28° Congresso Interassociativo AMD-SID Lombardia 2022

la Cura

14-15 ottobre 2022

Auditorium Giorgio Gaber - Grattacielo Pirelli
Piazza Duca d'Aosta, 3 - Milano

SID Società Italiana di Diabetologia
fondata nel 1964

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
1974 ANNO DI FONDAZIONE

28° Congresso Interassociativo
AMD-SID Lombardia 2022

Inibitori Proprotein Convertase Subtilisin/Kexin 9

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Il Prof. Livio Luzi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- MENARINI-MENARINI DIAGNOSTICI
- NOVO-NORDISK
- ELI LILLY
- IBSA
- ASTRA-ZENECA
- SUNSTAR
- HARMONIUM PHARMA
- NOVARTIS
- ALLERGAN
- MOVI
- MEDTRONIC

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Cardiovascular Disease (CVD)

- "group of disorders of the heart and blood vessels, including coronary heart disease (heart attacks), cerebrovascular disease (stroke), hypertensive heart disease, heart failure, peripheral artery disease, rheumatic heart disease, congenital heart disease and other conditions"

[WHO 2016]

- **CVD** remains the **leading cause of death worldwide**, is an increasing cause of morbidity and a major cause of disability and ill-health

[WHO 2015]

- It kills more women (2.2 million) than men (1.8 million), although CV deaths before the age of 65 years are more common in men (490 000 vs. 193 000)

[Nichols M et al, Eur Heart J. 2013]

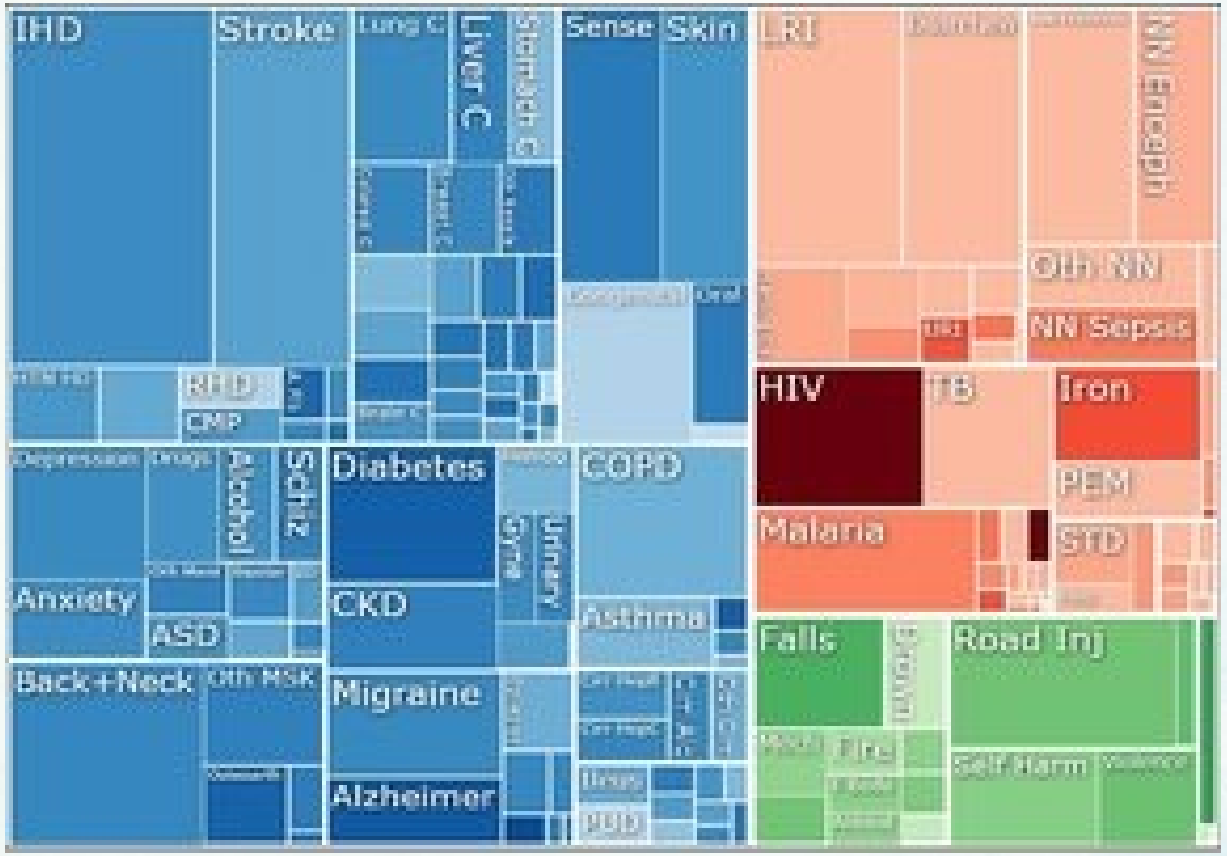
Healy B. *The Yentl syndrome*
N Engl J Med. 1991
Jul 25;325(4):274-6.
doi: 10.1056/NEJM199107253250408. PMID: 2057027.

Bernadine Healy, M.D. Cardiologist, Director N.I.H.

Yentl, the 19th-century heroine of Isaac Bashevis Singer's short story, had to disguise herself as a man to attend school and study the Talmud. Being "just like a man" has historically been a price women have had to pay for equality…

…They determined that **women had angina** before myocardial infarction as frequently and with more debilitating effect **than men**, **yet women underwent cardiac catheterization only half as often** — again, after the investigators controlled for variables such as age and coexisting disease. It is noteworthy that when women who had undergone cardiac catheterization were studied, there were no differences between the sexes in the likelihood of coronary surgery. Similarly, **once a woman had a myocardial infarction, she was as likely as a man to undergo cardiac catheterization and revascularization**. *The latter two findings demonstrate the Yentl syndrome at work.*

Disability-Adjusted Life Year (DALY)
Quantifying the Burden of Disease from mortality and morbidity



One DALY can be thought of as one lost year of "healthy" life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability.

Prevention

- "a co-ordinated set of actions aimed at eliminating or minimizing the impact of CV diseases and their related disabilities"

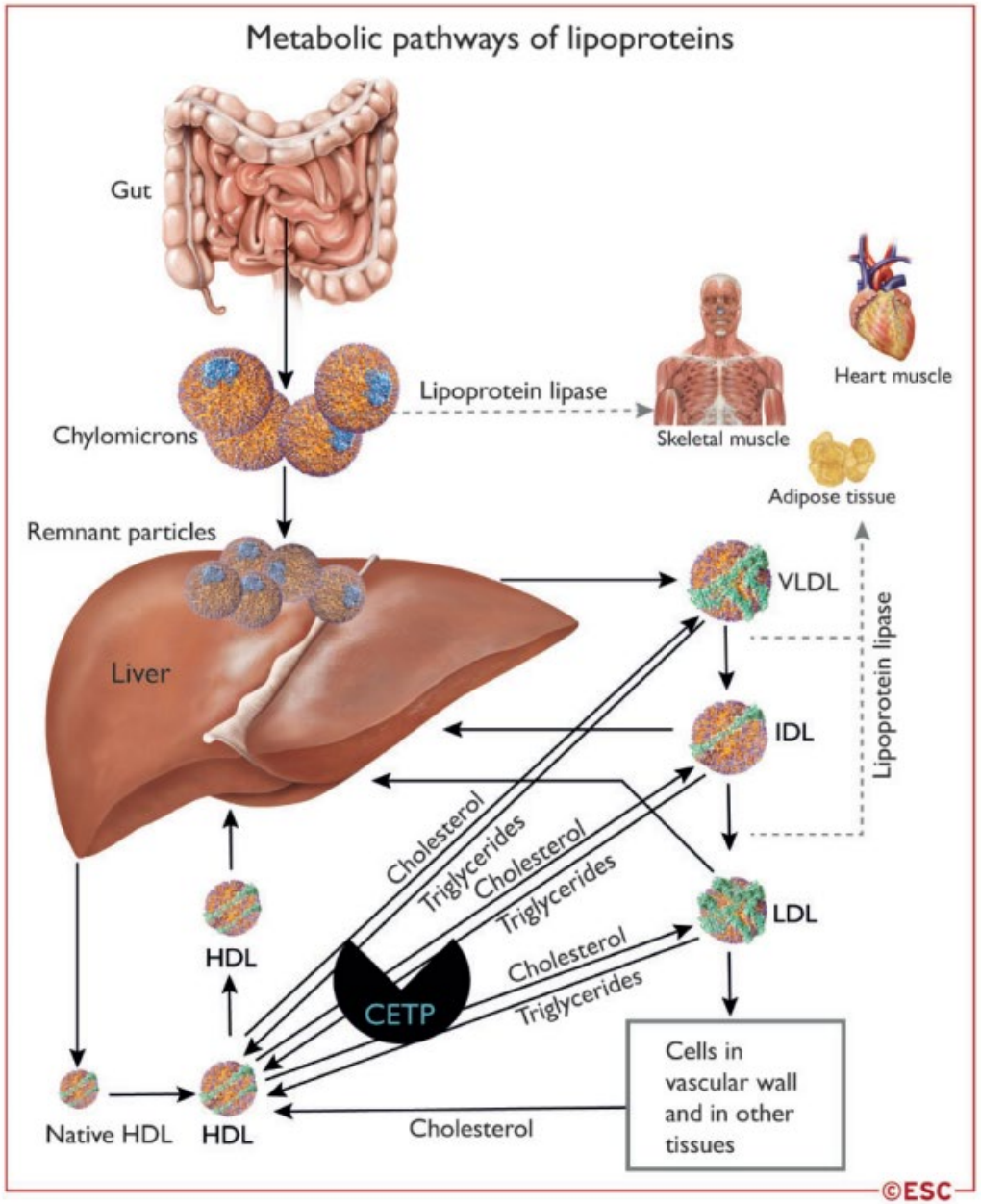
- ✓ More patients are surviving their first CVD event and are at high-risk of recurrences
- ✓ The prevalence of some risk factors, notably diabetes (DM) and obesity, is increasing
- ✓ It should be delivered at the general population level by **promoting healthy lifestyle behaviour** and at the individual level by **tackling unhealthy lifestyles** and by **reducing** increased levels of causal CV risk factors, such as **LDL-C** or blood pressure (**BP**) levels

ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188

Lipids and Lipoprotein

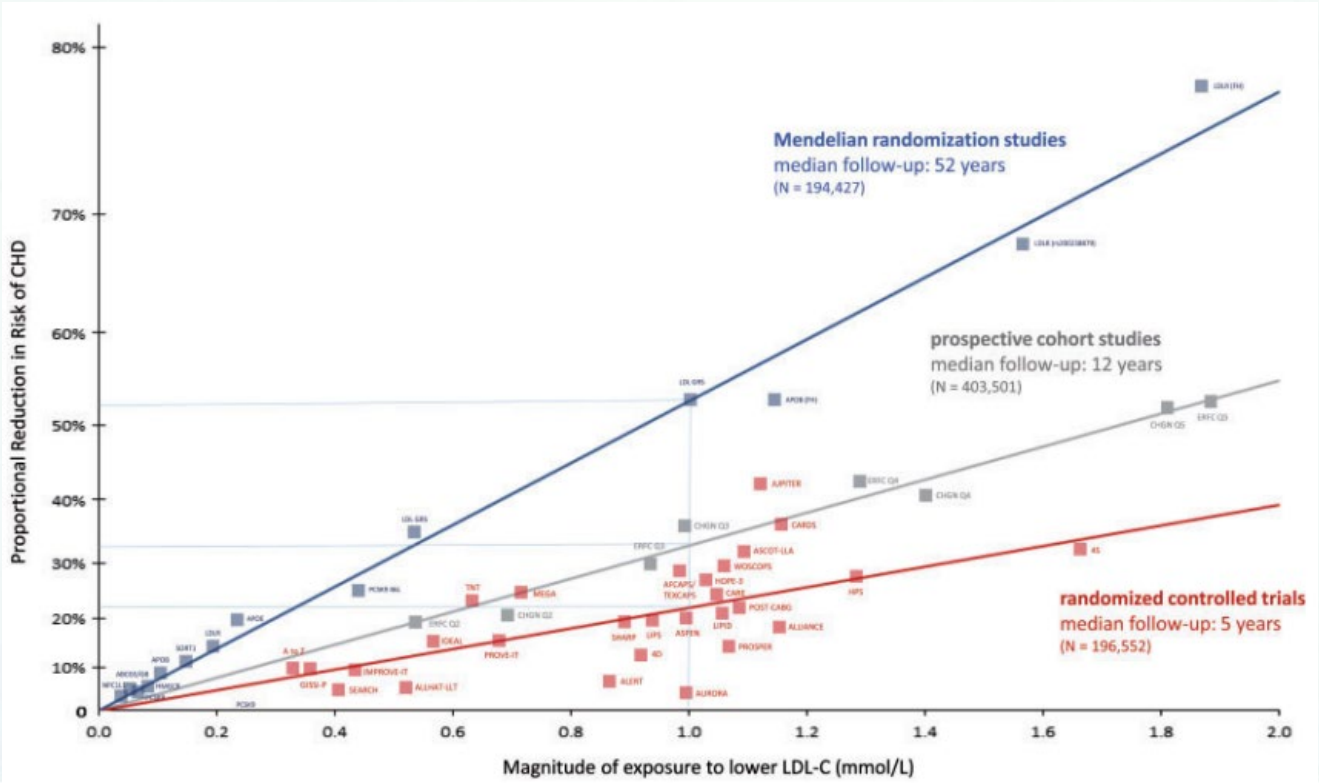
- ✓ Lipoproteins in plasma transport lipids to tissues for **energy** utilization, **lipid deposition**, **steroid hormone production**, and **bile acid formation**
- ✓ Lipoproteins consist of esterified and unesterified cholesterol, TGs, and phospholipids and protein components named **apolipoproteins** that act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors
- ✓ There are 6 major lipoproteins in blood: **chylomicrons**, very lowdensity lipoprotein (**VLDL**), intermediate-density lipoprotein (**IDL**), **LDL**, **Lp(a)**, and **HDL**

ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188



LDL-C and risk of atherosclerosis

- ✓Plasma LDL-C: a measure of the cholesterol mass carried by LDL particles
- ✓Numerous epidemiological studies, Mendelian randomization studies, and RCTs have consistently **demonstrated a log-linear relationship** between the absolute changes in plasma **LDL-C** and the risk of Atherosclerotic Cardiovascular Disease (**ASCVD**)



The remarkable consistency among these studies, in addition to biological and experimental evidence, provides compelling evidence that LDL-C is causally associated with the risk of ASCVD, and that lowering LDL-C ***reduces the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C***

LDL-C and risk of atherosclerosis

- ✓The clinical benefit of **lowering LDL-C** is determined by the **reduction in circulating LDL** particles as estimated by **ApoB**, which is usually mirrored by a **reduction of cholesterol** carried by those particles

- ✓The clinical benefit of **therapies** that **lower LDL-C** by reducing **LDL particle mass** will be proportional to the **absolute reduction in LDL-C** (the reduction in LDL-C and LDL particles will be concordant)

- ✓In contrast, the clinical benefit of therapies that ***lower LDL-C by a mechanism that may modify their composition may not be proportional to the observed absolute reduction in LDL-C, but instead*** would be expected to be proportional to the absolute change in LDL particle concentration as ***measured by a reduction in ApoB***

ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188

Treatment targets and goals

- ✓In previous EAS/ESC Guidelines for the management of dyslipidaemias and other major guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults, the importance of **LDL-C lowering** to **prevent ASCVD** was strongly emphasized

- ✓The Task Force retains a goal approach to lipid management and treatment goals are tailored to the total **CV risk level**

- ✓There is also evidence suggesting that **lowering of LDL-C** beyond the goals that were set in the previous EAS/ESC Guidelines is associated with **fewer ASCVD events**

It seems appropriate to reduce LDL-C to as low a level as possible, at least in patients at very high CV risk, and for this reason a minimum **50% reduction** is suggested for LDL reduction, together with reaching the tailored goal

ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188

Cardiovascular risk categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease

FH = familial hypercholesterolaemia

SCORE: Systematic Coronary Risk Estimation

Recommendations for treatment goals for LDL-C

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

ASCVD = atherosclerotic cardiovascular disease
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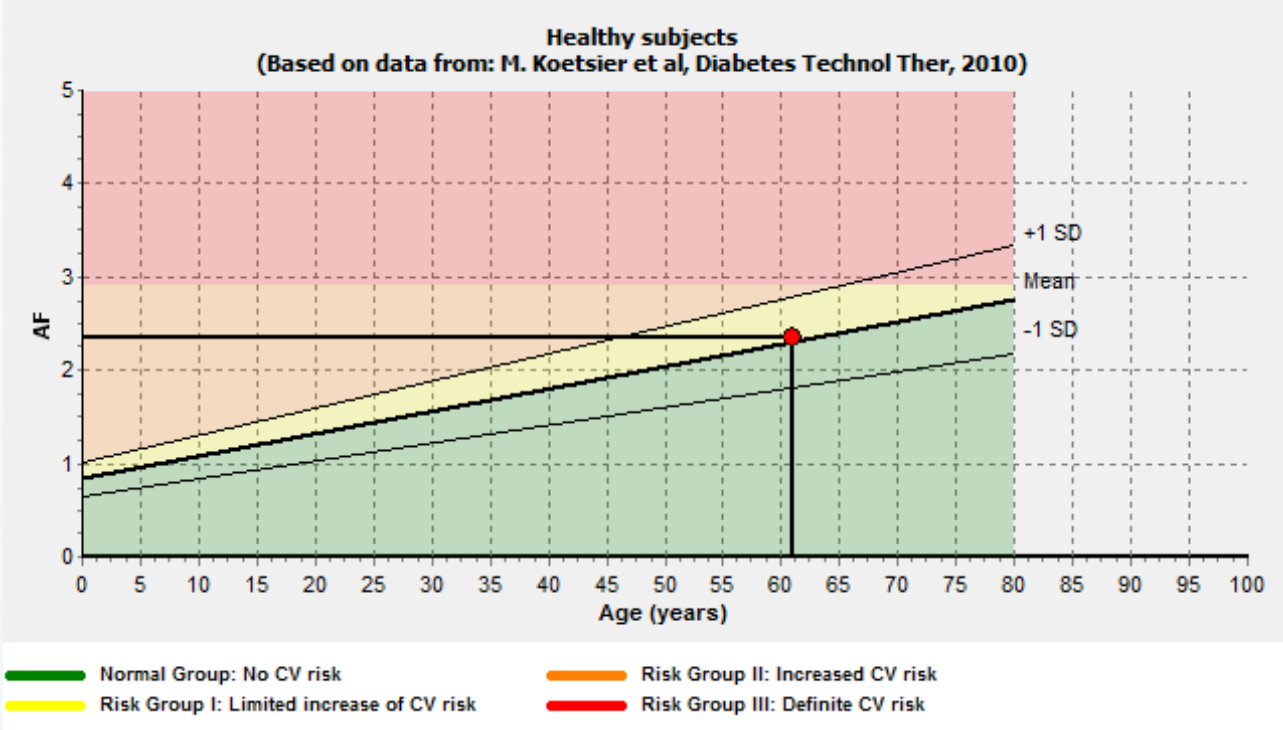
Treatment targets and goals for cardiovascular disease prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, 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% (<53 mmol/mol).

ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188

AGEs (Advanced Glycation End-products)



Score numerico: 2.3

Score qualitativo:

Risk Group I: Limited increase of CV risk

- The AGE Reader assesses the accumulation of advanced glycation endproducts (AGEs) in the skin using fluorescence of ultraviolet light
- AGEs plays a pivotal role in the development of chronic complications of diabetes and other common conditions
- The amount of AGEs in tissues serves as an important risk predictor of such complications

Drugs for treatment of dyslipidaemias

- ❑ **Statins**
- ❑ Cholesterol absorption inhibitors
- ❑ Bile acid sequestrants
- ❑ Proprotein convertase subtilisin/kexin type 9 inhibitors
- ❑ Lomitapide
- ❑ Mipomersen
- ❑ Fibrates
- ❑ n-3 fatty acids
- ❑ Nicotinic acid
- ❑ Cholesteryl ester transfer protein inhibitors

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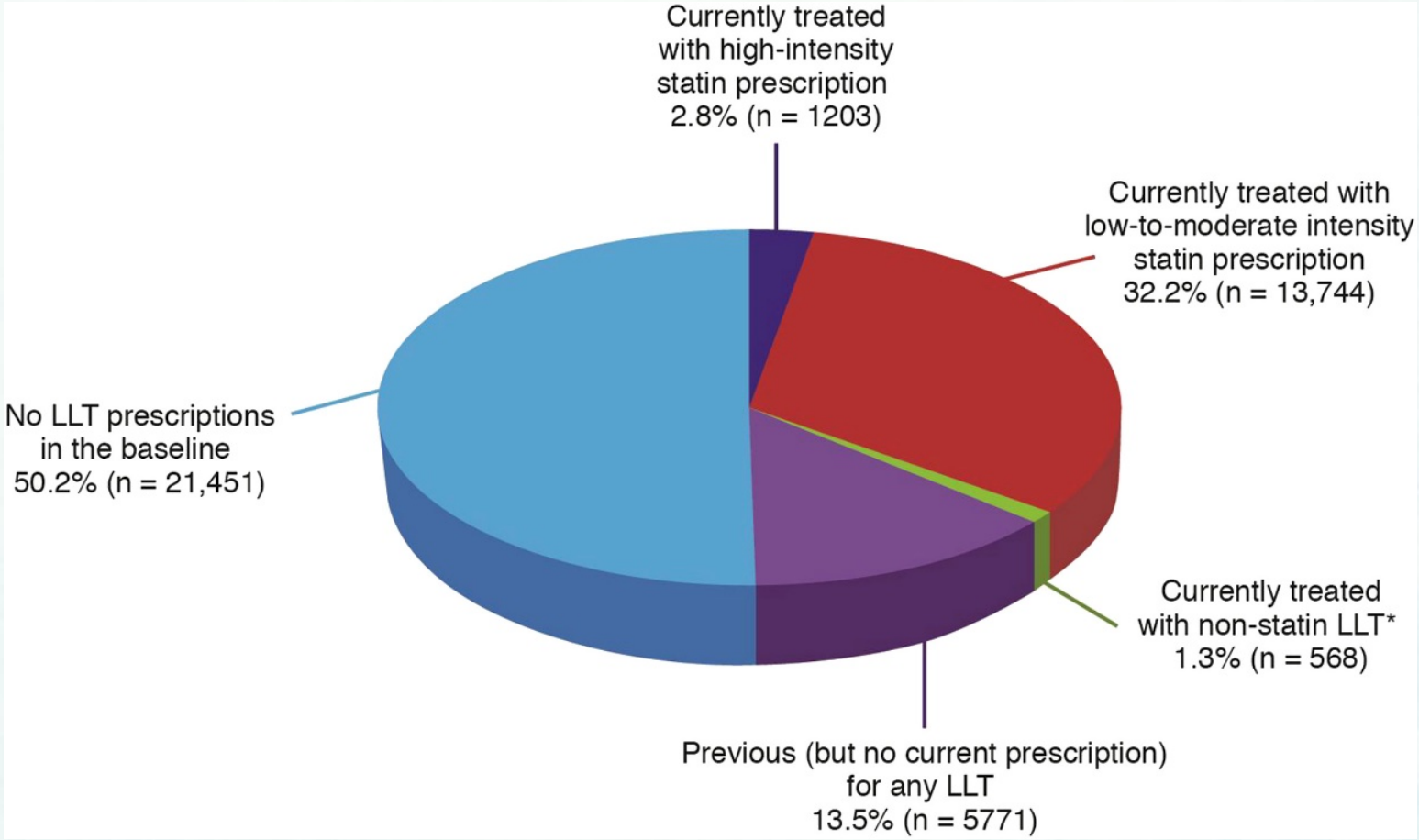
Utilization of lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients at high and very-high cardiovascular risk: Real-World Evidence from Germany



Marz, Atherosclerosis, 2018

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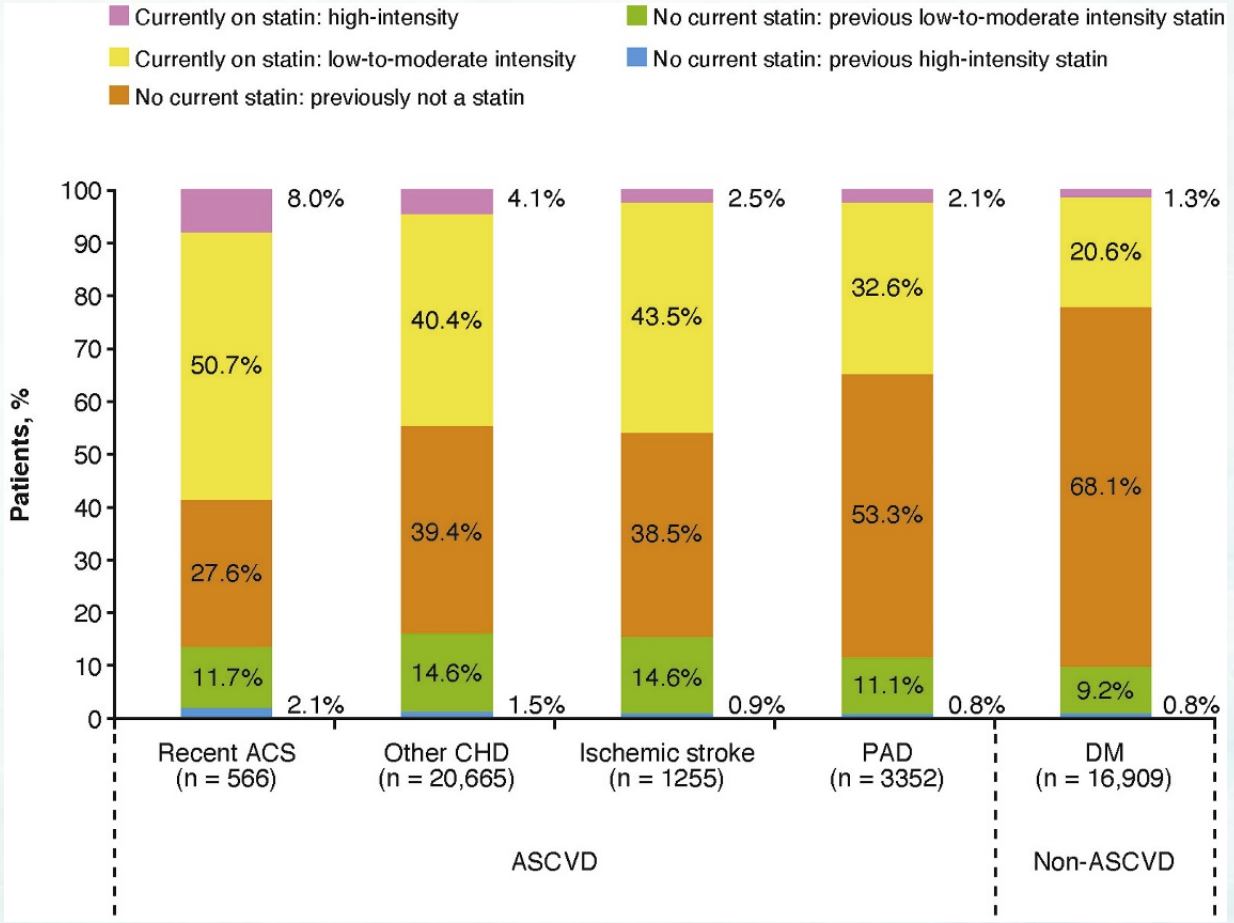

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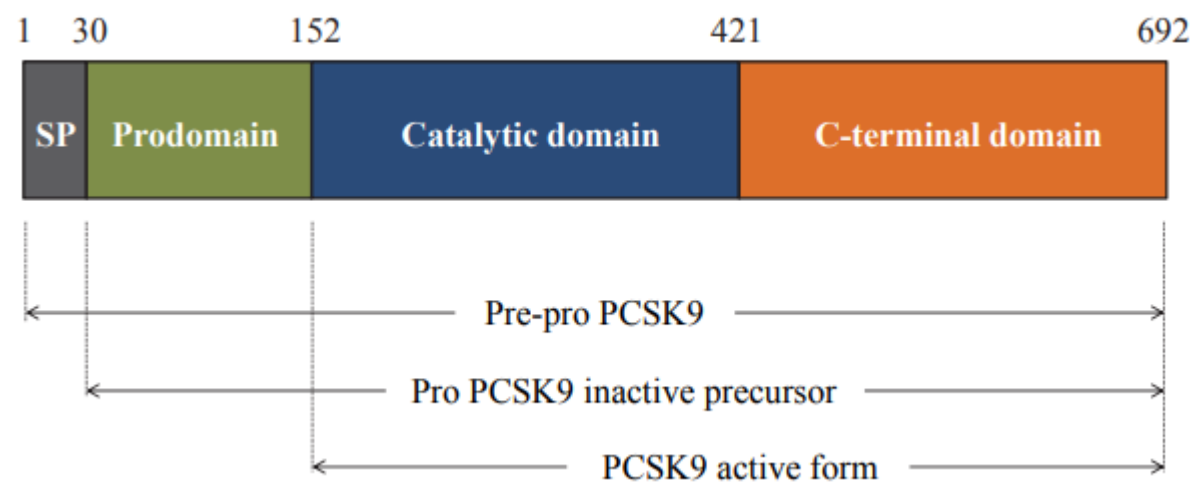
Proprotein convertase subtilisin/kexin type 9 inhibitors



PCSK9 protein structure.
PCSK9 comprises a signal peptide, a prodomain, a catalytic domain and a C-terminal domain

- ✓ Proprotein convertase subtilisin/kexin type 9 (PCSK9), also known as neural apoptosis-regulated convertase 1 (NARC-1), was first described in 2003
- ✓ PCSK9 is mainly secreted by the liver, but it is also highly expressed in the intestine and kidney
- ✓ **PCSK9 enhances** the endosomal and lysosomal **degradation of hepatic** low-density lipoprotein receptor (**LDLR**), resulting in **increased serum LDL-C concentrations**
- ✓ **PCSK9 is a key regulator of serum LDL-C levels**

Norata GD et al, Annu Rev Pharmacol Toxicol. 2014

Mechanism of action

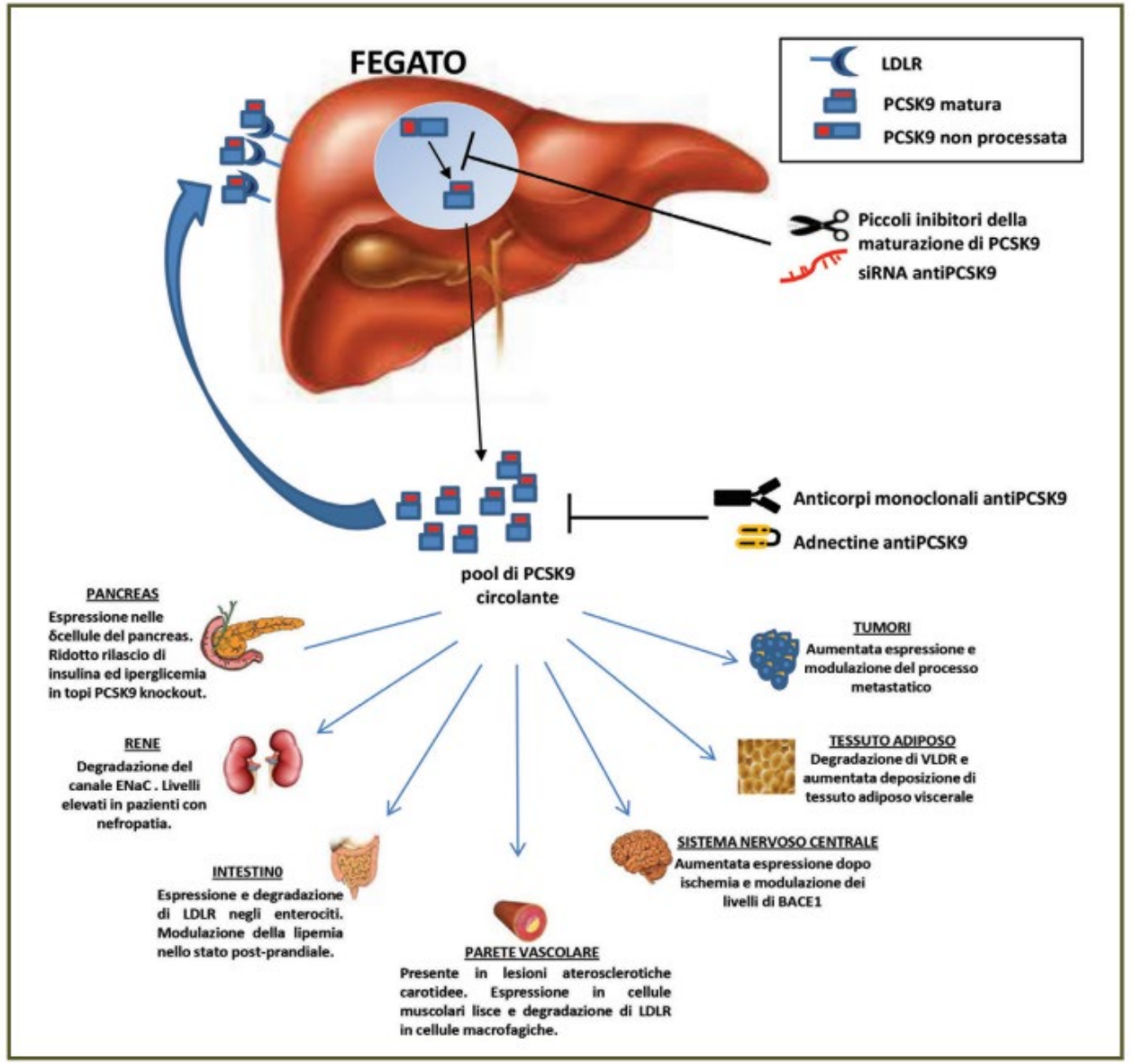
- **PCSK9 inhibitors** targets a protein (**PCSK9**) involved in the control of the **LDLR**
- **Elevated concentration** or function of **PCSK9** in plasma **reduces LDLR expression** by promoting, upon binding, LDLR lysosomal catabolism and a subsequent **increase in plasma LDL concentrations**
- **Lower concentration or function of PCSK9 is related to lower plasma LDL-C levels**
- **Therapeutic strategies** have been developed mainly using **mAbs**
- The mechanism of action relates to the **reduction** of the plasma level of **PCSK9**, which in turn is **not available to bind the LDLR**
- Since this **interaction** triggers the intracellular **degradation of the LDLR**, **lower** levels of circulating **PCSK9** will result in **increased expression of LDLRs** at the cell surface and therefore in a **reduction of circulating LDL-C levels**
- Currently, the only approved PCSK9 inhibitors are two fully human mAbs: **Alirocumab** and **Evolocumab**
- **Statin treatment increases circulating PCSK9 serum levels** and thus the best effect of these **mAbs** has been demonstrated in combination **with statins**

Mechanism of action

- **PCSK9** is mainly expressed in the **liver** where it is synthesized and released into the circulation as a functional protein capable of **binding LDLR and mediating its degradation**
- Circulating or locally produced PCSK9 regulates important functions in several tissues besides the liver, such as tumors, visceral adipose tissue, central nervous system, arterial vessels, intestines, pancreas and kidney
- The **4 main approaches** currently used for the **inhibition** of protein are:

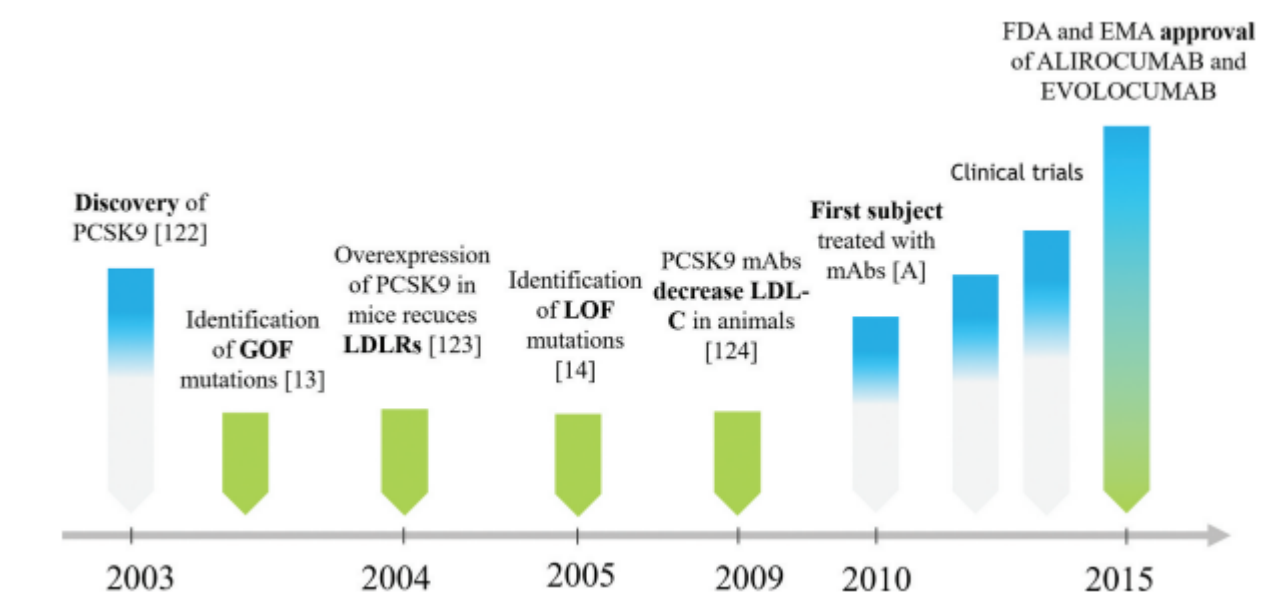
1) short interfering RNA (**siRNA**) and 2) small inhibitors of PCSK9 maturation act at the **intracellular level**, **reducing the synthesis or release of PCSK9 into the circulation**;

3) **monoclonal antibodies** and 4) **adnectins block the activity of the circulating protein**



Tibolla G, et al, Giornale Italiano dell'Arteriosclerosi 2014

Monoclonal antibodies for cholesterol-lowering



- The use of mAbs for blocking PCSK9 has been one of the fastest translations to the clinic in the history of drug development
- From the development of the first successful clinical-grade monoclonal antibodies, it took only a few years for the FDA and EMA approval for therapy

Malvandi AM, Expert Opin Biol Ther. 2020

Alirocumab: monomeric immunoglobulin G1 (IgG1) isotype
At low concentrations its elimination predominately occurs through saturable binding to PCSK9;
At higher concentrations it depends on a non-saturable proteolytic pathway;
Resulting in a median half-life at steady state of 17 to 20 days in monotherapy if administered once every two weeks (75 or 150 mg)

Evolocumab: dimeric immunoglobulin G2 (IgG2) isotype
The recommended therapy regime for evolocumab is 140 mg every two weeks or 420 mg monthly administration
It has two elimination phases, while it has an estimated half-life is 11–17 days

Effects on lipids: LDL-C

- ✓ **In clinical trials**, **alirocumab** and **evolocumab** have been shown to **significantly reduce LDL-C levels on average by 60%**, depending on dose
- ✓ The **efficacy** appears to be **largely independent of any background therapy**
- ✓ **In combination** with high-intensity or maximally tolerated **statins**, alirocumab and evolocumab **reduced LDL-C by 46-73% more than placebo**, and by **30% more than ezetimibe**
- ✓ Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C when administered in combination with ezetimibe
- ✓ Both alirocumab and evolocumab have also been shown to effectively **lower LDL-C levels in patients who are at high CV risk, including those with DM**

ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188

Effects on lipids: LDL-C

mAb – Study Name	Patients enrolled	Treatment	LDL reduction (%)
Evolocumab-MENDEL II	Fasting LDL-C 100–190 mg/dL.	Evolocumab 140 mg/Ezetimibe Every 2 weeks –12 weeks Evolocumab 420 mg/Ezetimibe Every 4 weeks –12 weeks	55–57 more than placebo 38–40 more than ezetimibe
Evolocumab-LAPLACEII	- Subjects not taking a statin LDL-C of at least 150 mg/dL - Subjects on a non-intensive statin with LDL-C ≥ 100 mg/dL -Subjects on an intensive statin with LDL-C ≥ 80 mg/dL	Evolocumab 140 mg+ Statin Every 2 weeks 12 weeks vs. placebo or Ezetimibe Evolocumab 420 mg+ Statin Every 4 weeks 12 weeks vs. placebo or Ezetimibe	66–75 vs. placebo 63–75 vs. placebo
Evolocumab - DESCARTES	- Fasting LDL-C ≥ 75 mg/dL and meeting the following LDL-C values on background lipid-lowering therapy: - < 100 mg/dL for subjects with CHD or CHD risk equivalent - < 130 mg/dL for subjects without diagnosed CHD or CHD risk equivalent	Evolocumab 420 mg Once a month 52 weeks	57 ± 2.1
Evolocumab-GAUSS2	- No statin or low dose of Statin with stable - History of intolerance to at least 2 Statins - Subject not at LDL-C goal	Evolocumab 140 mg Every 2 weeks 12 weeks vs. placebo or Ezetimibe Evolocumab 420 mg Every 4 weeks 12 weeks vs. placebo or ezetimibe	53–56 from baseline, corresponding to 37–39 vs. ezetimibe
Evolocumab - RUTHERFORD	- Diagnosis of heterozygous familial hypercholesterolemia - Fasting LDL-C ≥ 100 mg/dL - Taking Statin or other lipid-lowering therapies	Evolocumab Every 2 weeks 12 weeks vs. placebo Evolocumab Every 4 weeks 12 weeks vs. placebo	59,2 61,3
Alirocumab-ODISSEY-ALTERNATIVE	- Primary hypercholesterolemia - Statin intolerance	Alirocumab 75 mg Every 2 weeks 24 weeks Ezetimibe 10 mg/d 24 weeks Atorvastatin 20 mg/d 24 weeks	45 ± 2.2 (Alirocumab) vs. 14.6 ± 2.2 (Ezetimibe) Mean difference: 30.4 ± 3.1

Summary of phase III clinical trials with alirocumab or evolocumab.
Study design and endpoint as a reduction in LDL-C plasma levels.
The total number of patients enrolled: 4581

Malvandi AM, Expert Opin Biol Ther. 2020

Effects on lipids: TG and HDL-C

- **Lower TG levels** and **increase** those of **HDL-C** and **ApoA-I** as a function of the dosing regimen
- In phase II trials, evolocumab **lowered TG levels by 26%** and **raised HDL-C** by **9%** and **ApoA-I** by **4%**
- Similar findings have been reported for alirocumab
- However, the TG effect must be confirmed in populations with higher starting plasma TG levels

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Effects on lipids: Lipoprotein(a)

- In contrast to statins, inhibiting PCSK9 with mAbs **also reduces Lp(a) plasma levels**
- Pooled results of phase II trials have shown that treatment leads to an **Lp(a) reduction of about 30-40%**
- While recent investigations have attempted to unravel the mechanism, it remains unclear
- The relative contribution of this effect to the reduction of risk **remains to be addressed in appropriately designed studies**

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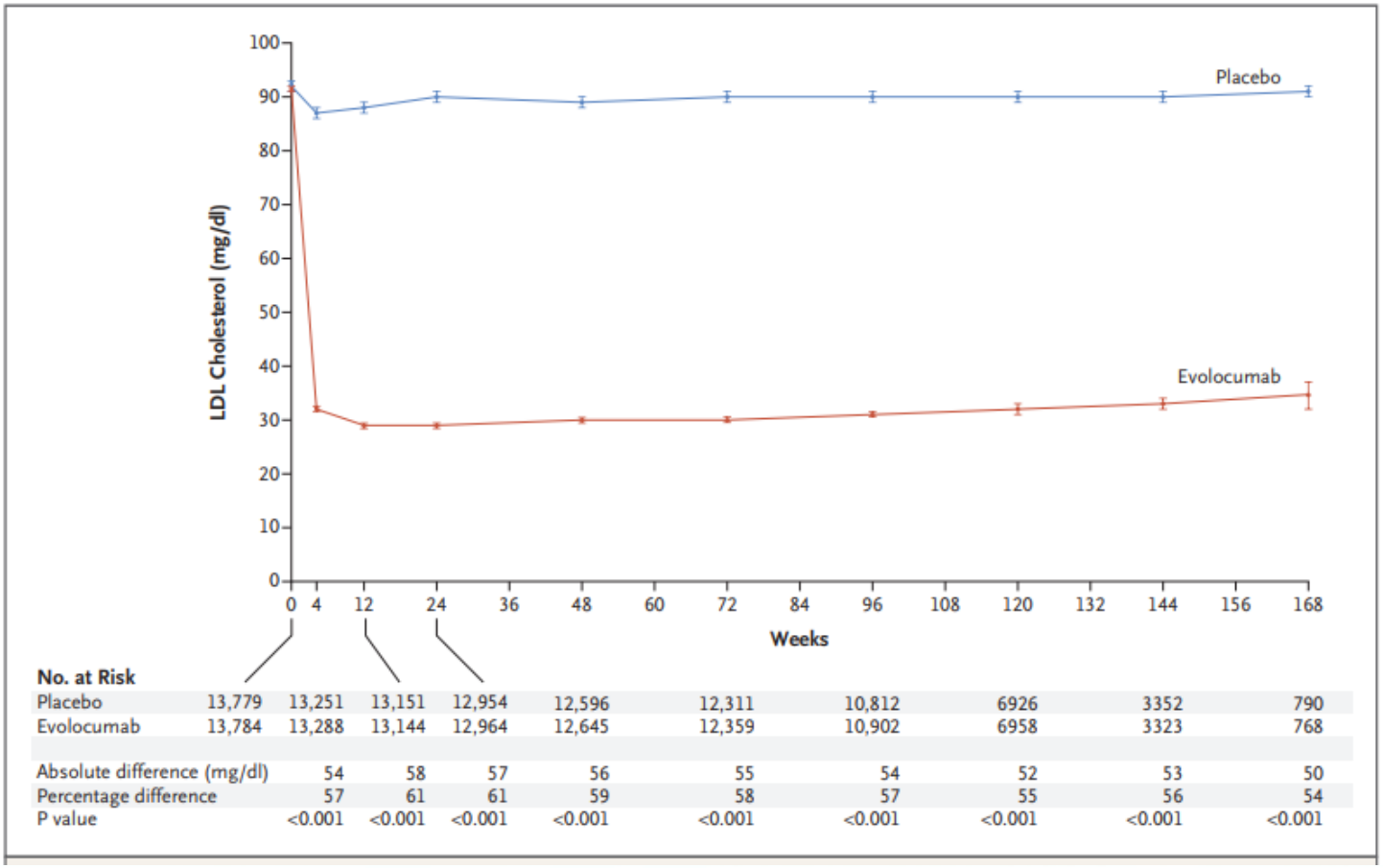
Effect on cardiovascular morbidity and mortality

- ✓Early preliminary data from phase III trials suggests a **reduction of CV events in line with the LDL-C reduction achieved**
- ✓Recently, two major studies were completed: 1) **FOURIER** and 2) **ODYSSEY Outcomes** trials
- ✓The designs of the trials were similar with regard to the settings of secondary prevention and background therapy; however, the populations enrolled had either stable CHD, peripheral arterial disease (PAD), or stroke or a recent (median 2.6 months) ACS
- ✓The relative benefit ranged from **15-20% reductions** in the risk of the primary endpoints
- ✓Both studies had relatively short follow-up periods and the evidence from statin trials indicates that the clinical benefits of LDL-lowering may only emerge after about 1 year, so these trials may have underestimated the potential impact of longer-term treatment

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*



FOURIER trial

- ✓ 27564 patients with atherosclerotic CVD, and LDL-C levels of 1.8 mmol/L (70 mg/dL) or higher who were receiving statin therapy, were randomly assigned to receive **evolocumab** or **placebo**
- ✓ Allocation to evolocumab **reduced** median **LDL-C from 92 mg/dL** at baseline **to** a mean of **30 mg/dL** at 48 weeks
- ✓ **After** a median follow-up of **2.2 years**, **evolocumab treatment significantly reduced the risk of the primary endpoint** (composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) **by 15%**

Sabatine MS et al, N Engl J Med. 2017

Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration

Brian A. Ference[1], Christopher P. Cannon[2], Ulf Landmesser[3], Thomas F. Lüscher[4], Alberico L. Catapano[5*†], and Kausik K. Ray[6†]

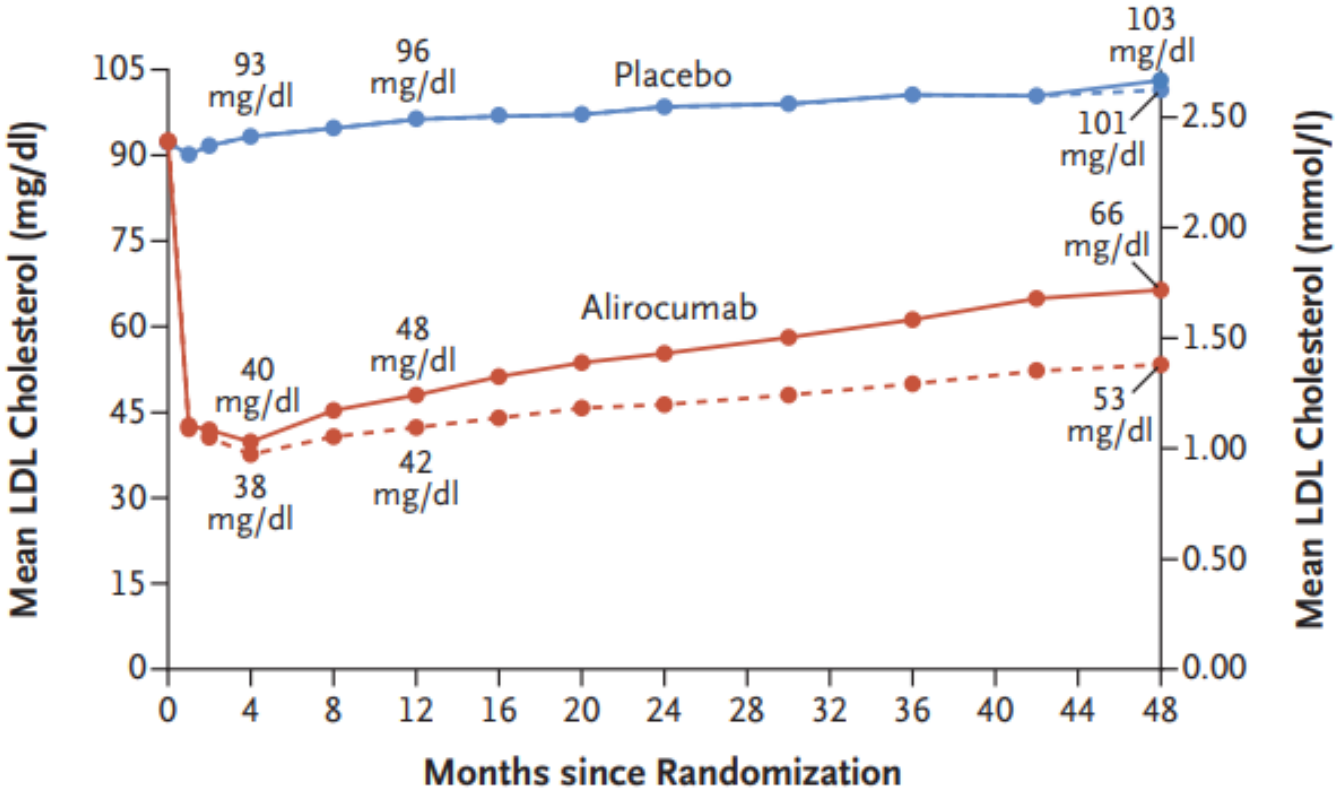
Year of treatment	No. of events in CTT	HR (95% CI) during each year of treatment in CTT	HR (95%) during each year of treatment in SPIRE-2	HR (95%) during each year of treatment in FOURIER	Cumulative duration of treatment (years)	HR (95%) for cumulative duration of statin treatment in CTT	HR (95%) by median duration of treatment in PCSK9 Trials	PCSK9 Trial
0–1	7449	0.88 (0.84–0.93)	0.86 (0.75–0.98)	0.87 (0.79–0.97)	1	0.88 (0.84–0.93)	0.86 (0.75–0.98)	SPIRE-2 trial
1–2	4757	0.77 (0.73–0.82)		0.78 (0.71–0.86)	2	0.83 (0.80–0.86)	0.83 (0.77–0.90)	FOURIER trial
2–3	4081	0.73 (0.69–0.78)			3	0.80 (0.77–0.83)	*0.80 (0.77–0.83)*	*Anticipated ODESSEY trial Results*
3–4	3462	0.72 (0.68–0.77)			4	0.78 (0.76–0.81)		
4–5	2710	0.77 (0.72–0.83)			5	0.78 (0.76–0.80)		
>5	1864	0.76 (0.69–0.85)			6	0.78 (0.76–0.80)		
Overall	24 323	0.78 (0.76–0.80)			Mean 5.1	0.78 (0.76–0.80)		

An analysis of the time to benefit also showed that there was a lower benefit in the first year than in subsequent years, consistent with the effects of statins observed within the CTT meta-analysis

Ference BA et al, Eur Heart J. 2018

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*



Schwartz GG et al, N Engl J Med. 2018

The ODYSSEY Outcomes trial

- ✓ 18924 randomized patients after hospitalization for acute MI or unstable angina, treated with statins, and with LDL-C >_70 mg/dL, non-HDL cholesterol >_100 mg/dL or ApoB >_80 mg/dL, to receive injections of alirocumab or matching placebo
- ✓ Allocation to alirocumab **reduced** the mean baseline **LDL-C** **from 92 mg/dL to 48 mg/dL at 12 months**
- ✓ **There was a 15% relative reduction in the primary outcome** (composite of CHD death, nonfatal MI, ischaemic stroke, or unstable angina requiring hospitalization) (HR 0.85, 95% CI 0.780.93) after a median follow-up of **2.8 years**

Adverse effects and interactions

- Anti-PCSK9 mAbs are **injected subcutaneously**, every other week or once a month, at different doses depending on the agent used

- The potential for **interaction with orally absorbed drugs is absent**, as they will not interfere with pharmacokinetics or pharmacodynamics

- Among the most frequently reported side effects are **itching** at the **site of injection and flu-like symptoms**

[Cicero AF et al, Expert Opin Drug Saf. 2014]

- In some studies, an **increase of patient-reported neurocognitive effects** has been described

[Lipinski MJ et al, Eur Heart J. 2016]

- However, the EBBINGHAUS trial, which was **specifically designed to detect neurocognitive function changes**, was reassuring, as were the **safety reports in both the FOURIER and ODYSSEY trials**

[Giugliano RP et al, N Engl J Med. 2017]

Recommendations for pharmacological LDL-C lowering

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[197,265,353]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.[197,265,353]	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

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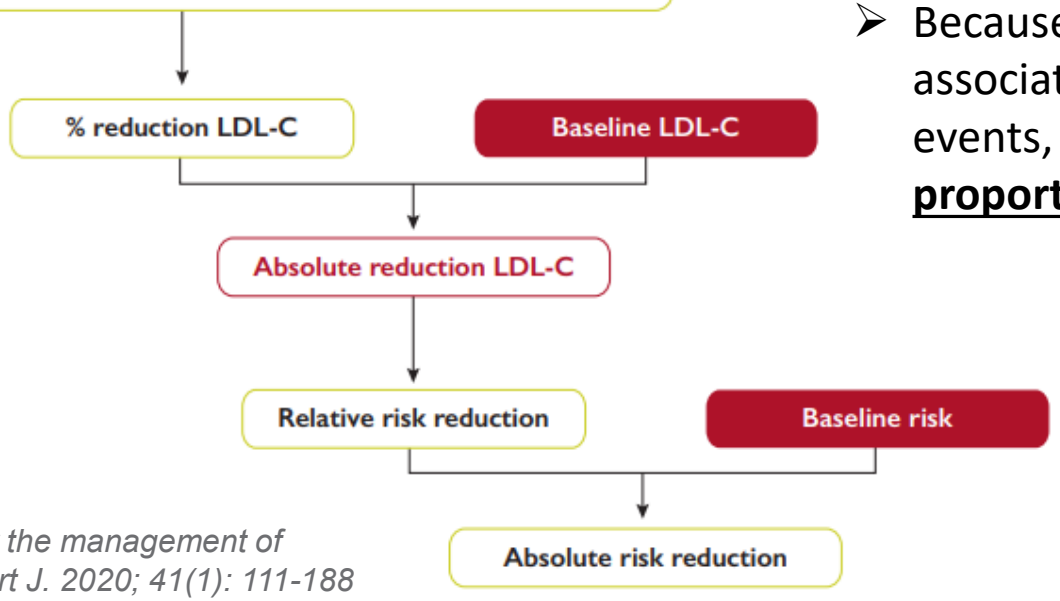
Expected clinical benefits of LDL-C lowering therapies

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%



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- Intensity of therapy: should be selected to achieve the recommended proportional reduction in LDL-C based on the person's estimated risk of atherosclerotic cardiovascular disease
- Multiplying the proportional reduction in LDL-C by a person's baseline LDL-C level estimates the expected absolute reduction in LDL-C that is likely to be achieved with that therapy
  - Because each 1.0 mmol/L absolute reduction in LDL-C is associated with a 20% reduction in the risk of cardiovascular events, **larger absolute reductions in LDL-C lead to larger proportional reductions in risk**
    - Multiplying the proportional reduction in risk expected for the achieved absolute reduction in LDL-C by a person's estimated baseline risk of atherosclerotic CV disease **determines the expected absolute risk reduction for that person**

Treatment algorithm for pharmacological LDL-C lowering

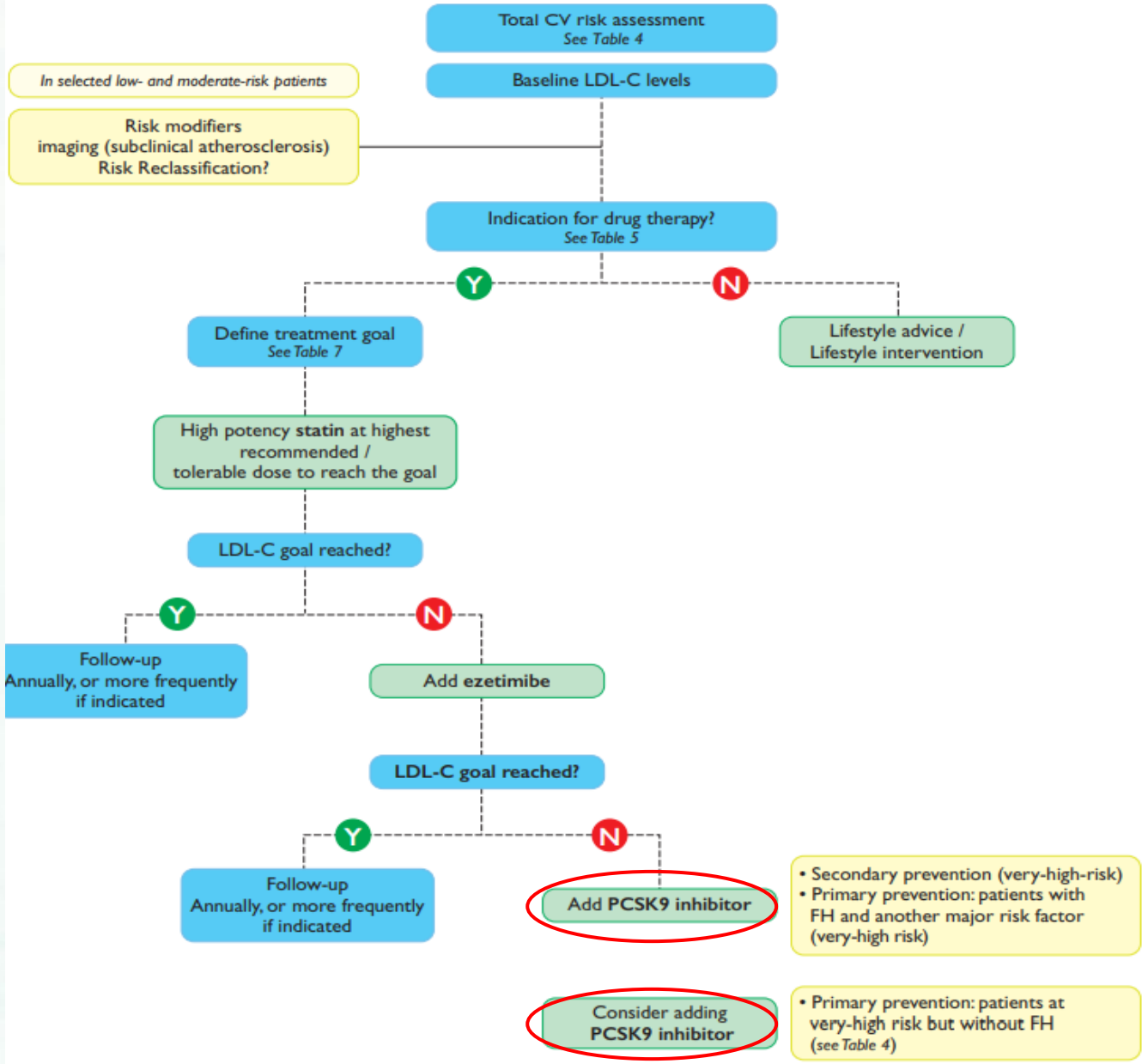
- Although LDL-C goals are attained with monotherapy in many patients, a significant proportion of patients at high-risk or with very high LDL-C levels need additional treatment

  ↓

  In this case, **combination therapy is reasonable**

- In patients at very-high risk and with persistent high-risk despite being treated with a maximally tolerated statin, **combination** with **ezetimibe** is recommended and, if still not at goal, the **addition** of a **PCSK9 inhibitor is recommended**

- **Addition of a PCSK9 inhibitor directly to a statin is also feasible**



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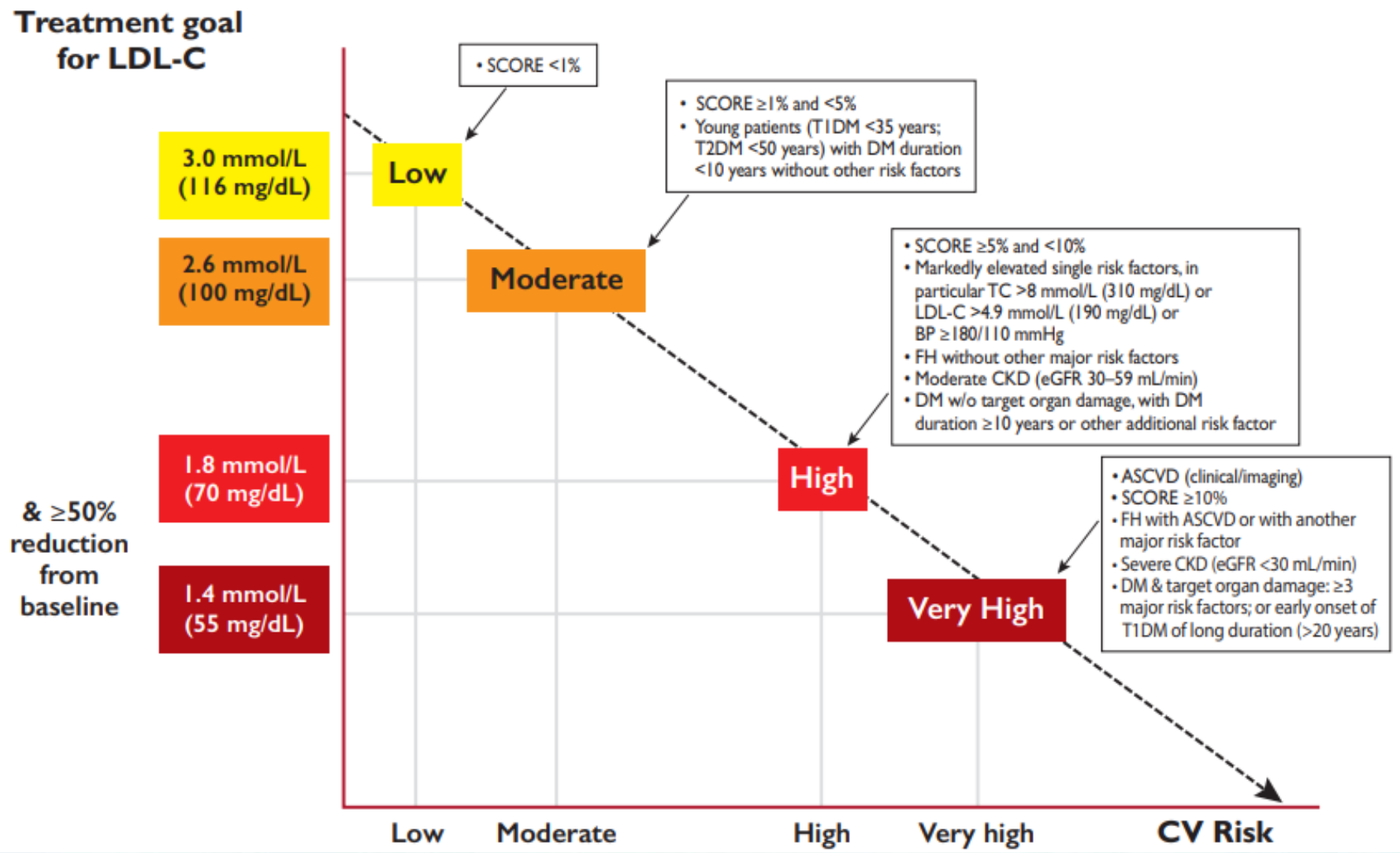
Treatment goals for LDL-C across categories of total CV disease risk



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RECOMMENDATIONS

CVD risk estimation

Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults aged >40 years without evidence of CVD, DMCKD, FH, or LDL >4.9 mmol/L (>190 mg/dL).	I	C
High- and very-high-risk individuals may be identified on the basis of documented CVD, DM, moderate-to-severe renal disease, very high levels of individual risk factors, FH, or a high SCORE risk, and are a priority for advice and management of all risk factors.	I	C
Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM or FH.	III	C

Lipid analyses for CVD risk estimation

TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as a part of the routine lipid analysis approach.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or MetS, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C

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Treatment goals for LDL-C

In secondary prevention for patients at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In primary prevention for individuals at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In patients at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

Pharmacological LDL-C lowering

It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For secondary prevention in patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C

Drug treatment of patients with hypertriglyceridaemia

Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with HTG [TGs >2.3 mmol/L (>200 mg/dL)].	I	B

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Management of patients with heterozygous familial hypercholesterolaemia

It is recommended that a diagnosis of FH is considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives having tendon xanthomas, in people with severely elevated LDL-C levels [in adults >5 mmol/L (>190 mg/dL), in children >4 mmol/L (>150 mg/dL)], and in first-degree relatives of FH patients.	I	C
It is recommended that FH is diagnosed using clinical criteria and confirmed, when possible, with DNA analysis.	I	C
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk.	I	C
For FH patients with ASCVD who are at very-high risk, treatment to achieve a ≥50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C
Treatment with a PCSK9 inhibitor is recommended in very-high risk FH patients if the treatment goal is not achieved on a maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.	I	C

Treatment of dyslipidaemias in older people

Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years.	I	A
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

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Treatment of dyslipidaemias in DM

In patients with T2DM at very-high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
In patients with T2DM at high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.[c]	I	A
Statin therapy is not recommended in pre-menopausal patients with or without DM who are considering pregnancy, or not using adequate contraception.	III	C

Management of patients with acute coronary syndrome

In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.	I	A
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B

Lipid-lowering therapy for prevention of ASCVD events in patients with prior ischaemic stroke

Patients with a history of ischaemic stroke or TIA are at very-high risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy.	I	A

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Treatment of dyslipidaemias in chronic HF or valvular heart diseases

Initiation of lipid-lowering therapy is not recommended in patients with HF in the absence of other indications for their use.	III	A
Initiation of lipid-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use.	III	A

Lipid management in patients with moderate-to-severe (Kidney Disease Outcomes Quality Initiative stages 3-5) CKD

It is recommended that patients with stage 3–5 CKD are considered to be at high or very-high risk of ASCVD.	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.	I	A
In patients with dialysis-dependent CKD who are free of ASCVD, commencement of statin therapy is not recommended.	III	A

Lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)

In patients with PAD, lipid-lowering therapy—including a maximum tolerated dose of a statin, plus ezetimibe, or a combination with a PCSK9 inhibitor if needed—is recommended to reduce the risk of ASCVD events.	I	A

Lipid-lowering drugs in patients with chronic immune-mediated inflammatory diseases

The use of lipid-lowering drugs only on the basis of the presence of CIID is not recommended.	III	C

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Key messages

- Prospective studies, randomized trials, and Mendelian randomization studies have all shown that **raised LDL-C is a cause of ASCVD**

- Throughout the range of LDL-C levels, 'lower is better' with no lower threshold, **at least down to 1 mmol/L**

- Lowering LDL-C may yield worthwhile benefits in patients with average or below average LDL-C who are already receiving LDL-C-lowering treatment

- The proportional **reduction in ASCVD risk** achieved by **lowering LDL-C** (e.g. with a statin, ezetimibe or PCSK9-inhibitor) depends on the absolute reduction in LDL-C, with each **1 mmol/L reduction** corresponding to a **reduction of about one-fifth in ASCVD**

Key messages

- Although **PCSK9 inhibitors** are very effective drugs that can **reduce LDL-C and CV events** on top of statin and/or ezetimibe treatment, considering the **costs** of the treatments and the limited data on long-term safety

PCSK9 inhibitors are likely to be considered cost-effective only in those patients at very high-risk of ASCVD and their use may not be possible in some countries with limited healthcare resources

- Large trials have shown that **PCSK9 inhibitors** further reduce **ASCVD risk** when given **on top of statin-based therapy** and their use may need to be restricted to those at the highest risk for ASCVD

Key messages

- **More evidence is needed for PCSK9 inhibitors** in specific populations, including patients with severe CKD and on dialysis, patients with HIV infection, in children and adolescents with FH, after heart transplantation, and during pregnancy

- **The effects of PCSK9 inhibition** on specific body compartments (as with siRNA or antisense) or only within plasma (as with monoclonal antibodies) **remain to be established**

How early should a PCSK9 inhibitor be initiated in patients with **ACS** or **stroke**?

In view of evidence of sustained clinical benefit associated with the early initiation of statin treatment in the acute phase of ACS or stroke, the optimal timing of PCSK9 inhibitor **remains to be addressed in outcome studies**

- Whether **very low LDL-C levels** achieved with the combination of **statin**, **ezetimibe**, and **PCSK9 inhibitor** reduce the need for **further PCI** **remains to be addressed in outcome studies**