statin Therapy in Statin Eligible According to Sex



In 2017, 72.8% of men were statin eligible, compared to 53.1% of women.
Of statin eligible men, 66.4% were prescribed a statin compared to 57.4% of statin eligible women (P < .001).

FIGURE 2 Statin use prevalence by ACC/AHA eligibility categories in 2013 and 2017, by sex. ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol

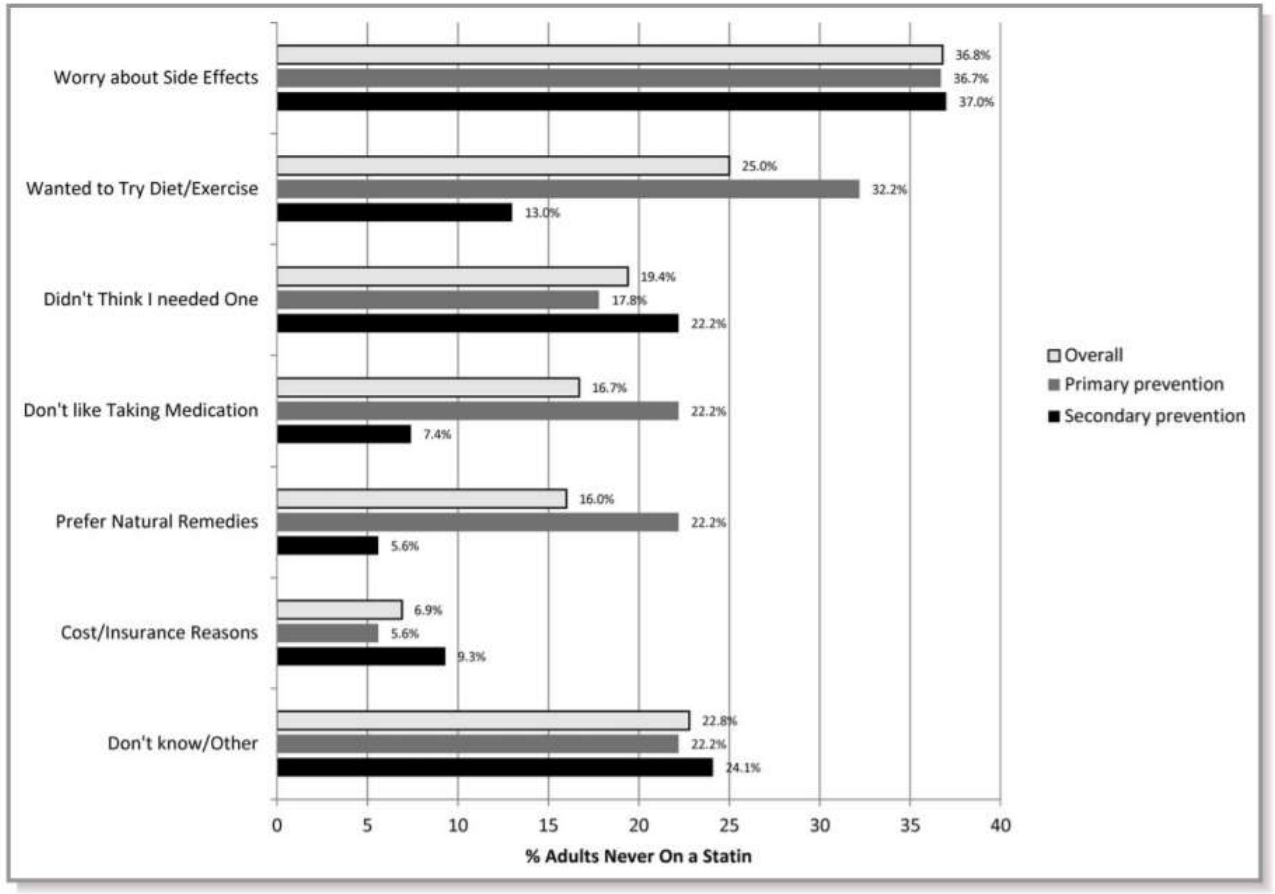
Clin Cardiol. 2020;43:560–567

Statin Therapy Remain Suboptimal

- Statin use in adults eligible by the 2013 ACC/AHA guidelines has minimally changed over time with approximately 60% of statin eligible adults prescribed a statin in 2013 and 2017.
- There was a modest increase in use of high intensity statins in 2017 compared to 2013 but still only half of patients with clinical ASCVD in 2017 were on a high intensity statin.
- For adults in 2017 with an estimated ASCVD risk >7.5% eligible for a risk-based discussion to consider statin therapy, only 42% were on a statin.
- More than half of patients eligible for statin therapy but not on treatment reported never being offered one by their doctor.

Clin Cardiol. 2020;43:560–567
J Am Heart Assoc. 2019;8:e011765

Reasons for Lack of Statin Utilization: Patient-Reported Reasons

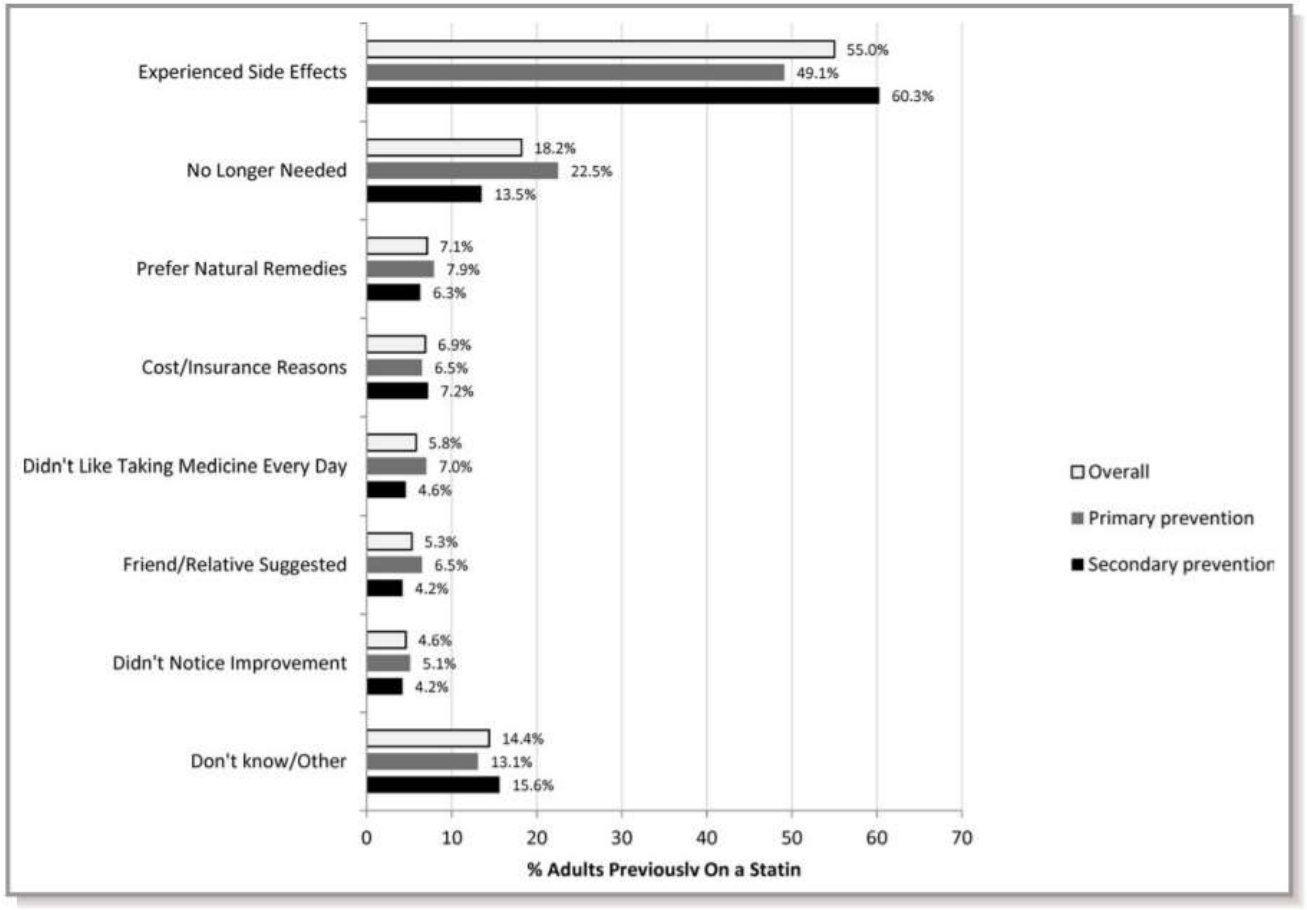


Patient-reported reasons for declining statin therapy

Among the 153 patients who declined statin therapy, fear of side effects was the most commonly cited reason (36.8% overall, 36.7% primary prevention, and 37.0% secondary prevention), followed by a preference to focus on diet or exercise (25.0%) and belief that statins were not necessary (19.4%)

J Am Heart Assoc. 2019;8:e011765

Reasons for Lack of Statin Utilization: Patient-Reported Reasons



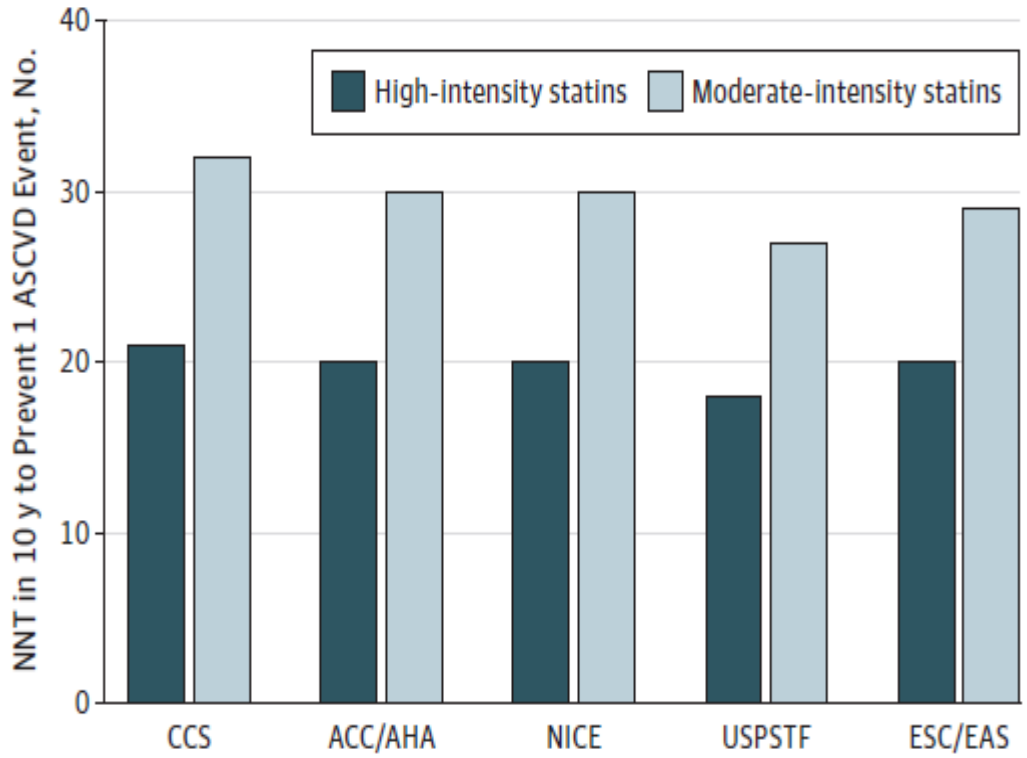
Patient-reported reasons for statin discontinuation

The most common reason patients reported for stopping statin therapy was perceived side effects (55.0%)

J Am Heart Assoc. 2019;8:e011765

Benefits of Statins outweigh the side-effects: NNT10 to prevent 1 ASCVD event during 10 years

Number Needed to Treat (NNT) to Prevent 1 Atherosclerotic Cardiovascular Disease (ASCVD) Event With the 5 Major Guidelines on Statin Use for Primary Prevention



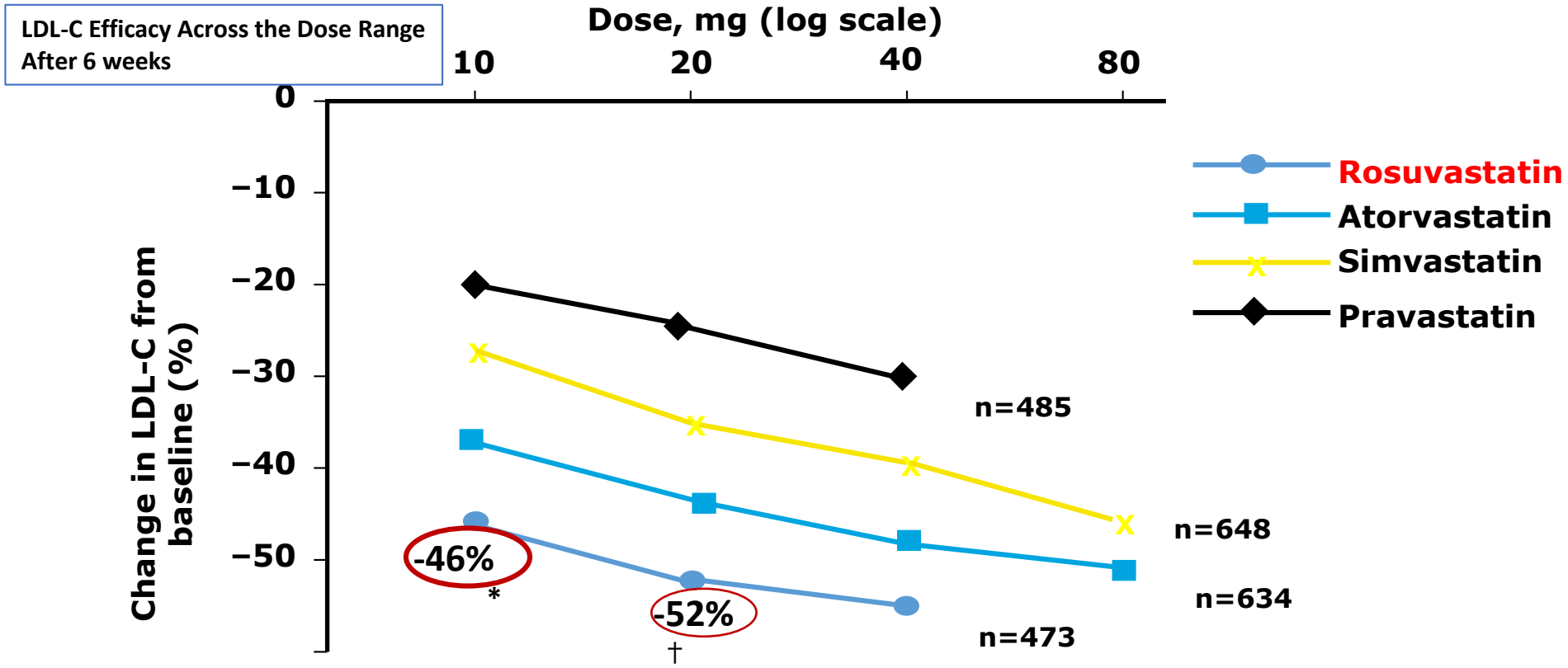
ACC indicates American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; RRR, relative risk reduction; USPSTF, US Preventive Services Task Force.

- The estimated NNT10 using high-intensity statins was 18 to 21 across the 5 guidelines.
- The corresponding numbers for the moderate-intensity statins were 27 and 32, respectively.

JAMA Cardiol. 2019;4(11):1131-1138

STELLAR Study

Different statins across dose range



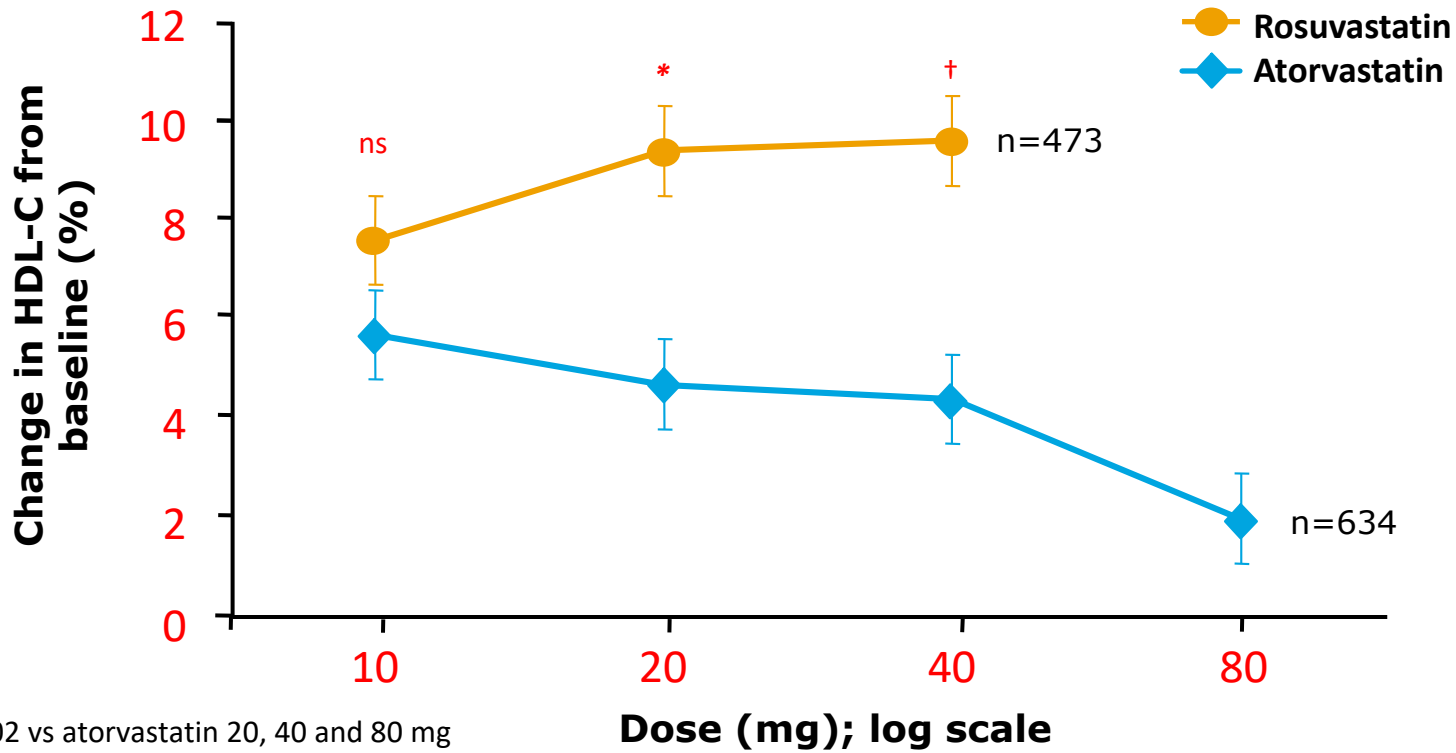
*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
†p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

Adapted from Jones PH et al. Am J Cardiol 2003;92:152–160

STELLAR Study

Different statins across dose range

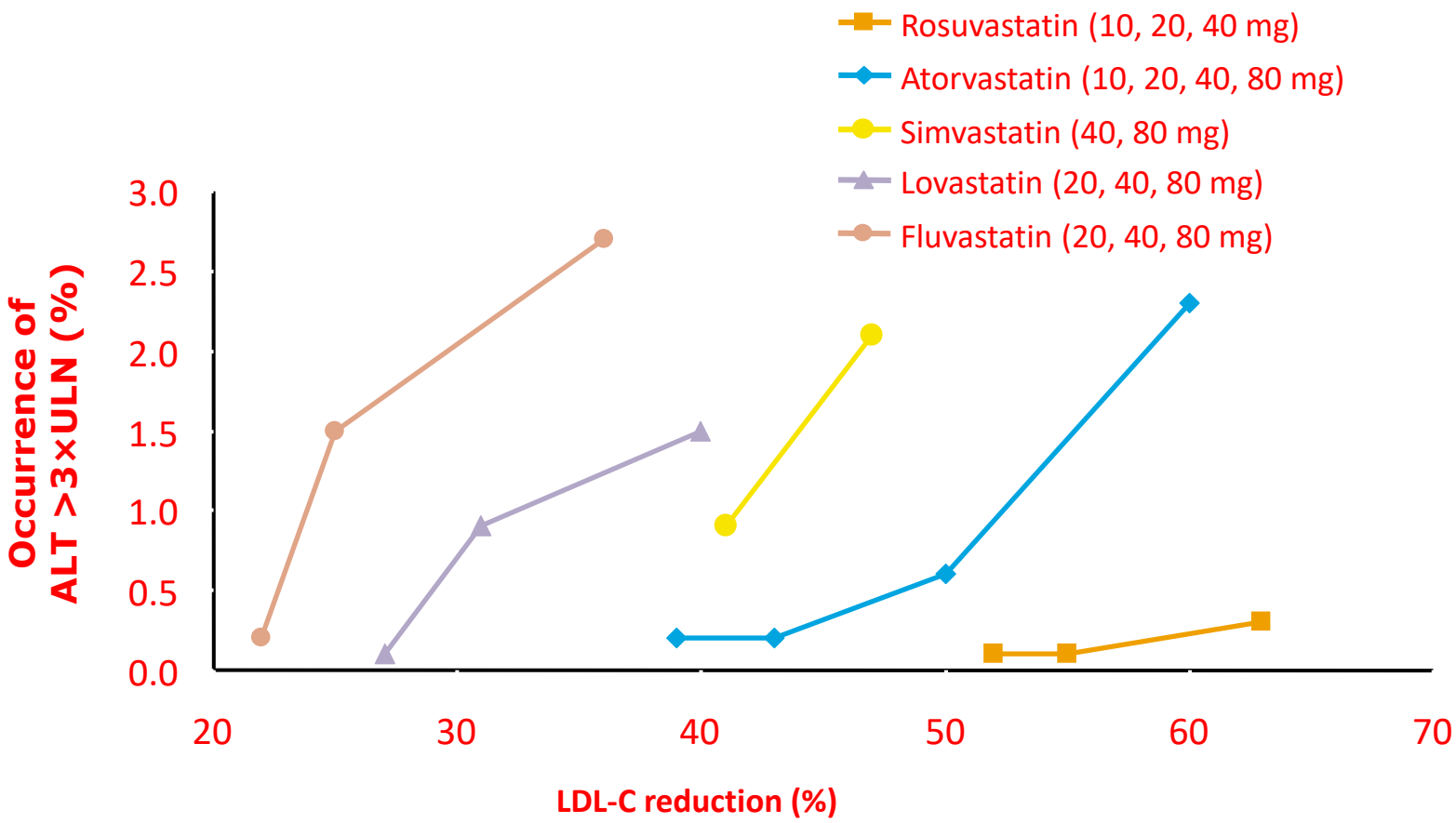
Change in HDL-C from baseline



*p<0.002 vs atorvastatin 20, 40 and 80 mg
†p<0.002 vs atorvastatin 40 and 80 mg

Adapted from Jones PH et al. Am J Cardiol 2003;92:152–160

Rosuvastatin safety Benefit:Risk
Liver effects



Persistent elevation is elevation to >3 x ULN on 2 successive occasions

Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K

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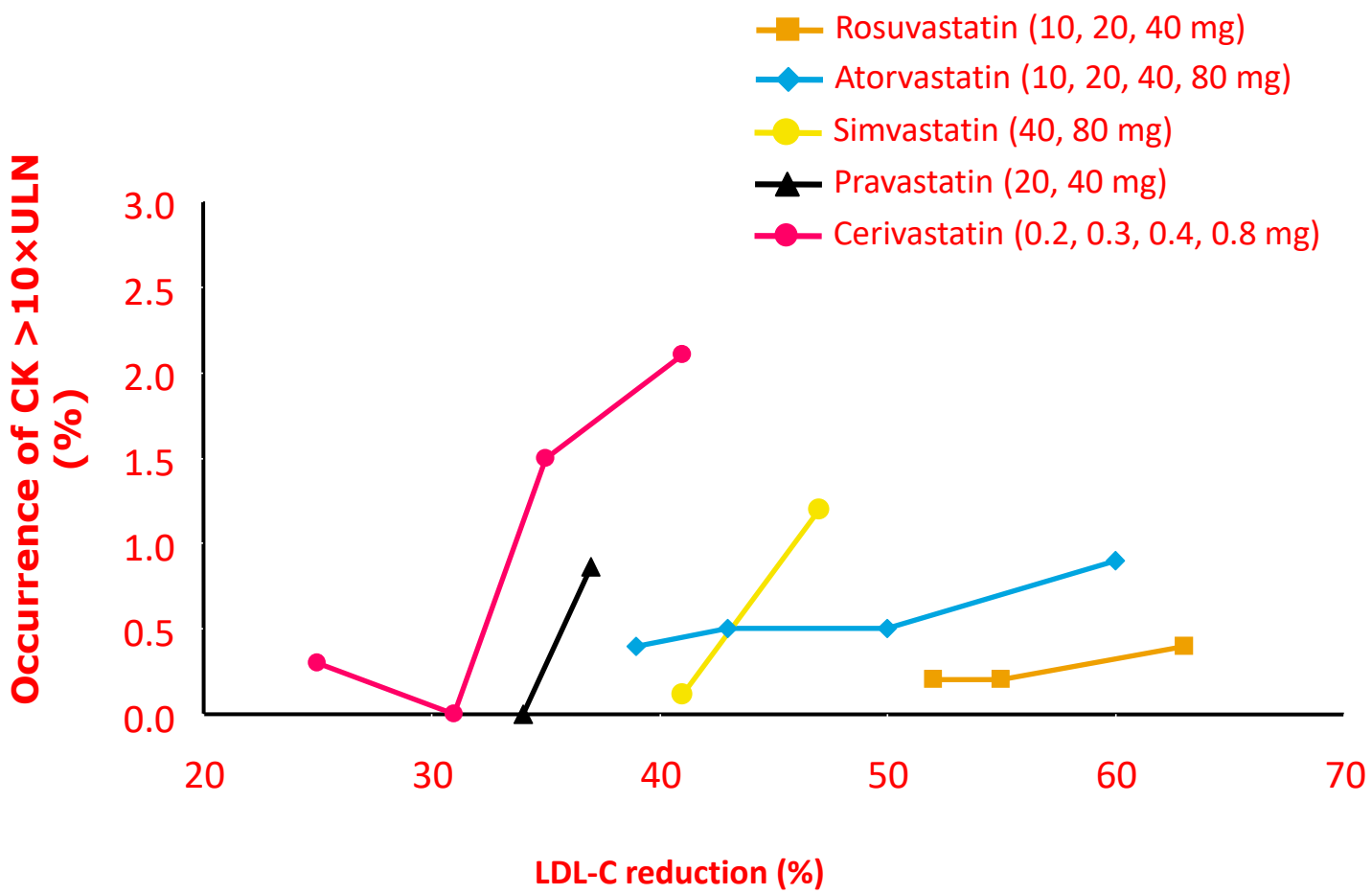
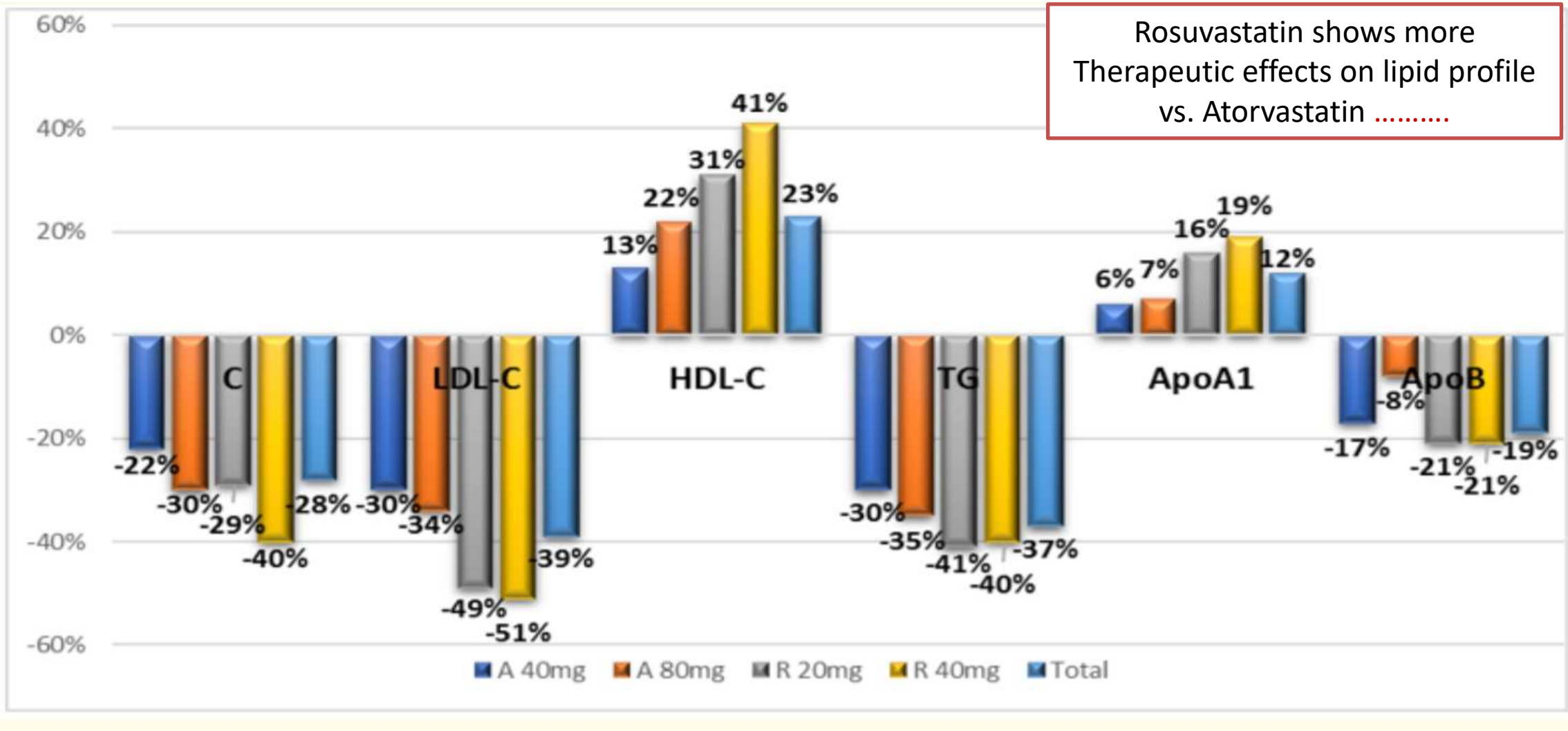
Rosuvastatin safety Benefit: Risk Muscle effects



Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K

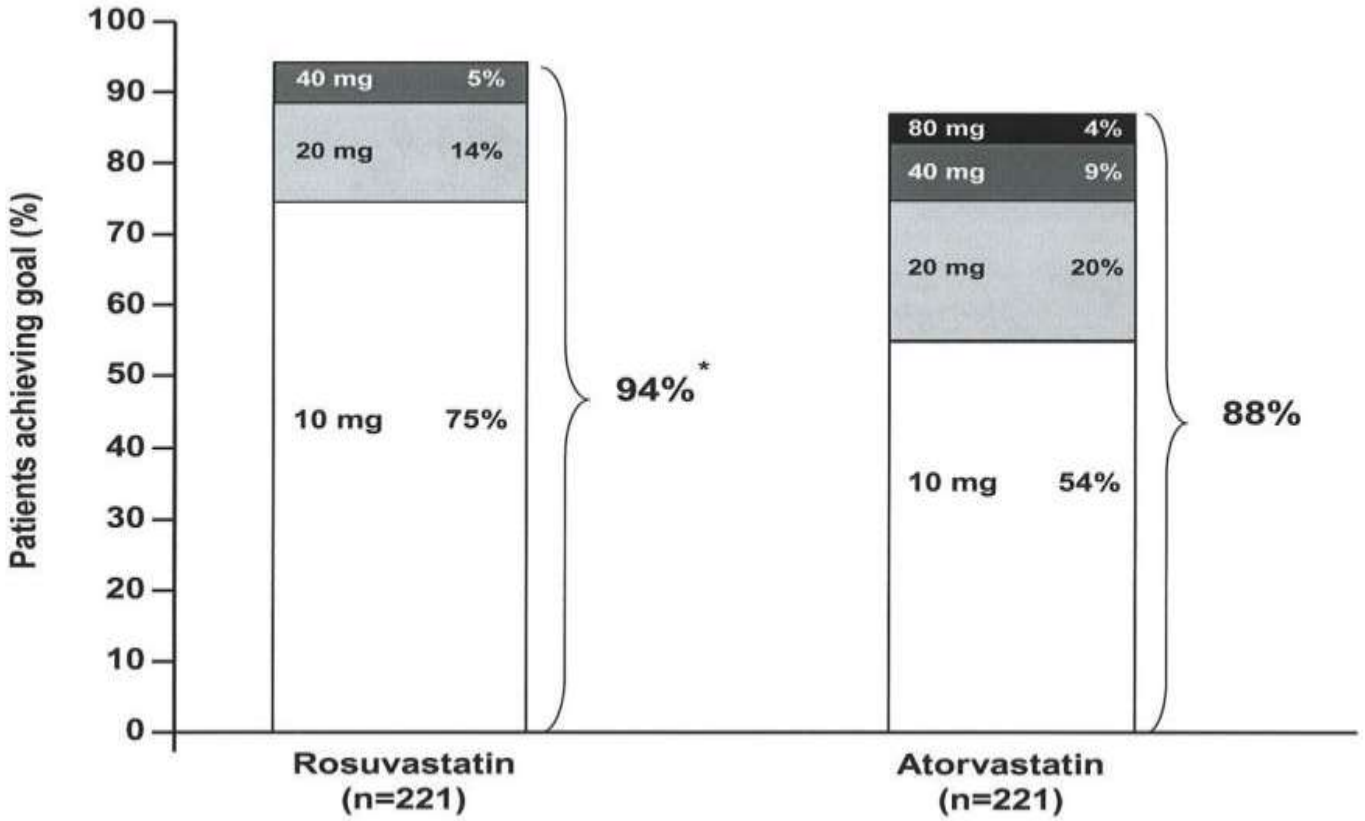
Head to Head Comparison of Efficacy and Safety of Atorvastatin and Rosuvastatin



A: Atorvastatin; Apo: Apolipoprotein; C: Cholesterol; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; R: Rosuvastatin.

EC Pharmacology and Toxicology 7.1 (2019): 46-59

Rosuvastatin vs. Atorvastatin, Achieving Lipid Goals in Diabetes



Rosuvastatin is significantly more effective than Atorvastatin in achieving LDL-C goal

RSV: Rosuvastatin, **ATV**: Atorvastatin, **LDL-C**: Low-density lipoprotein cholesterol

Clin Med Insights Cardiol. 2012;6:17-33

Comparing effectiveness of high-dose Atorvastatin and Rosuvastatin among patients undergone Percutaneous Coronary Interventions

Association of Post PTCA Statin regime (Ref: Atorvastatin 80mg) with safety and tolerability among patients receiving high-dose of two statins after undergoing Percutaneous Coronary Interventions (PCI) in a tertiary cardiac care hospital of Kolkata, 2009–2016 (N = 942).

			Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
			A_1OR (95% CI)	p value	A_2OR (95% CI)	p value	A_3OR (95% CI)	p value
Safety	Any adverse effects which needed dose reduction or discontinuation of statins (Ref = No)	Yes	2.16 (0.61–7.71)	0.2338	2.20 (0.61–7.87)	0.2274	2.07 (0.58–7.41)	0.2617
	Overall safety profile (Ref = Good)	Poor	1.27 (0.55–2.91)	0.5801	1.30 (0.56–3.02)	0.5379	1.23 (0.53–2.83)	0.6355
Tolerability	Suffered from: GERD/Gastritis (Ref = No)	Yes	2.09 (0.90–4.84)	0.0846	1.96 (0.84–4.56)	0.1171	2.16 (0.93–5.00)	0.0728
	Overall Tolerability (Ref = Good)	Poor	1.69 (0.93–3.06)	0.0869	1.63 (0.90–2.98)	0.1091	1.69 (0.93–3.07)	0.0854

Model 1 adjusted for age, gender, tobacco use and stent type.

Model 2 additionally adjusted for Comorbidity Index.

Model 3 additionally adjusted for Medication Index.

The use of high intensity rosuvastatin compared to high-intensity atorvastatin therapy in patients with ACS had resulted in comparable cardiovascular effectiveness and safety outcomes.

Curr Probl Cardiol 2021;00:100956

Prevention of Myocardial Infarction in Young Adults

One-half the patients with premature MI did not meet the criteria in current clinical practice guidelines for antecedent treatment with statin medication for primary prevention.
Younger patients, in particular, are less likely than older individuals to exhibit high-risk features for which intensive lipid lowering therapy is generally recommended, despite their high rate of ischemic events.

Better strategies for risk assessment are needed to improve primary prevention of MI in young adults.

J Am Coll Cardiol 2020;76:653–64

Balance the Benefit: Risk

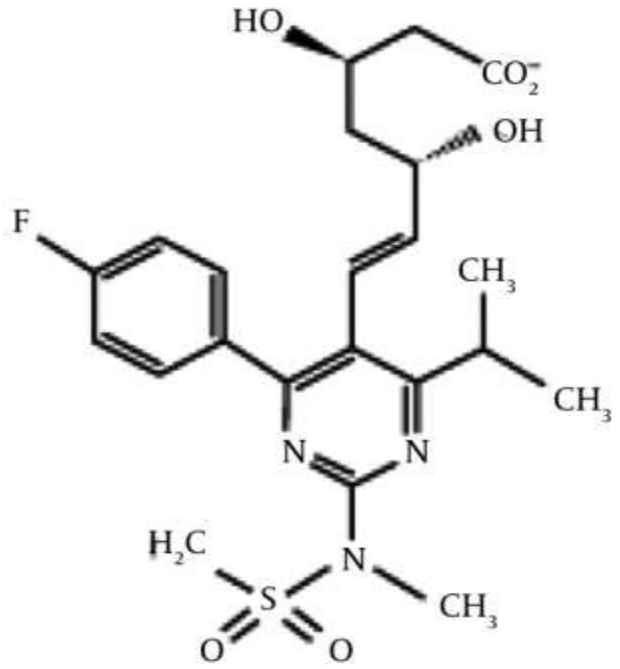
To balance the benefits and risks of statins in patients, 2 facts should be emphasized:

I. Statins with great benefits in decreasing cardiovascular and cerebrovascular events.

II. Best tolerated statins.

Int J Endocrinol Metab. 2017 April; 15(2):e43319..

Rosuvastatin



Rosuvastatin

Hydrophilic rosuvastatin has a greater efficacy on HDL-C than lipophilic simvastatin, atorvastatin and pravastatin.

HDL has antiatherogenic properties both in terms of antioxidant and cholesterol efflux capacities.

Drug	*Approximate Potency (% LDL lowering)*[3]			
• **Atorvastatin**	10 mg (35-39%)	20 mg (43%)	40 mg (50%)	80 mg (55-60%)
• **Rosuvastatin**	5 mg (45%)	5 mg (45%)	10 mg (46-49%)	20 mg (50-55%) 40 mg (55-63%)

Int J Endocrinol Metab. 2017 April; 15(2):e43319

Are All Statins the Same?

- ✓ **With Rosuvastatin, along with LDL-C decrease, HDL-C increases across the dose range, unlike atorvastatin.**
- ✓ **As the doses of rosuvastatin, simvastatin and pravastatin increased, HDL-C also increased, with rosuvastatin having the greatest effect.**
- ✓ **Rosuvastatin hydrophilic nature helps to eliminate the dependence on metabolic conversion to a water-soluble molecule, especially in the presence of other drugs.**
- ✓ **Rosuvastatin has low potential for significant drug–drug interactions.**

Int J Endocrinol Metab. 2017 April; 15(2):e43319..

Thank You For Your Attention

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