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Review current guideline recommendations for lipid-lowering therapy

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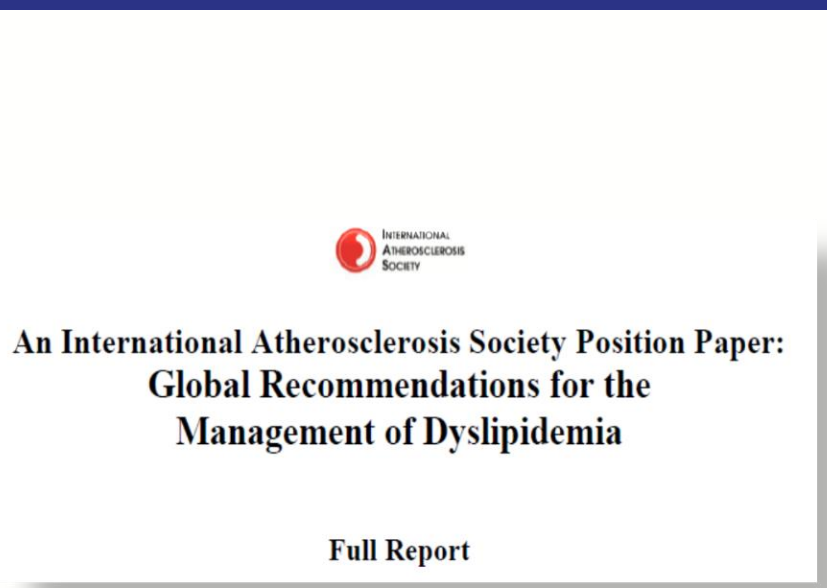
Disclosure potential conflicts of interest

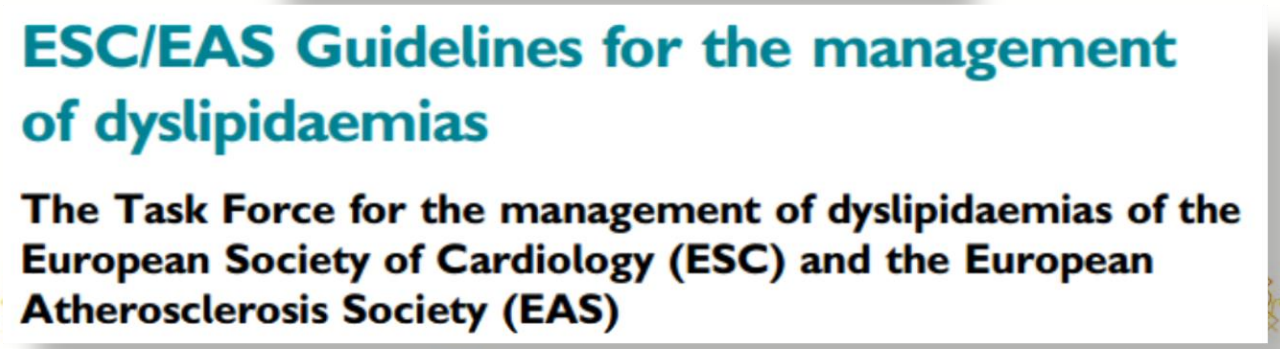
Consulting, Research contracts (2014-2017)

Abbot, Aegerion, Amgen, Genzyme, MSD, Mylan, Pfizer, Sanofi, Sanovel, Shire

Current Guidelines for Cholesterol Treatment



- ACCE
- US Preventive Task Force
- Canadian
- British/NICE

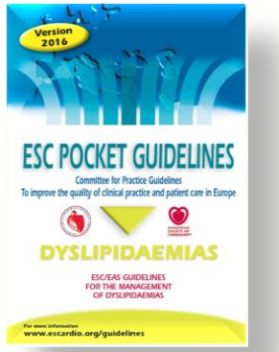


	Age	Gender	Smoking	HT	T Cholest	HDL Chol	DM	Race	Family hist T	Ch/HDL hsCRP	CACs	CKD	RA	Atrial fib	BMI
FGR	+	+	+	+	+	+	+								
PCE	+	+	+	+	+	+	+	+							
Reynolds	+	+	+	+	+	+			+	+					
MESA	+	+	+	+	+	+	+	+	+		+				
QRISK	+	+	+	+			+	+		+		+	+	+	+
SCORE	+	+	+	+	+										

FGR: Framingham Global Risk;
PCE: Pooled cohort equation;
MESA: Multi-Ethnic Study of Atherosclerosis;

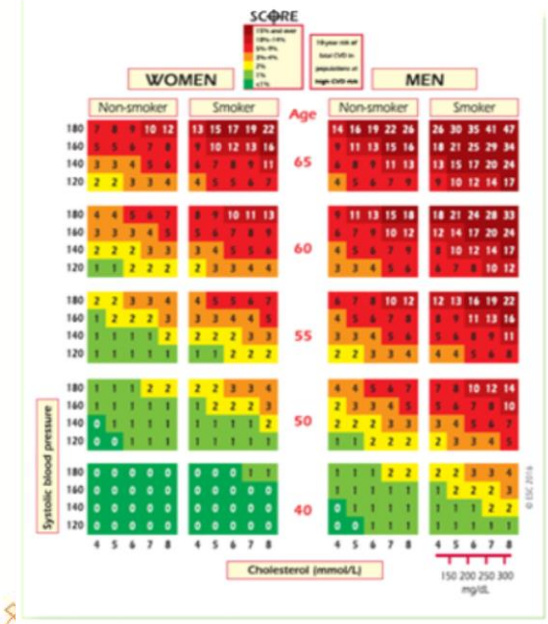
Score risk estimation

10 years CV mortality

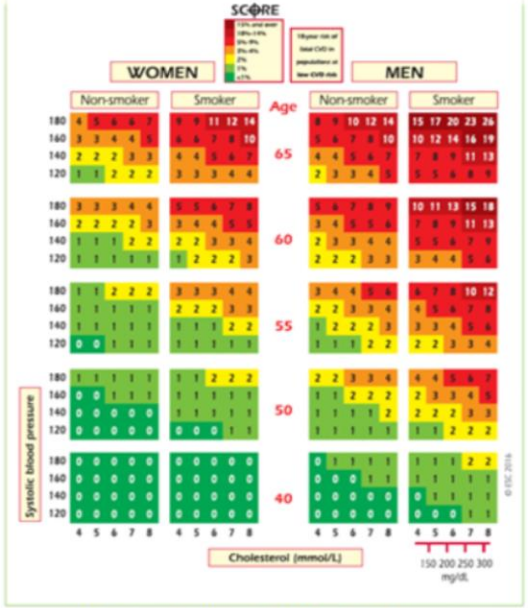


5 parameters:
Age, Gender, total Cholesterol, Systolic BP, and Smoking

SCORE charts: high vs. low CVD risk countries

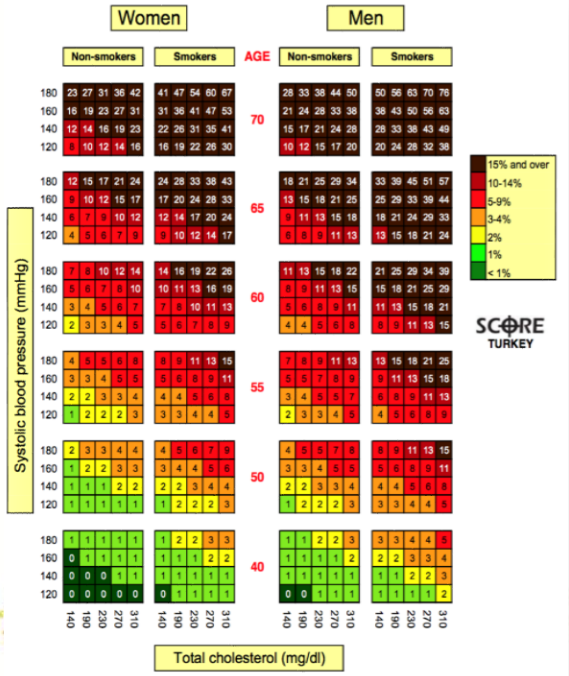


(CVD mortality > 450/100 000 in men and < 350/100 000 in women)

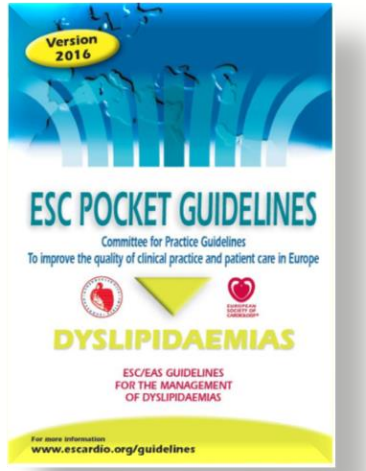


(CVD mortality < 225/100 000 in men and <175/100 000 in women)

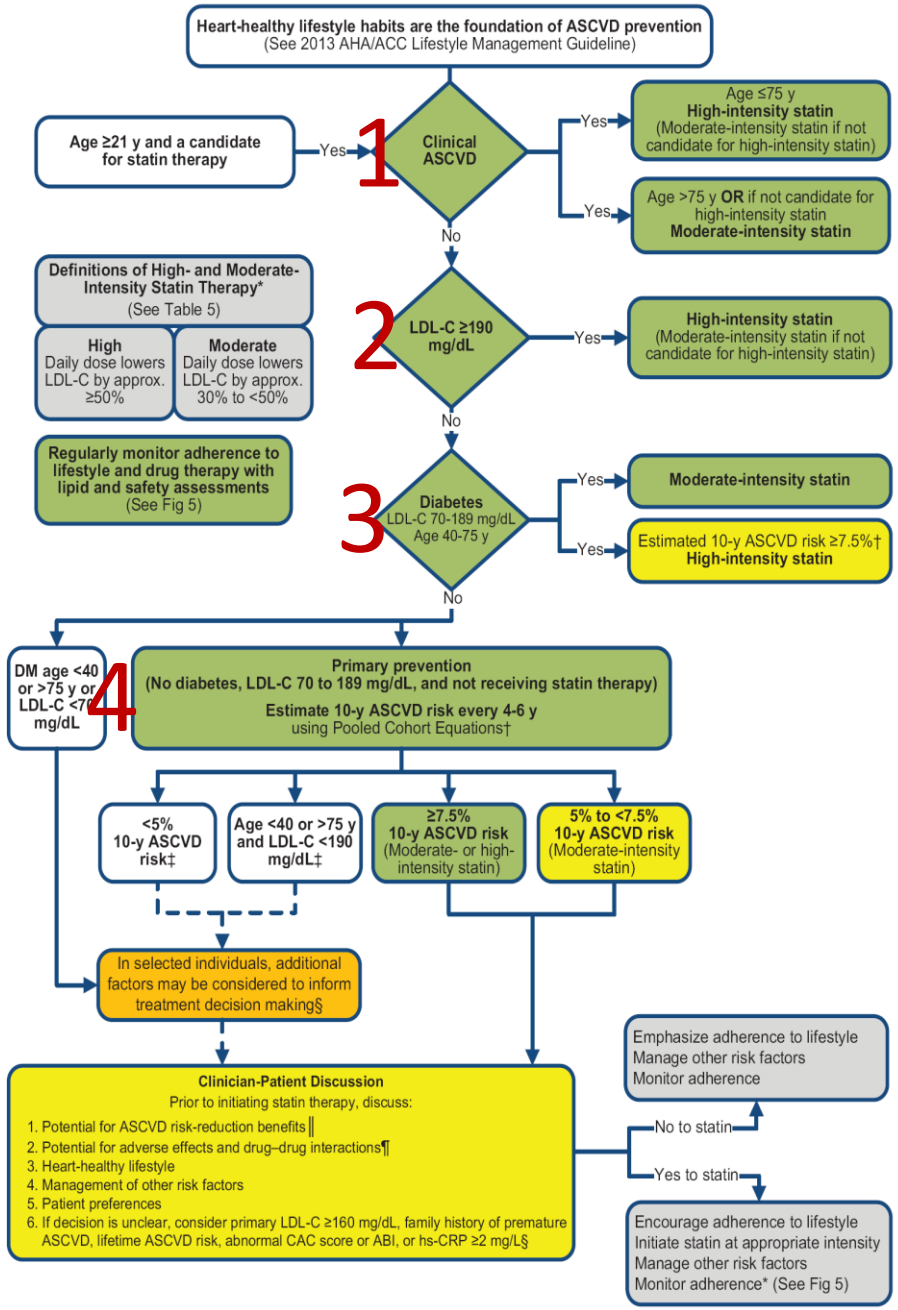
Piepoli et al. Joint ESC guidelines 2016. *Eur Heart J* 2016)



ESC – EAS
Dyslipidaemia Guidelines 2016



- Maintain global CV risk assessment by the SCORE
- Keep treatment targets
- Proposal of a treatment scheme
- New recommendation for non-statin treatments and drug combinations
- Recommendations for PCSK-9 inhibitors



2013 ACC/AHA guidelines

Groups most likely to benefit from statin therapy are identified:

1. Patients with any form of clinical ASCVD
2. Patients with primary LDL-C levels of 190 mg per dL or greater
3. Patients with diabetes mellitus, 40 to 75 years of age, with LDL-C levels of 70 to 189 mg per dL
4. Patients without diabetes, 40 to 75 years of age, with an estimated 10-year ASCVD risk ≥ 7.5%

OPEN

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

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	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

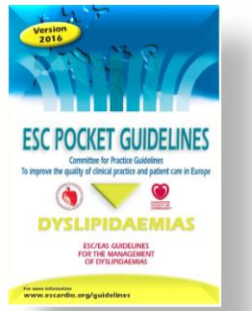
Case

- **55 y/o male** with **CAD**
- Recent PCI after an ACS
- Family history of CAD,
- No other risk factors

Total Cholesterol	290 mg/dl	7.5 mmol/l
TG	80 mg/dl	0.9 mmol/l
HDL-C	47 mg/dl	1.2 mmol/l
LDL-C	**203 mg/dl**	**5.3 mmol/l**

- **What should be the treatment decision?**

1. **Identify the LDL-C goal for that risk level**
2. **Calculate % of LDL-C reduction required to achieve that goal**
3. **Choose a statin and a dose that could provide this reduction**

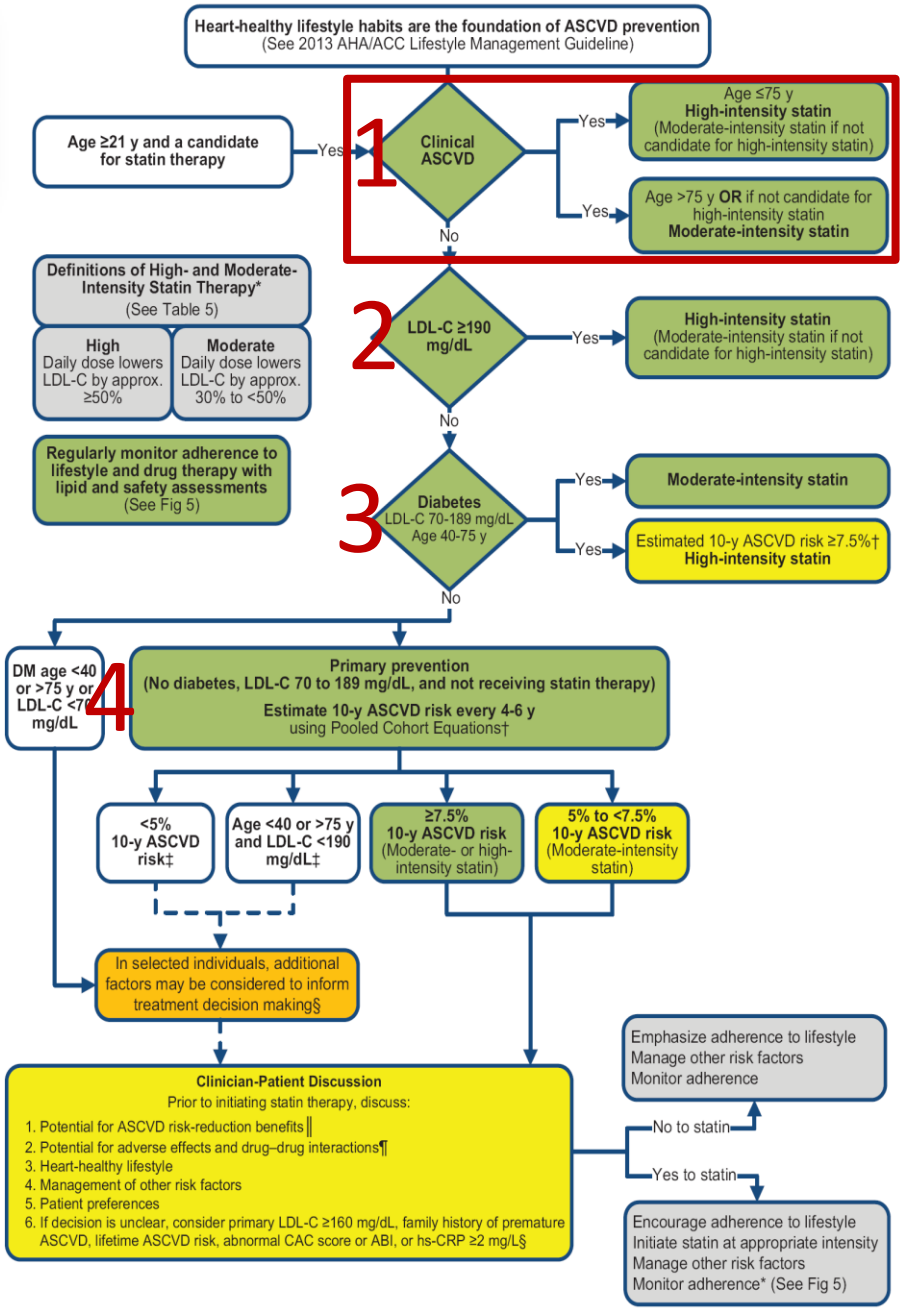


Recommendations	Class	Level
In patients at **VERY HIGH CV risk**, an **LDL-C goal of <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL), 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

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines



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- Family history of CAD,
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Total Cholesterol	290 mg/dl	7.5 mmol/l
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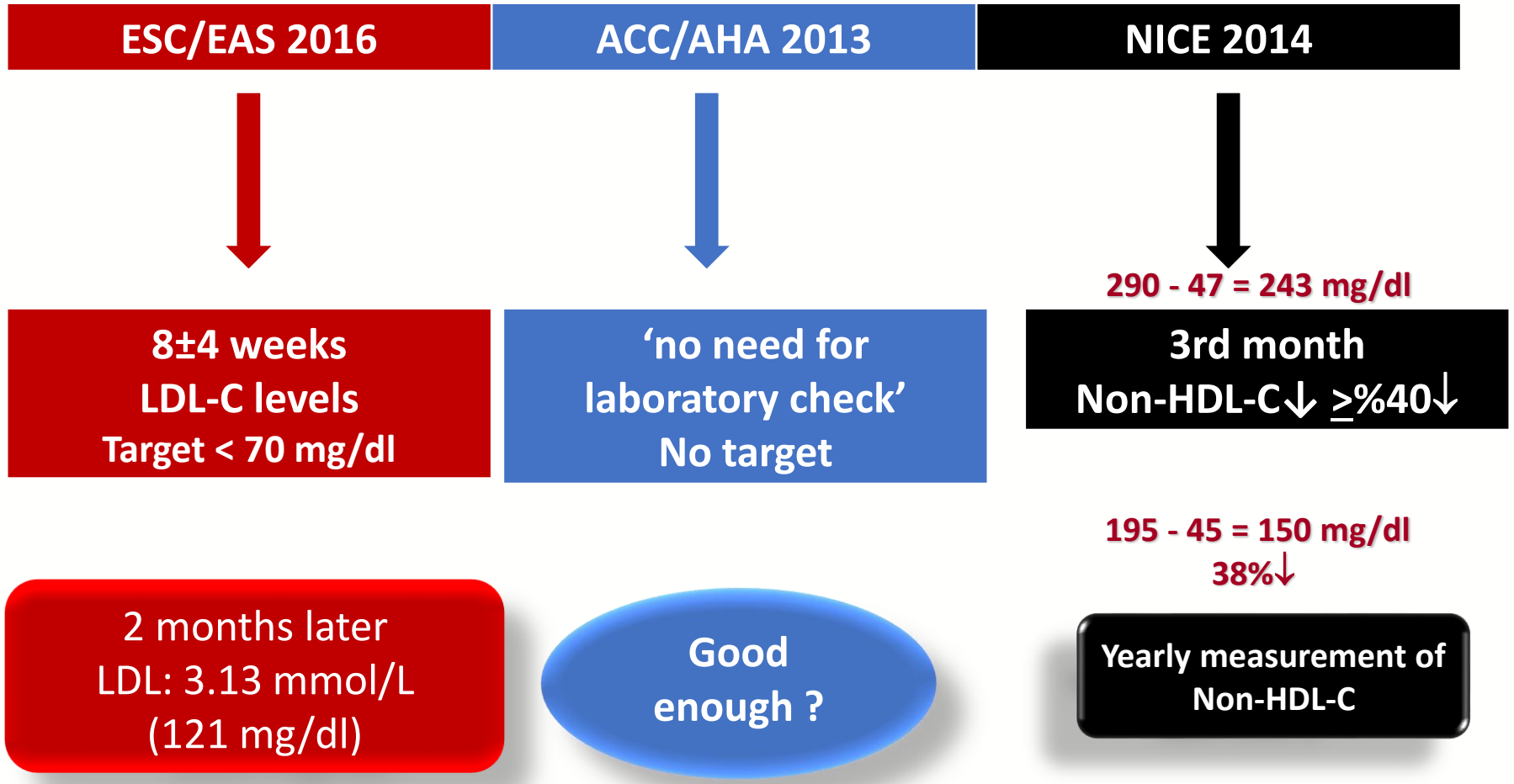
LDL-C	**203 mg/dl**	**5.3 mmol/l**

- **Atorvastatin 40-80 mg/day**

When should be patient evaluated for efficacy?



Case

- **55 y/o male** with **CAD**
- Recent PCI after an ACS
- Family history of CAD

Total Cholesterol	290 mg/dl	7.5 mmol/l
TG	80 mg/dl	0.9 mmol/l
HDL-C	47 mg/dl	1.2 mmol/l
LDL-C	**203 mg/dl**	**5.3 mmol/l**

- Atorvastatin 40-80 mg/dl was added

- **Should we add ezetimibe?**

What do the guidelines say?

ESC-EAS 2016
Dyslipidaemia Guidelines

Recommendations	Class	Level
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contraindication or history of intolerance, regardless of initial LDL-C values.	I	A
If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients.	IIa	B

2017 Addendum to ACC/AHA guideline

Consider adding other agents such as ezetimibe who have less than 50% LDL-C reduction for secondary prevention or PCSK9 inhibitors.

Case

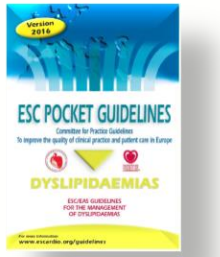
- **55 y/o male** with **CAD**
- Recent PCI after an ACS
- Family history of CAD

Total Cholesterol	290 mg/dl	7.5 mmol/l
TG	80 mg/dl	0.9 mmol/l
HDL-C	47 mg/dl	1.2 mmol/l
LDL-C	~~203 mg/dl~~ **78 mg/dl**	~~5.3 mmol/l~~ **2.02 mmol/l**

- What should be the treatment decision?
- Should we add a statin?
- Which dosage should be used?

Should we use statins in patients with near to target LDL levels?

1. **Identify the LDL-C goal for that risk level**
2. **Calculate % of LDL-C reduction required to achieve that goal**
3. **Choose a statin and a dose that could provide this reduction**



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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

Case

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- ~~Recent PCI after an ACS~~
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LDL-C	**203 mg/dl**	**5.3 mmol/l**

- **What should be the treatment decision?**

Treatment goals for LDL-cholesterol

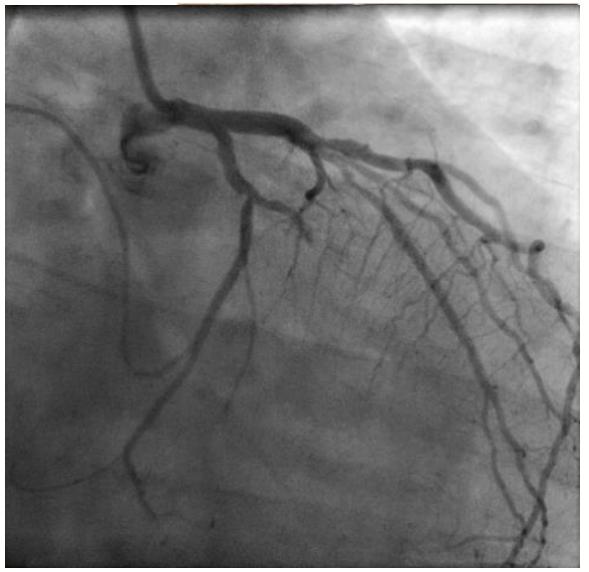
Recommendations	Class	Level
In patients at VERY HIGH CV risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients **at HIGH CV risk**, an **LDL-C goal of <2.6 mmol/L (100 mg/dL),** 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

Familial hypercholesterolemia (FH)

is a common genetic disease (OD) characterized by

- High cholesterol levels
- Premature atherosclerosis
- Cholesterol depositions

Age	LDL-C	
> 21 y	> 190 mg/dl	> 4.9 mmol/L
< 20 y	> 160 mg/dl	> 4.1 mmol/L



Premature CVD (F< 65y, M< 55y)
Prevelance is high in Turkey (1:150)

All guidelines suggest FH at high risk

ESC/EAS 2016 SCORE	ACC/AHA 2013	NICE 2014 QRISK2

FH patients:
No need for risk calculation
Have already high risk for CV events in all ages

25 y/o female

LDL-C	**203 mg/dl**	**5.3 mmol/l**

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
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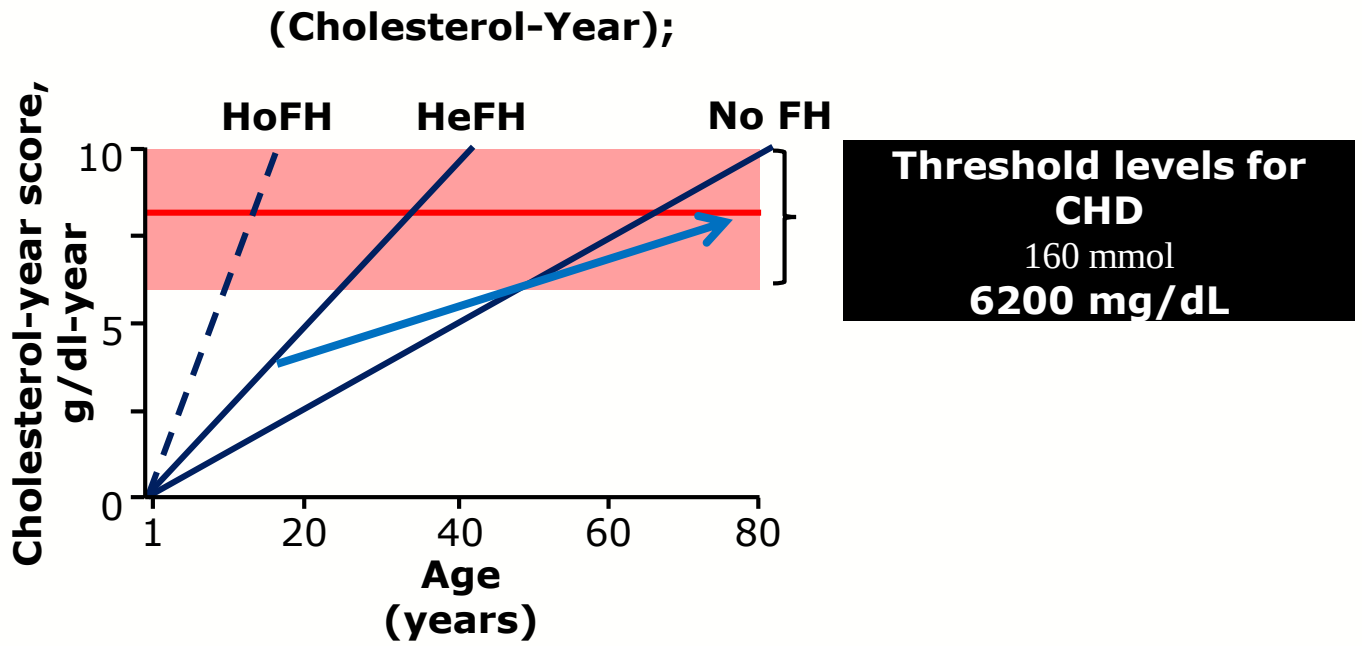
In subjects at LOW or MODERATE risk an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

FH Exposes People to Very High Cholesterol from Birth, thus Reaching a Threshold for CHD Earlier in Life



AACE 2017 Guidelines

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical CV disease in individuals with DM, stage 3 or 4 CKD, 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% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD 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

Case

- **55 y/o male ~~with CAD~~**
- ~~Recent PCI after an ACS~~
- Family history of CAD
- **Not FH**

Total Cholesterol	290 mg/dl
TG	80 mg/dl
HDL-C	47 mg/dl
LDL-C	~~203 mg/dl~~ **140 mg/dl**

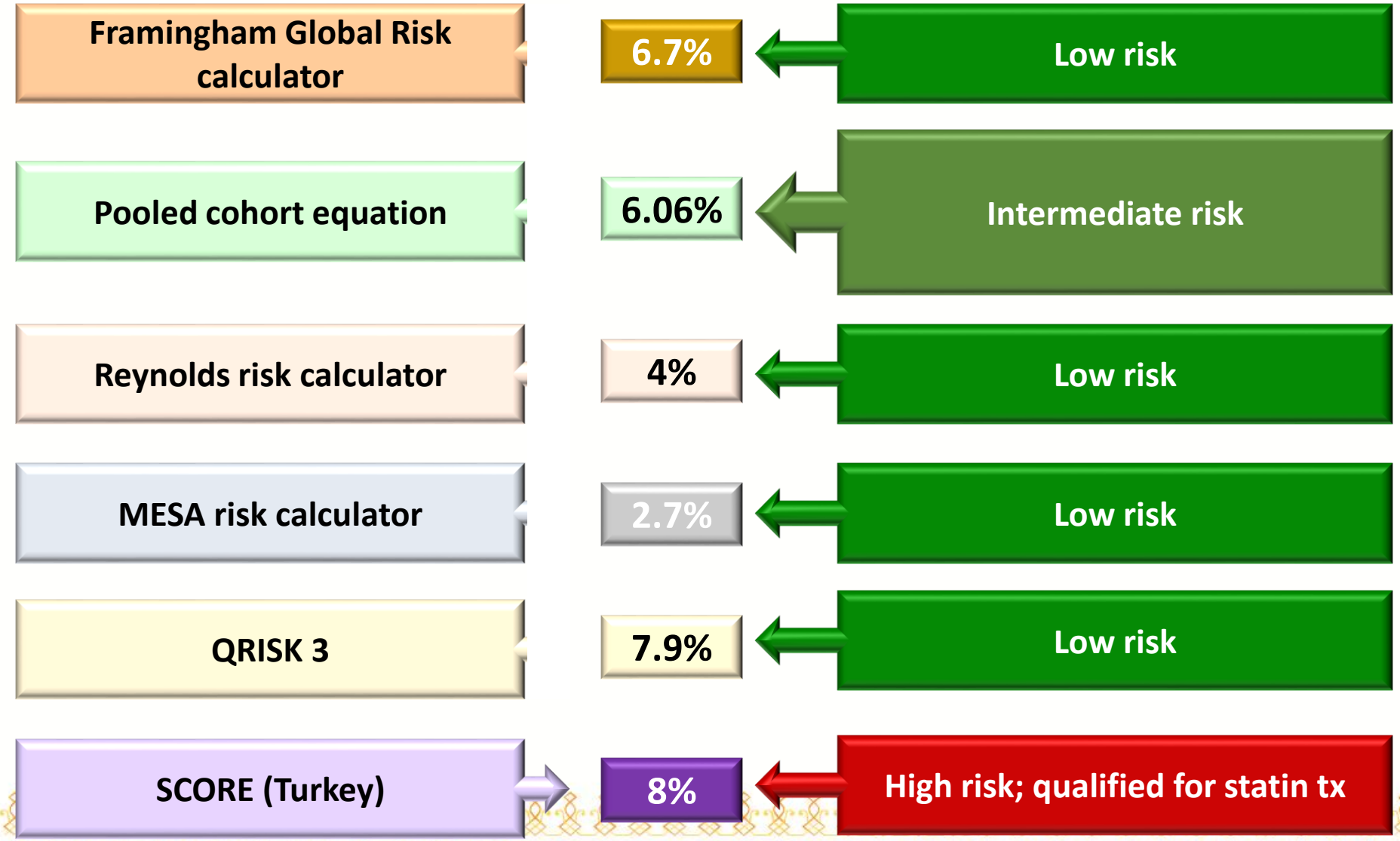
- **What should be the treatment decision?**

ESC/EAS 2011 SCORE	ACC/AHA 2013 Risk calculator	NICE 2014 QRISK2
0	1,8%	3,4%
10 years	10 years	10 years
≥5%	≥7,5%	≥10%

Age
Gender
T. Cholesterol
SBP
Smoking

Age
Gender
Etnicity
T. Cholesterol
HDL
SBP
Treatment for BP
DM
Smoking

Age
Gender
Heigth
Weigth
Etnicity
Cholesterol/HDL-C
SBP
Treatment for BP
DM, CKD, AF, CTD
Smoking
Family history


Framingham Global Risk calculator
6.7%
Low risk
Pooled cohort equation
6.06%
Intermediate risk
Reynolds risk calculator
4%
Low risk
MESA risk calculator
2.7%
Low risk
QRISK 3
7.9%
Low risk
SCORE (Turkey)
8%
High risk; qualified for statin tx

Treatment goals for LDL-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
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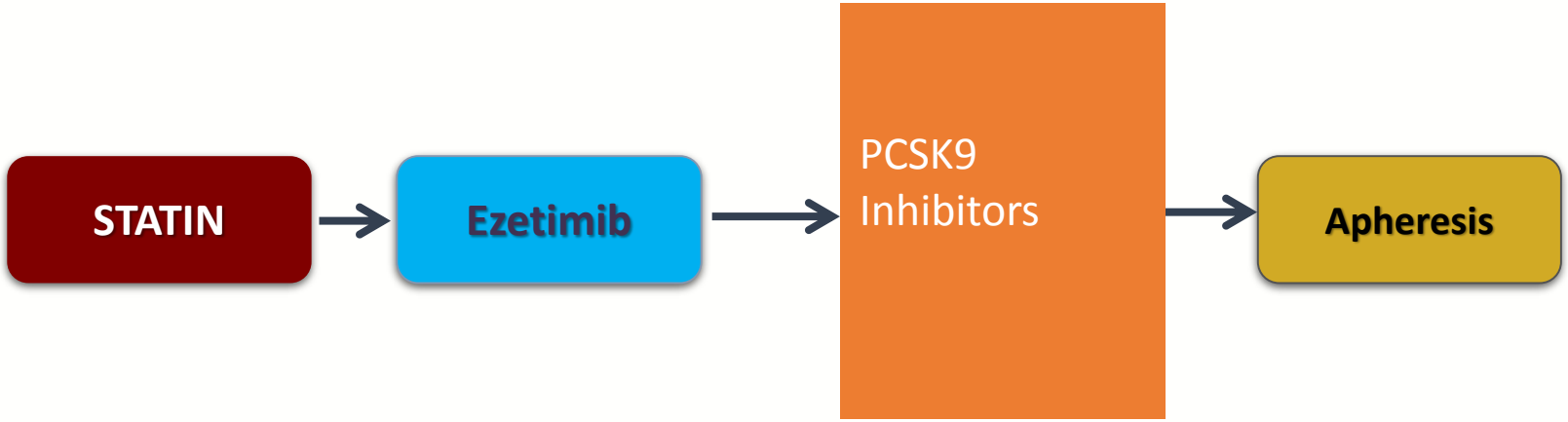
In subjects at LOW or MODERATE risk an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

If treatment goals cannot be attained?



Patient Populations with an Unmet Need for Additional LDL-C Lowering

Heterozygous Familial Hypercholesterolemia

Statin intolerant high risk

High CV risk

ACS Incidence (< 1 year) & CVD

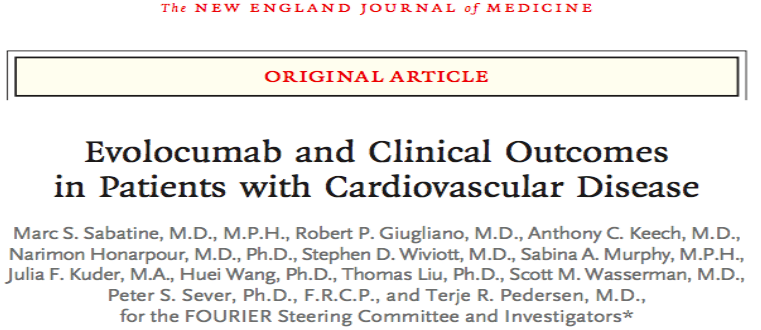
New Evidence
After the ESC 2016 Lipid Guidelines

Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound

JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

The GLAGOV Randomized Clinical Trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

PCSK-9 inh : translating LDL-C lowering into plaque regression and CV event reduction

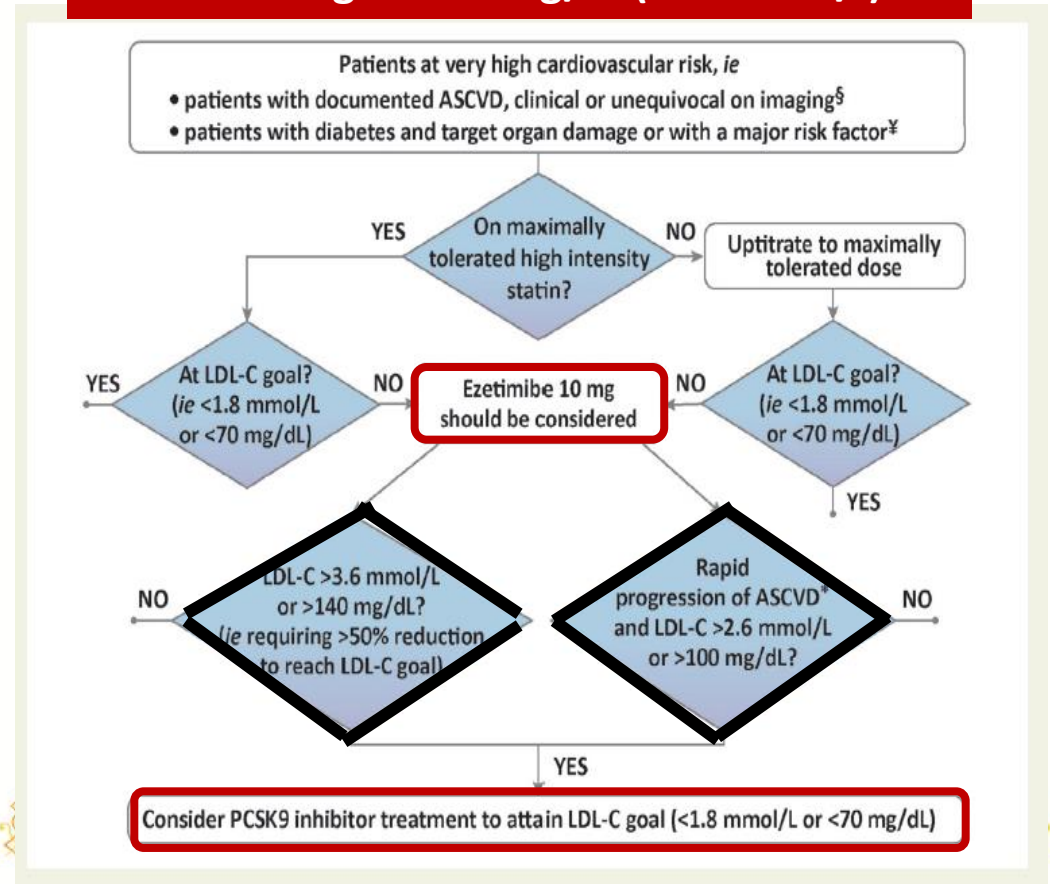
EXPERT CONSENSUS DECISION PATHWAY

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

ACC Middle East Conference 2017

For whom PCSK9 inh may be considered?
ESC/EAS consensus statement on PCSK9 inhibitors

Secondary Prevention FH
LDL-C target < 70 mg/dl (1.8 mmol/l)



Rapid progression of ASCVD:
repeated ACS,
repeated unplanned revascularizations,
or repeated ischaemic strokes
within 5 years of the index event

European Heart Journal (Oct 27, 2016)

Current Guidelines for Cholesterol Treatment

References

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5. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: *a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation*. 2014;129(suppl 2):S1–S45.
6. Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497

Thanks for Attention

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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.

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.

Approach to Risk Management

Who, how when to screen?

How to evaluate risk?

When to initiate treatment?

Monitoring and surveillance?

	ACCF-AHA and AASE	ESC-EAS
Men	>20 yrs	>40 yrs
Women	>20 yrs	>50 yrs (or postmenopausal)
Methods	● Assess traditional risk factors every 4-6 years in subjects aged 20-79 years; ● Assess 10-y risk in those 40-79 y of age using Pooled Cohorts Equation Risk Score ● Assess 30-y or lifetime risk in those 20-59 y of age ---------- ● The 10-year risk of a coronary event should be determined by detailed assessment using one or more of the following tools: Framingham, MESA, Reynolds, and UKPDS methods.	● Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk using SCORE charts.

Risk categories	ACC 2013 Guidelines	ESC 2016 Guidelines
Very high-risk	• Clinical ASCVD	• Documented CVD, clinical or unequivocal on imaging, including previous ACS, coronary revascularization and other arterial revascularization procedures, stroke and **TIA, aortic aneurysm** and PAD. • 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%.
High-risk	• LDL-C >190 mg/dL • Diabetes mellitus (LDL-C 70-189 mg/dL) and age 40-75 y • A pooled cohort equation risk score of ≥7,5%	• Markedly elevated single risk factors, in particular **TC (>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 m2). • A calculated SCORE ≥5% and <10%.
Moderate-risk		SCORE ≥1% and <5%
Low-risk		SCORE <1%

When to start statins

Clinical atherosclerosis

- Myocardial infarction, acute coronary syndromes, stable coronary artery disease, documented coronary disease (>10% stenosis)
- Stroke, TIA, documented carotid disease
- Peripheral artery disease, claudication and/or ABI <0.9
- Abdominal aorta >3.0 cm
- Previous aneurysm surgery

Diabetes mellitus

- ESC
- All patients

- ACC:
- 40–75 years of age and LDL-C >70 mg/dl

LDL-C ≥5.0 mmol/L

- ESC:
- Documented familial hypercholesterolemia; TC >310 mg/dL

- ACC:
- Adults aged ≥21 years of age and LDL-C ≥190 mg/dL

Global CV Risk

- ESC:
- SCORE >5

- US:
- Adults aged ≥40 years of age, ≥7.5% of 10 yr-risk for ASCVD and LDL-C ≥70 mg/dL