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Premium Selection

StudyOverview

Strategies for lowering LDL cholesterol to reduce cardiovascular risk

When even PCSK9 inhibitors are not sufficiently effective ...

Reprint Publications

Introduction

Medication to lower elevated LDL cholesterol levels has been shown to reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD), such as coronary heart disease (CHD). CHD and its counterpart in the brain, cerebrovascular disease (CeVD), are the leading causes of death in the Western world. Atherosclerosis is an inflammatory process in which lipids are deposited in the form of plaques in the inner wall of arteries. This can lead to narrowing of the lumen of the affected vessels and, if the plaque ruptures, to the detachment of thrombi with acute complications such as myocardial infarction or stroke.

Effective drugs for lowering LDL cholesterol levels are (1) statins, which interfere with cholesterol synthesis, (2) ezetimibe, which inhibits the absorption of cholesterol in the small intestine, and (3) proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which inhibit the lysosomal degradation of LDL receptors in the liver, which are responsible for transporting LDL cholesterol from the blood to the body's cells.

Both the guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommend statins as first-line therapy and ezetimibe as second-line therapy if statin intolerance exists or if the target LDL cholesterol level is not achieved despite maximum dosage. If further LDL cholesterol reduction is still necessary, PCSK9 inhibitors are recommended.

The publications summarized below begin with the ESC/EAS guideline recommendations for LDL cholesterol reduction. These guidelines also strongly recommend additional therapy with PCSK9 inhibitors for high-risk cardiovascular patients, such as those with familial hypercholesterolemia or type 2 diabetes. For these patients, the guidelines recommend lowering LDL cholesterol levels by at least 50 % from baseline to a target value of < 55 mg/dL. As the studies from Italy and the United States presented below on the real-world care of patients with ASCVD show, PCSK9 inhibitors are indeed an effective treatment option. However, their use is often hampered by regulatory and billing-related obstacles, and approximately half of all high-risk patients do not achieve the target level of < 55 mg/dL.

Contents

Guidelines on dyslipidemias

2019 ESC/EAS guidelines for the management of dyslipidemias: Lipid modification to reduce cardiovascular risk*

Mach F, Baigent C, Catapano AL et al., ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies

Introduction

The guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) on the management of lipid metabolism disorders, which were published in 2019, became necessary after a number of new scientific findings had been obtained in the previous years that needed to be taken into account. These included the results of several placebo-controlled studies showing that ezetimibe or PCSK9 inhibitors can enhance the lipid-lowering effect of statins and thus further reduce the risk of atherosclerotic cardiovascular disease (ASCVD). While ezetimibe is a specific inhibitor of the cholesterol transporter NPC1L1, the monoclonal anti-PCSK9 antibodies are directed against proprotein convertase subtilisin kexin type 9. Clinical studies havealso shown that the lower the LDL cholesterol levels achieved, the greater the atherosclerotic protective effect of the therapy.

2019 guideline recommendations (selection)

- In order to better assess the individual risk in patients with **low or moderate ASCVD risk**, consideration should be given to determining the arterial plaque burden (carotid or femoral arteries) by sonography or the coronary artery calcium (CAC) score by computed tomography.
- At least once in a patient's lifetime, consideration should be given to determining the lipoprotein(a) level. In patients with very high levels (>180 mg/dL or >430 nmol/L), the risk of ASCVD may be equivalent to those with heterozygous familial hypercholesterolemia (FH).
- In the primary prevention of high-risk patients with familial FH (or the aforementioned risk status), consideration should be given to reducing LDL cholesterol levels by at least 50 % from baseline and to a target of <1.4 mmol/L (<55 mg/dL).

*A "focused" update of the ESC/EAS guidelines on the management of dyslipidemias has recently been published (Mach F et al. Eur Heart J 2025;46:4359-78). The most important new features are: (1) The integration of SCORE2 and SCORE2-OP for better risk assessment of acute cardiovascular events; (2) New treatment options for lowering LDL-C (bempedoic acid, evinacumab, and inclisiran) and triglyceride levels (icosapent ethyl); (3) the early use of lipid-lowering combination therapy after an acute coronary event; and (4) the mandatory (once-in-a-lifetime) determination of Lp(a) as a risk-enhancing factor (see also Ray KK, Kronenberg F. Atherosclerosis 2026;413:120636)

- The following guidelines apply to **diabetics with dyslipidemia**:
  - For patients with type 2 diabetes and very high risk, a reduction of LDL cholesterol by ≥ 50 % from baseline and to a target of < 1.4 mmol/L (< 55 mg/dL) is recommended.
  - In patients with type 2 diabetes and high risk, a reduction of LDL cholesterol by ≥ 50 % from baseline and to a target of < 1.8 mmol/L (< 70 mg/dL) is recommended.
  - Statin therapy is recommended for patients with type 1 diabetes and high to very high risk.
  - In general, diabetics with dyslipidemia should first consider intensification of statin therapy. If the LDL cholesterol level cannot be lowered sufficiently with this, statin combination with ezetimibe should be considered.
  - Statin therapy is not recommended for premenopausal women with diabetes or those who are considering pregnancy or are not using adequate contraception.

- If the LDL cholesterol levels in patients with **acute coronary syndrome (ACS)** are not within the target range at the time of the event despite a maximum tolerated statin dose plus ezetimibe, the addition of a PCSK9 inhibitor early after the event – if possible during inpatient treatment – should be considered.

Changed or tightened recommendations compared to the 2016 guideline version (selection)

Lipid analysis to assess the cardiovascular risk

- Apolipoprotein B analysis is recommended (previously: should be considered), especially in patients with high triglyceride levels, diabetes, obesity or metabolic syndrome, or very low LDL cholesterol levels.

Medication to lower LDL cholesterol

- If the target value is not reached despite the maximum tolerated statin dose, combination therapy with ezetimibe is now recommended (previously: combination with a cholesterol absorption inhibitor).

- In secondary prevention, if the target value is not reached despite the maximum tolerated statin dose plus ezetimibe, the combination with a PCSK9 inhibitor is recommended (previously: should be considered).

Treatment of patients with heterozygous FH

- A PCSK9 inhibitor is now also recommended for FH patients at very high risk (i.e. with ASCVD or another serious risk factor) in addition to a statin and ezetimibe if the two-drug combination fails to reduce LDL cholesterol levels by ≥ 50 % and to levels below 1.4 mmol/L (< 55 mg/dL).

Treatment of patients with acute coronary syndrome

- If the target value of LDL cholesterol is not reached after 4 – 6 weeks despite maximum tolerated statin doses plus ezetimibe, it is recommended to additionally administer a PCSK9 inhibitor.

New/changed treatment concepts at a glance

- For all categories of cardiovascular risk (moderate, high, very high) (➔ Table 1) and primary and secondary prevention, the 2019 guideline defines strict LDL cholesterol target values, some of which are lower than in the 2016 guidelines. This extends to <1.0 mmol/L (<40 mg/dL) for patients with ASCVD who have had two vascular events within 2 years.

- Patients with FH without ASCVD or another significant risk factor are classified as high-risk patients. If ASCVD or another major risk factor is also present, the patient is classified as very high risk.
- Based on new study data, the recommendations on PCSK9 inhibitors are updated and in some cases expanded.

Table 1 Categories of cardiovascular risk

Very high risk	– ASCVD clearly documented clinically or by imaging – Diabetes with end organ damage or ≥3 significant risk factors or type 1 diabetes that has been present for >20 years – Severe chronic kidney disease (eGFR <30 mL/min/1.73 m²) – A calculated SCORE ≥10% for the 10-year risk of fatal cardiovascular disease – FH with ASCVD or another major risk factor
High risk	– Significantly elevated single risk factors, in particular triglycerides >8 mmol/L (>310 mg/dL), LDL cholesterol >4.9 mmol/L (>190 mg/dL) or blood pressure ≥180/110 mm Hg – FH without other significant risk factors – Diabetes without end organ damage, with a duration of ≥10 years or another risk factor – Moderate chronic kidney disease (eGFR 30–59 mL/min/1.73 m²) – A calculated SCORE ≥5% for the 10-year risk of fatal cardiovascular disease
Moderate risk	Young patients (type 1 diabetes <35 years, type 2 diabetes <50 years) with a diabetes duration of <10 years without other risk factors. A calculated SCORE ≥1% and <5% for the 10-year risk of fatal cardiovascular disease
Low risk	A calculated SCORE <1% for 10-year risk of fatal cardiovascular disease

Source: Modified according to Mach et al, 2019

Abbreviations: **ASCVD** = atherosclerotic cardiovascular disease, **eGFR** = estimated glomerular filtration rate, **FH** = familial hypercholesterolemia, **SCORE** = Systematic Coronary Risk Estimation

Edited, shortened version of the article by Mach F et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019;290:140–205

"Real world" data on PCSK9 inhibitors

Real-world effectiveness of PCSK9 inhibitors in reducing LDL cholesterol in patients with familial hypercholesterolemia in Italy: a retrospective cohort study based on the AIFA monitoring registries

Arca M, Celant S, Olimpieri PP, Colatrella A, Tomassini L, D'Erasmo L, Averna M, Zambon A, Catapano AL, Russo P

Introduction

Familial hypercholesterolemia (FH) is the most common genetic disorder of lipid metabolism, characterized by significantly elevated LDL cholesterol levels and a considerably increased risk of early-onset atherosclerotic cardiovascular disease (ASCVD). This applies to an even greater extent to homozygous FH (hoFH), which, however, is much rarer than the heterozygous form (heFH). Statins and ezetimibe are the established first-line therapy for lowering LDL cholesterol levels in FH patients. The target values are very low, at ≤70 mg/dL (<55 mg/dL) in the European guidelines – in connection with a reduction of ≥50 % from baseline – in cases where ASCVD is already present.[1] However, published real-world data show that even with combination therapy of a statin and ezetimibe, these values are not achieved, especially in patients with hoFH. Lipoprotein apheresis is therefore necessary for many of these patients. The present study from clinical practice in Italy investigated the extent to which PCSK9 inhibitors can contribute to achieving LDL cholesterol target values more frequently in patients with hoFH or heFH.

Patients and Methods

- The data for this retrospective cohort study were taken from the monitoring registries of the Italian regulatory authority AIFA.
- Inclusion in the registry is mandatory for all patients with heFH or hoFH who have started therapy with the PCSK9 inhibitors alirocumab or evolocumab, provided they meet the following **inclusion criteria**:
  - confirmed diagnosis of FH (Dutch Lipid Clinic Network Score >8)[2]
  - LDL cholesterol ≥130 mg/dL (≥100 mg/dL for secondary prevention) despite highest-dose statin + ezetimibe
  - or clinically confirmed statin intolerance
  - age ≤80 years
  - eGFR ≥30 mL/min/1.73 m²
- During treatment with a PCSK9 inhibitor, it was permitted to modify or discontinue background lipid-lowering therapy.
- The prescription status of PCSK9 inhibitors was assessed after 6, 12, 18, and 24 months.

Table 2 Characteristics of Italian patients with heFH or hoFH from the AIFA PCSK9 registry

	heFH (n=2,484)	hoFH (n=62)
Age, mean (SD), years	56.2 (12.1)	48.2 (17.8)
Male sex, n (%)	1,219 (49.07)	36 (58.06)
FH diagnosis		
DCLN score, mean (SD)	11.98 (3.44)	15.71 (6.39)
Patients genotyped, n (%)	449 (18.08)	25 (40.32)
LDLR mutation	409 (16.47)	22 (35.48)
APOB mutation	25 (1.01)	3 (4.84)
PCSK9 mutation	15 (0.60)	1 (1.61)
Risk factors, n (%)		
Current | Ex-smokers	411 (16.55) | 635 (25.56)	3 (4.84) | 16 (25.81)
Hypertension | Diabetes	1,173 (47.22) | 156 (6.28)	19 (30.65) | 1 (1.61)
CKD mild* | moderate**	94 (3.78) | 39 (1.57)	1 (1.61) | 0 (0.00)
ASCVD, n (%)		
CHD | CeVD | PAD	463 (18.64) | 218 (8.78) | 469 (18.88)	28 (45.16) | 3 (4.84) | 4 (6.45)
Prevention, n (%)		
Primary | Secondary	1,489 (59.94) | 995 (40.06)	31 (50.00) | 31 (50.00)
Lipid-lowering therapy, n (%)		
None/not maximal | High/maximal	1,147 (46.17) | 1,337 (53.83)	19 (30.65) | 43 (69.35)
Statins | Ezetimibe	1,314 (54.11) | 2,484 (100.00)	43 (69.35) | 62 (100.00)
LDL apheresis	23 (0.93)	7 (11.29)
Fibrates | PUFA-N3	35 (1.41) | 85 (3.42)	1 (1.61) | 3 (4.84)
Patients with statin intolerance, n (%)	1,140 (45.89)	19 (30.65)
Plasma lipids, mean (SD), mg/dL		
Total cholesterol	279.8 (57.8)	325.1 (110.2)
LDL-C | HDL-C	197.7 (52.3) | 53.4 (13.5)	245.6 (108.3) | 51.1 (10.4)
Non-HDL-C | Triglycerides	226.5 (55.9) | 144.1 (74.8)	274.1 (108.2) | 142.6 (69.0)
Type and dosage of PCSK9i, n (%)		
Alirocumab q2w 75 mg | 150 mg	647 (26.05) | 481 (19.36)	- | -
Evolocumab 140 mg q2w | 420 mg qmo	1,348 (54.27) | 8 (0.32)	43 (69.35) | 19 (30.65)

Source: Modified according to Arca et al., 2023

*eGFR 60–89 ml/min, **eGFR 30–59 ml/min

Abbreviations: **ASCVD** = atherosclerotic cardiovascular disease, **CHD** = coronary heart disease, **CKD** = chronic kidney disease, **CeVD** = cerebrovascular disease, **DCLN** = Dutch Lipid Clinic Network, **eGFR** = estimated glomerular filtration rate, **FH** = familial hypercholesterolemia, **HDL-C** = HDL cholesterol, **heFH** = heterozygous familial hypercholesterolemia, **hoFH** = homozygous familial hypercholesterolemia, **LDL-C** = LDL cholesterol, **PAD** = peripheral artery disease, **PCSK9i** = PCSK9 inhibitor, **PUFA-N3** = n3 polyunsaturated fatty acids, **q2w** = every 2 weeks, **qmo** = once a month, **SD** = standard deviation

Results

- For the cohort study, data from a total of 2,546 patients with heFH (n=2,484) or hoFH (n=62) were extracted from the AIFA registry between 2017 and 2019, for whom follow-up data were available for at least 24 months. The characteristics of these patients are listed in ➔ Table 2.

- Only about half of all patients – 1,236 patients with heFH and 36 with hoFH – could be evaluated for PCSK9 inhibitor prescription status at least once at the scheduled follow-up appointments, and only 971 and 24 patients, respectively, could be evaluated at all time points.
- At all time points, PCSK9 inhibitor **persistence** was over 80 % in evaluable patients, and mean **adherence** ranged from 93.4 % to 94.5 %. However, the proportion of patients with **100 % adherence** to therapy decreased from approximately 44 % after 6 months to approximately 11 % after 24 months.
- Over the course of the 24-month follow-up, total cholesterol in **patients with heFH** decreased from 279.8 ± 57.7 mg/dL to 157.8 ± 50.6 mg/dL and LDL cholesterol from 197.7 ± 52.5 mg/dL to 79.7 ± 45.9 mg/dL. However, only 43.25 % of patients achieved the LDL cholesterol target level (➔ Table 3).
- In **patients with hoFH**, total cholesterol decreased from 328.8 ± 104.9 mg/dL to 170.5 ± 66.1 mg/dL and LDL cholesterol from 248.0 ± 105.0 mg/dL to 95.1 ± 60.2 mg/dL. Only 37.50 % of patients in this subpopulation achieved the LDL cholesterol target level (➔ Table 3).

Table 3 Evolution of mean total and LDL cholesterol levels in patients with heFH and hoFH undergoing treatment with PCSK9 inhibitors

mg/dL (SD)	Baseline	6 months	12 months	18 months	24 months
heFH, n	**1,263**	**1,102**	**1,060**	**1,032**	**971**
Total cholesterol	279.8 (57.7)	165.2 (80.8)*	158.7 (51.1)*	158.7 (51.1)*	157.8 (50.6)*
LDL cholesterol	197.7 (52.5)	86.6 (76.3)*	80.6 (46.2)*	80.5 (45.5)*	79.7 (45.9)*
Achievement of target value					
% reduction in LDL-C from baseline (SD)		56.2 (35.2)	58.4 (20.8)	58.5 (20.8)	58.6 (20.5)
Patients achieving LDL-C target, n (%)		**462 (41.9)**	**452 (42.64)**	**449 (43.51)**	**420 (43.25)**
hoFH, n	**36**	**32**	**29**	**27**	**24**
Total cholesterol	328.8 (104.9)	209.3 (82.8)†	184.7 (86.5)†	175.5 (61.2)†	170.5 (66.1)†
LDL-C	248.0 (105.0)	133.3 (82.8)†	113.3 (76.7)†	102.5 (56.2)†	95.1 (60.2)†
Achievement of target value					
% reduction in LDL-C from baseline (SD)		43.89 (29.2)	48.93 (28.8)	53.03 (22.7)	57.55 (25.3)
Patients achieving LDL-C target, n (%)		**5 (15.6)**	**5 (17.2)**	**8 (29.6)**	**9 (37.5)**

Source: Modified according to Arca et al., 2023

* $p < 0.05$ from baseline; † $p < 0.01$ from baseline

Abbreviations: **heFH** = heterozygous familial hypercholesterolemia, **hoFH** = homozygous familial hypercholesterolemia, **LDL-C** = LDL cholesterol, **SD** = standard deviation

- A significant proportion of heFH patients who did not achieve the target LDL cholesterol level after 6 months discontinued therapy before the 24-month time point (14.4 %). Among patients with hoFH, this proportion was as high as 29.6 %.

- The number of patients with **heFH** who underwent lipoprotein apheresis decreased from 15 (1.2 %) to 6 (0.5 %) within the first 6 months and remained largely unchanged until the end of the study. Among patients with **hoFH**, the rate of lipoprotein apheresis use was 16.7 % at baseline, decreased to 6.3 % by month 6, but then increased again, reaching 12.5 % after 24 months.

Conclusions

- This Italian cohort study significantly expands the evidence on the efficacy of PCSK9 inhibitors in patients with heterozygous and homozygous FH in real-world practice.

- The results demonstrate the efficacy of PCSK9 inhibitors even in patients with very high baseline LDL cholesterol levels. Approximately 2 out of 5 patients with heFH and 2 out of 6 patients with hoFH achieved target levels.

- Conversely, however, this means that more than 50 % of heFH patients and more than 60 % of hoFH patients did not achieve the target values recommended by the European Atherosclerosis Society/European Society of Cardiology even after 2 years of therapy with a PCSK9 inhibitor.

Edited, shortened version of the article by Arca M et al. Real-world effectiveness of PCSK9 inhibitors in reducing LDL-C in patients with familial hypercholesterolemia in Italy: A retrospective cohort study based on the AIFA monitoring registries. *J Am Heart Assoc* 2023;12(21):e026550

1 Mach F et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019;290:140-205

2 https://www.athero.org.au/fh/wp-content/uploads/Dutch-Lipid-Clinic-Network-Score2.pdf

US health insurance data on PCSK9 inhibitors

Trends in patient access to and utilization of prescribed PCSK9 inhibitors in a large US claims database from 2015 to 2021

MacDougall DE, Baum SJ, Ahmed CD, McGowan MP, Wilemon KA

Introduction

In the United States, PCSK9 inhibitors were approved in 2015 for further lowering LDL cholesterol levels in patients with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolemia (FH). After 2017, approval was extended to the prevention of additional events in patients with ASCVD and further reduction of LDL cholesterol in primary hypercholesterolemia. The partial rejection of prescriptions or cost coverage for PCSK9 inhibitors prior to 2017 led to a higher incidence of cardiovascular events in this patient group compared with self-payers who were prescribed a PCSK9 inhibitor. After 2017, the extension of the approval, but also the adjusted guideline recommendations, the positive results of two clinical studies, and a significant reduction in costs led to the increasingly frequent use of this drug class.

Patients and Methods

- Using the Family Heart Database, which collects reimbursement claims for medical care services for more than half of the US population, a retrospective cohort study was conducted to analyze new prescriptions for PCSK9 inhibitors in more detail.
- A distinction was made between
  - paid prescriptions (covered by insurance and reimbursed to the insured)
  - prescriptions rejected by insurance
  - costs for the prescription covered by the insured themselves and not reimbursed
- Prescription data for the periods **2015–2018** and **2019–2021** were compared (→ Table 4). The initial cost coverage status referred to the first 90 days of the prescription. Permanent cost coverage was defined as a patient being reimbursed for the cost of a PCSK9 inhibitor for at least 168 days within any 12-month period. These data were compared with the initial cost coverage status for other cardiometabolic oder cardiometa-bolic drugs recommended in the guidelines with proven efficacy as a reference.

Results

- Between 2015 and 2018, a total of 238,704 patients who were newly prescribed a PCSK9 inhibitor were recorded in the Family Heart Database. This number increased to 470,018 between 2019 and 2021. The demographic characteristics of the patients were similar in both periods: approximately 50 % were women, 60 % were white, 7 % were black, 5 % were Hispanic, and 28–29 % were of unknown ethnicity. The income of two-thirds of the patients was unknown.

Table 4 Insurance coverage of PCSK9 inhibitors and other drugs for modifying cardiometabolic risk factors

	From July 2015 to December 2018 (n=238.704)				From January 2019 to December 2021 (n=470.018)			
	Coverage	Rejection	Waiver	Coverage <168 days*	Coverage	Rejection	Waiver	Coverage <168 days*
Initial and ongoing insurance coverage of PCSK9 inhibitors, % (n)								
Initial coverage	35.70 % (85,215)	45.86 % (109,479)	18.44 % (44,010)	NA	49.93 % (234,703)	30.95 % (145,472)	19.11 % (89,843)	NA
Continuous coverage	34.91 % (83,343)	41.23 % (98,416)	19.66 % (46,940)	4.19 % (10,005)	42.48 % (199,659)	26.26 % (123,437)	22.31 % (104,865)	8.95 % (42,057)
Initial insurance coverage of other cardiometabolic drugs, % (n)								
Apixaban	82.87 % (2,594,317)	4.97 % (155,514)	12.17 % (380,923)	NA	84.45 % (3,632,818)	3.53 % (151,824)	12.02 % (516,981)	NA
Sacubitril/Valsartan	73.73 % (252,063)	12.22 % (41,774)	14.05 % (48,041)	NA	78.63 % (487,376)	7.10 % (44,034)	14.26 % (88,400)	NA
Dapagliflozin	70.78 % (518,601)	14.69 % (107,626)	14.53 % (106,455)	NA	68.98 % (698,834)	13.19 % (133,588)	17.83 % (180,666)	NA
Empagliflozin	72.46 % (789,444)	10.53 % (114,758)	17.01 % (185,326)	NA	76.71 % (1,654,301)	6.36 % (137,078)	16.94 % (365,292)	NA
Liraglutide	70.53 % (707,412)	13.24 % (132,798)	16.23 % (162,735)	NA	68.49 % (358,376)	14.61 % (76,444)	16.90 % (88,435)	NA

Source: Data from the US Family Heart Database (according to MacDougall et al., 2023)

*Discontinuation of therapy without cost rejection or waiver. The reasons are unknown, but possible causes include removal from the database, discontinuation of prescription by the physician, or death

Abbreviation: NA = not applicable

- From the first to the second period, the number of new prescriptions for PCSK9 inhibitors covered by health insurance increased 2.7-fold. However, with just under 50 %, their proportion out of the total number of prescriptions was still significantly lower than for other cardiometabolic drugs recommended in the guidelines, for which the cost coverage ranged from 68.5 % (liraglutide) to 84.5 % (apixaban) (➔ Table 4).

Conclusions

- The results of this analysis of healthcare practice in the United States show that the prescription of PCSK9 inhibitors still faces major obstacles there.
- The associated stagnation in the effective implementation of guideline-compliant LDL cholesterol reduction also means that the societal burden of atherosclerotic vascular disease still continues.

Edited, shortened version of the article by MacDougall DE et al. Trends in patient access to and utilization of prescribed PCSK9 inhibitors in a large US claims database from 2015 to 2021. *Circ Cardiovasc Qual Outcomes* 2024;17(2):e009988

Observational study on PCSK9 inhibitors

Efficacy, safety, adherence and persistence of PCSK9 inhibitors in clinical practice: A single country, multicenter, observational study (AT-TARGET-IT)

Gargiulo P, Basile C, Cesaro A, Marzano F, Buonocore D, Asile G, Abbate V, Vicidomini F, Paolillo S, Spaccarotella CAM, Catalano A, Spirito G, Angelica Merlini PA, Maloberti A, Iannuzzo G, Ciccone MM, Zito AP, Paloscia L, D'Alleva A, Varbella F, Corleto A, Brunetti ND, Corbo MD, Calabrò P, Indolfi C, Perrone-Filardi P

Introduction

It all began with evidence from clinical studies showing that very low LDL cholesterol levels achieved through therapy can further reduce the incidence of cardiovascular events in patients with dyslipidemia. These findings prompted the American and European guideline committees to tighten their recommendations for LDL cholesterol target values and to intensify treatment regimens accordingly. This also included the addition of PCSK9 inhibitors to the therapeutic armamentarium. However, there is currently very little information available on how often and how successfully this new class of drugs is used in clinical practice. To change this, the AT-TARGET-IT patient registry was established in Italy to document the use of PCSK9 inhibitors (evolocumab and alirocumab) and treatment outcomes.

Patients and Methods

- Between March 1, 2020, and January 30, 2022, ten Italian centers enrolled patients who had newly started therapy with a PCSK9 inhibitor in the registry. The following criteria were required for registration:
  - Minimum age of 18 years
  - First-time prescription of a PCSK9 inhibitor after January 15, 2017, and at least 6 months prior to inclusion in the database
  - Patient consent to inclusion and data analysis

Results

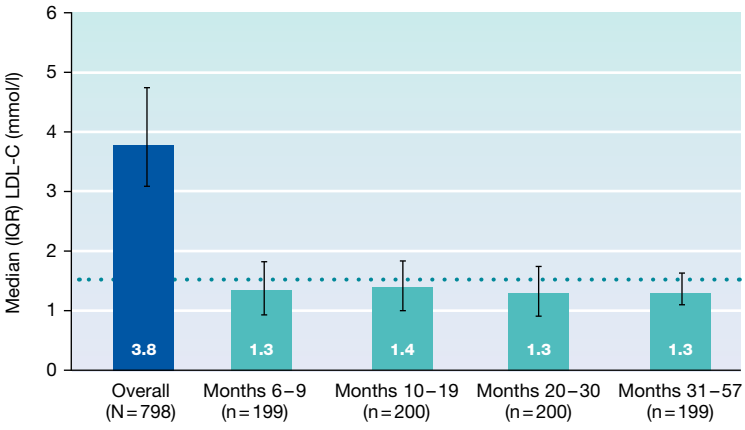
Study population and follow-up

- A total of 798 registered patients met the criteria for study participation. Their average age was 62 ± 7.8 years, 48.4 % had a family history of ASCVD (atherosclerotic cardiovascular disease) and 26.7 % had familial hypercholesterolemia (FH), 72.6 % had hypertension, 18 % had type 2 diabetes, and 34.7 % were current smokers.

- The patients were assigned to the following **disease categories**:
  - 472 (59 %) ASCVD without FH
  - 75 (9 %) ASCVD with FH
  - 138 (18 %) FH without ASCVD
  - 113 (14 %) without ASCVD and without FH

- The diagnosis of “confirmed” FH was defined as a Dutch Lipid Clinical Network (DLCN) score >8. The category “without ASCVD and without FH” included patients who had a high or very high cardiovascular risk and who were prescribed a PCSK9 inhibitor in accordance with guidelines due to statin intolerance.

- Before being prescribed a PCSK9 inhibitor, 423 patients (53 %) received statin therapy (87 alone, 336 in combination with ezetimibe), 246 (30.8 %) received ezetimibe, and 129 (16.2 %) received no lipid-lowering drugs.

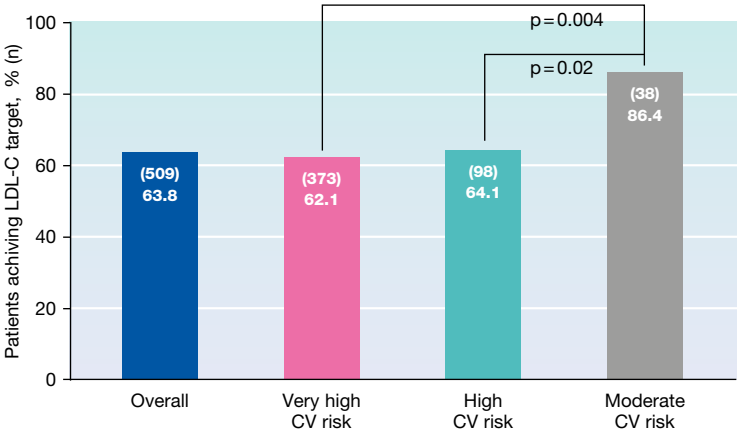


Relative reduction from baseline median (IQR), %	-64.7 (-50.6; -76.0)	-61.4 (-52.6; -74.5)	-67.1 (-51.4; -75.4)	-66.4 (-55.8; -75.9)
Absolute reduction from baseline median (IQR), mmol/l	-2.23 (-2.95; -1.57)	-2.22 (-2.92; -1.50)	-2.28 (-2.97; -1.55)	-2.22 (-2.93; -1.53)

Abbreviations: **IQR** = interquartile range, **LDL-C** = LDL cholesterol

Figure 1 LDL cholesterol levels in the overall population at the start of treatment with PCSK9 inhibitors and during the course of therapy

Source: Own representation based on Gargiuolo et al, 2023



Abbreviations: **CV** = cardiovascular, **LDL-C** = LDL cholesterol

Figure 2 Achievement of LDL cholesterol target values in the overall population and for subgroups according to risk status

Source: Own representation based on Gargiuolo et al, 2023

- The median follow-up for all patients was 19.33 (6–57) months.

Effectiveness of PCSK9 inhibitors

- The LDL cholesterol-lowering effect of PCSK9 inhibitors is shown in ➔ Figure 1 for different time intervals after the start of therapy.

- The relative reduction in LDL cholesterol levels was similar in all disease subpopulations (between 64.1 % and 68.7 %), with the absolute reduction ranging from 89.4 mg/dL (2.31 mmol/L) in patients with ASCVD without FH to 105.9 mg/dL (2.74 mmol/L) in the group with FH without ASCVD.

Adherence and persistence

- The large majority of patients, namely 95.2 %, showed high treatment adherence (medication possession ratio [MPR] ≥ 80 %). After 6 months, 99.7 % of patients had remained on their therapy, and after 18 months, 97.5 % had maintained their treatment. Twenty-eight patients (3.5 %) discontinued therapy with a PCSK9 inhibitor prematurely, 13 on their own decision and 15 on medical advice (in 4 cases due to side effects).

Achievement of LDL cholesterol target values

Of the total of 798 study participants, 509 (63.8 %) achieved the target LDL cholesterol value; most of them (424 [83.3 %]) received lipid-lowering basic therapy at the start of PCSK9 inhibitor therapy, 212 of them (41.7 %) received a fixed combination of a statin and ezetimibe. ➔ Figure 2 shows the success rates depending on the risk status of the patients.

Cardiovascular events during follow-up

- Within a median follow-up of 19.33 (6–57) months, 19 patients (2.4 %) had an acute coronary syndrome, 18 (2.3 %) were hospitalized, 3 (0.4 %) had a stroke, and in 6 cases (0.8 %), heart failure with reduced ejection fraction was newly diagnosed.

Conclusions

- According to the results of the AT-TARGET-IT study, PCSK9 inhibitors are well tolerated in real-world practice and can be prescribed with high adherence and persistence.

- Almost two-thirds of patients (63.8 %) achieved the therapeutic target value, mostly in combination with lipid-lowering basic therapy.

Edited, shortened version of the article by Gargiulo P et al. Efficacy, safety, adherence and persistence of PCSK9 inhibitors in clinical practice: A single country, multicenter, observational study (AT-TARGET-IT). *Atherosclerosis* 2023;366:32-39

US disease registry data on lipid-lowering drugs

Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US

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Introduction

Lipid-lowering therapy is one of the most effective strategies for reducing cardiovascular morbidity and mortality. The clinical benefits of lowering LDL cholesterol levels have been demonstrated in numerous large randomized trials with statins, ezetimibe, and, more recently, PCSK9 inhibitors. However, despite the good efficacy of these lipid-lowering drugs, their potential is often not exploited in the routine care of high-risk patients and the LDL cholesterol target levels are not achieved. A recent evaluation of the US GOULD registry once again highlighted these shortcomings.

Patients and methods

- The primary objective of the GOULD registry is to prospectively and non-interventionally document changes in the use of lipid-lowering drugs in patients with atherosclerotic cardiovascular disease (ASCVD) over time. This publication presents the 2-year results.

- **The following criteria were required for inclusion in the registry**:
  - Minimum age of 18 years
  - Confirmed diagnosis of ASCVD, i.e., myocardial infarction, coronary heart disease (CHD), arterial revascularization, ischemic stroke or transient ischemic attack, carotid stenosis, or peripheral arterial disease in the patient's medical history

- Patients were assigned to one of **three cohorts**:
  1. Current treatment with a PCSK9 inhibitor
  2. No PCSK9 inhibitor and LDL cholesterol of ≥100 mg/dL
  3. No PCSK9 inhibitor and LDL cholesterol of 70–99 mg/dL

- All patients, including those in the PCSK9 inhibitor cohort, should have received a lipid-lowering agent at a stable dose for at least four weeks prior to inclusion in the registry.

Results

Study population

- Of the 119 participating centers, a total of 5,006 patients were enrolled in the registry between the end of 2016 and mid-2018. Their average age was 67.8 ± 9.9 years, 60 % were men and 86 % were white, 80.5 % had coronary heart disease (CHD) and 34 % had type 2 diabetes (→ Table 5).

- As of the cut-off date of October 5, 2020, a total of 4,257 (85 %) of the registered patients had reached a follow-up of 2 years. Of these, 512 were in the PCSK9 inhibitor cohort and 3,745 were in the two cohorts defined on the basis of their LDL cholesterol.

Table 5 Baseline characteristics of ASCVD patients from the GOULD registry

Characteristics	Patient cohort, n (%)			
		LDL cholesterol		
	PCSK9 inhibitor (n=554)	≥100 mg/dL (n=1,801)	70–99 mg/dL (n=2,651)	Total (N=5,006)
Mean age (SD), years	65.9 (9.7)	66.6 (10.3)	69.0 (9.6)	67.8 (9.9)
Male gender, n (%)	310 (56.0)	959 (53.2)	1,752 (66.1)	3,021 (60.3)
White ethnicity, n (%)	505 (91.2)	1,463 (81.2)	2,344 (88.4)	4,312 (86.1)
Mean BMI (SD)	30.2 (5.3)	30.8 (6.4)	30.5 (6.0)	30.6 (6.1)
Cardiovascular disease				
Coronary heart disease	489 (88.3)	1,361 (75.6)	2,178 (82.2)	4,028 (80.5)
Cerebrovascular event	47 (8.5)	214 (11.9)	252 (9.5)	513 (10.2)
Peripheral arterial disease	73 (13.2)	256 (14.2)	347 (13.1)	676 (13.5)
Myocardial infarction	156 (28.2)	572 (31.8)	857 (32.3)	1,585 (31.7)
Type 2 diabetes	143 (25.8)	655 (36.4)	900 (33.9)	1,698 (33.9)
Median lipid level (IQR), mg/dL				
LDL cholesterol	67 (42–104)	120 (108–141)	82 (75–89)	91 (78–113)
HDL cholesterol	49 (41–60)	47 (39–58)	47 (39–57)	47 (39–58)
Triglycerides	128 (92–178)	137 (97–193)	115 (84–159)	124 (89–173)
Total cholesterol	146 (119–188)	200 (182–224)	156 (144–168)	168 (149–195)
Lipid-lowering therapy, n (%)				
Statin	193 (34.8)	1,558 (86.5)	2,525 (95.2)	
High dose		717 (39.8)	1,225 (46.2)	
Ezetimibe	114 (20.6)	194 (10.8)	228 (8.6)	

Source: Modified from Cannon et al., 2021 **Abbreviations:** **BMI** = body mass index, **IQR** = interquartile range, **SD** = standard deviation

Changes in lipid-lowering therapy during follow-up

- By the end of follow-up, only 17.1 % of all patients and only 12.5 % of patients in the PCSK9 inhibitor cohort had undergone intensification of their lipid-lowering therapy (additional or higher-dose statin, additional ezetimibe, or additional PCSK9 inhibitor).

LDL cholesterol levels

- The median LDL cholesterol level fell most sharply in the cohort with the highest baseline values of ≥100 mg/dL (from 120 mg/dL [interquartile range 108–141] to 95 [73–118] mg/dL; p<0.001). It decreased slightly but also significantly in the cohort with a baseline level of 70–99 mg/dL (from 82 [75–89] mg/dL to 77

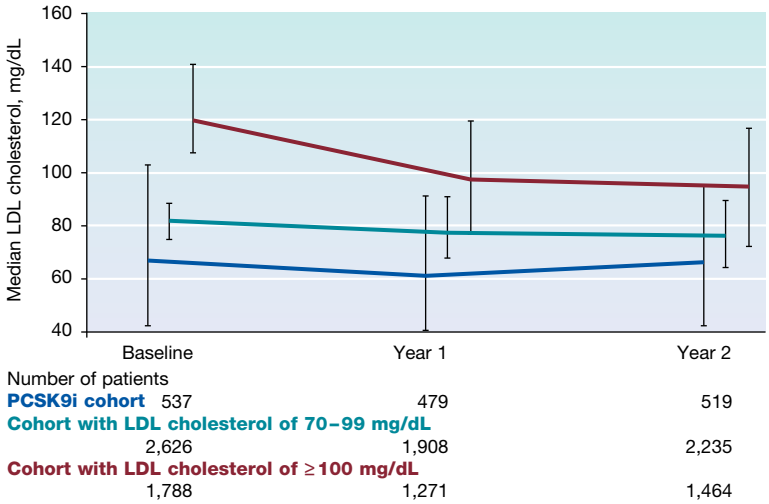
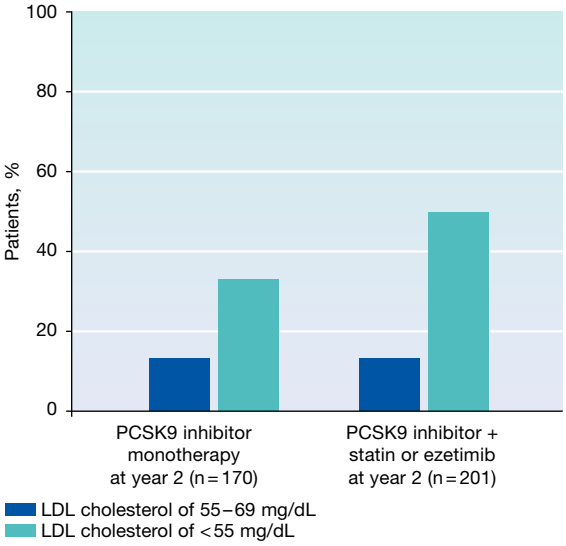


Figure 3 Change in median LDL cholesterol levels over the course of the 2-year follow-up in patients in the GOULD registry

Abbreviation: **PCSK9i** = PCSK9 inhibitor
Source: Own representation based on Cannon et al., 2021



Abbreviation: **PCSK9i** = PCSK9 inhibitor

Figure 4 Patients in the PCSK9 inhibitor cohort in GOULD who achieved LDL cholesterol levels of 55–69 mg/dL or < 55 mg/dL

Source: Own representation based on Cannon et al., 2021

[65–90] mg/dL; p < 0.001) and remained largely unchanged at approximately 67–68 mg/dL in the PCSK9 inhibitor cohort (➔ Figure 3).

- Based on the strict European target value for LDL cholesterol of < 55 mg/dL for high-risk patients, only approximately 10 % and 12 % of patients in the cohorts with baseline LDL cholesterol levels of ≥ 100 mg/dL and 70–99 mg/dL, respectively, achieved this value after 2 years.

- In the PCSK9 inhibitor cohort, a total of 39.9 % of patients achieved the target value of < 55 mg/dL (33 % with monotherapy and 50 % in combination with a statin ± ezetimibe) (➔ Figure 4). On the other hand, 25.1 % of patients still had LDL cholesterol levels above 100 mg/dL even after 2 years of therapy with a PCSK9 inhibitor.

Conclusions

- According to data from this US registry, ASCVD patients, most of whom had elevated LDL cholesterol levels at baseline, received only moderate intensification of lipid-lowering therapy over a 2-year period.

- Of the patients whose LDL cholesterol levels were measured again after 2 years, only about 1 in 3 patients achieved a level below 70 mg/dL and only 1 in 10 patients achieved a level below 55 mg/dL.

- Even when treated with a PCSK9 inhibitor + statin/ezetimibe, LDL cholesterol levels fell below 55 mg/dL in only half of the patients.

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Abbreviations

ACS	acute coronary syndrome
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CHD	coronary heart disease
CKD	chronic kidney disease
CeVD	cerebrovascular disease
DLCN	Dutch Lipid Clinic Network
eGFR	estimated glomerular filtration rate
FH	familial hypercholesterolemia
HDL	high-density lipoprotein
heFH	heterozygous familial hypercholesterolemia
hoFH	homozygous familial hypercholesterolemia
LDL	low-density lipoprotein
PAD	peripheral arterial disease
PCSK9	proprotein convertase subtilisin/kexin type 9
SD	standard deviation

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