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Retrospective Observational Analysis in a Cohort Patients in Treatment with Alirocumab and Evolocumab: Focus on C-LDL Values

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Abstract

Hypercholesterolemia is the main risk factor for cardiovascular disease. Statins are the drugs of first choice, but many patients fail to reach the recommended levels of LDL cholesterol, or are intolerant. The PCSK9 inhibitor drugs (Alirocumab and Evolocumab) are anti-PCSK9 antibodies: represent a new pharmacological approach, and have been approved as an adjunct to Statins or in intolerant patients. The aim of the work was to carry out a retrospective observational analysis of a cohort of patients treated with anti-PCSK9 antibodies. The AIFA Therapeutic Plans were received by the Pharmacy from 01/01/2021 to 06/30/2023 by extrapolating data such as: sex, age, prescribed PCSK-9, adverse reactions, LDL cholesterol values before treatment and at the first re-evaluation. Out of 329 patients on treatment, 215 (65.3%) were treated with Evolocumab, 114 (34.7%) with Alirocumab. The 329 patients analyzed , have an average age of 64 years (minimum 30 - maximum 87). Our analysis has highlighted that in post-treatment patients the percentage change in LDL cholesterol values compared to baseline is equal to 59.8% in line with what was observed in the ODISSEY and FOURIER studies. PCSK9 inhibitors are state-of-the-art therapies and are well tolerated and effective in the management of the statin-intolerant patient, or as an adjunct to existing lipid-lowering therapies. Furthermore, statins increase serum PCSK9 levels; therefore, the best effect of these inhibitors is seen in combination with them.

Keywords: Hypercholesterolemia, Low Density Lipoprotein, PCSK-9, Pharmacovigilance.

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Introduction

Dyslipidemia represents one of the main risk factors for the development of cardiovascular diseases and atherosclerosis, which is considered among the leading causes of morbidity and mortality throughout the world. In the case of hypercholesterolemia, cholesterol accumulates in the blood in the form of light lipoproteins (LDL), aggregates of fats and proteins that favor the formation of atherosclerotic plaques in the artery walls. The presence of high levels of LDL cholesterol in the blood leads to the formation of atherosclerotic plaques which can lead to the onset of angina, heart attack, stroke in the heart, brain, kidneys, lungs and liver[1].

There are many lipid-lowering drug therapies currently available on the market, including statins, fibrates, and PCSK9 inhibitors. Statins, which can be prescribed by the National Health Service according to AIFA Note 13[2], reduce the synthesis of endogenous cholesterol by competitively inhibiting the enzyme HMG-CoA (3-Hydroxy-3Methyl-Glutaryl-Coenzyme A) reductase. The decrease in the intracellular cholesterol content determines an increase in LDL receptors, a greater uptake and internalization of circulating cholesterol and, consequently, its reduction.

Despite their widespread use in daily clinical practice, treatment with statins is unfortunately not always well tolerated, especially due to the known possible side effects (hepatotoxicity and myopathy). Myopathy is found in 27% of patients while hepatotoxicity in 3%[3,4].

The most common hepatic adverse event consists of an asymptomatic and clinically insignificant increase in aminotransferase levels[4]. Furthermore, in a fair percentage of patients (10-15%) (low responders), statin therapy does not allow the achievement of adequate therapeutic targets.

Fibrates (Ciprofibrate, Clofibrate, Fenofibrate, Gemfibrozil) act on the catabolism of VLDL (lipoprotein particles used for the transport of triglycerides, and to a lesser extent cholesterol in blood) through the activation of lipoprotein lipase or LPL (a plasma enzyme that hydrolyses circulating triglycerides). In addition to increasing the speed with which they are removed from the circulation, fibrates reduce the synthesis of VLDL in the liver[5].

In 2017, two monoclonal antibodies were authorized in Italy (Alirocumab and Evolocumab) for the treatment of primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia in association with a statin or a statin with other lipid-lowering therapies in patients who do not achieve target LDL cholesterol levels with the maximum tolerated dose of a statin. These drugs have been approved as monotherapy or in combination with other lipid-lowering drugs in intolerant patients or in whom there are contraindications in the use of statins[6,7], and are classified in the A-PHT group, can be prescribed with a limited repeatable prescription (Cardiologists and Internists), subjected to monitoring additional AIFA fee, and dispensed, in the Sicily Region, under the direct distribution regime[8,9], or at the pharmacies of the Prescribing Centers belonging to the ASP of residence of the patient. This distribution channel allows for more careful monitoring of treatment in patients, both in terms of compliance with the correct drug withdrawal times linked to the administration periods, and in terms of any adverse reactions to the treatment.

The prescription for Alirocumab and Evolocumab can be written in three different cases: if optimal LDL-C levels are not reached; if the previous drug combination was not sufficient to reach the new target

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of 1.4 mmol/l, or in addition to the Statin-Ezetimibe association, in patients with familial hypercholesterolemia, and to Ezetimibe, in patients truly intolerant to statins at any dose with reporting on the National Pharmacovigilance Network. With resolution no. 1771/2019, published in December 2019, the "fast-track" was guaranteed precisely for the categories at very high cardiovascular risk; for patients with recent myocardial infarction (within 12 months) or those with a history of multiple cardiovascular events[10]. In the Sicily Region, Evolocumab and Alirocumab drugs were included in the Regional Hospital Therapeutic Handbook in 2017 with updates n.15 and n. 19 while AIFA, with determination no. 434 and 435 of 06/30/2022, modified the SSN conditions of use, on the monitoring register, of medicines[11]. Furthermore, starting from 06/16/2022, the prescription of these two drugs in secondary prevention is reserved for patients with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia or mixed dyslipidemia with LDL-C levels ≥ 70 mg/dL.

Alirocumab is available in 75 and 150 mg formulations, based on the lipid target to be achieved; Evolocumab, on the other hand, is marketed in a single 140 mg dosage. Both are administered subcutaneously every 14 days. Experimental studies have shown that, using these active ingredients, circulating LDL levels are reduced by 60% after a few weeks from the start of therapy, improving cardiovascular outcomes (myocardial infarction, stroke)[12,13].

Evolocumab and Alirocumab work by inhibiting the activity of the PCSK9 protein in the blood. The PCSK9 glycoprotein acts by preventing the detachment of the LDL receptor (LDLR) from LDL-C, on the surface of hepatocytes or other cells, determining the deterioration of lysosomes and blocking the interaction with LDL-C and the subsequent internalization and endocytosis of clathrin-employee. Circulating levels of PCSK9 are regulated by the intracellular cholesterol content and, in particular, the depletion of cholesterol in the hepatocyte stimulates its production, due to the effect of lipid-lowering drugs. However, in order to have effect using these two drugs, at least a small part of the LDL receptors must be present and functioning.

According to the 2019 ESC/EAS Guidelines (Table. I) on the clinical management of dyslipidemia, in patients being treated with a statin at the maximum tolerated dose in which the LDL-C target values have not yet been reached, the association is recommended with Ezetimibe. In very high-risk patients with persistently high LDL-C levels despite treatment with a statin at the maximum tolerated dose in combination with Ezetimibe, the addition of a PCSK-9 inhibitor is recommended for secondary prevention, while it can be considered in primary prevention.

Based on the risk class in which the patient is put, the therapeutic target of LDL-C values varies. For patients belonging to the very high-risk class, the target value to be achieved is 55 mg/dL (1.4 mmol/L); for the high-risk class 70 mg/dL (1.8 mmol/L); for the moderate class 100 mg/dL (2.6 mmol/L); for the low-risk class 116 mg/dL (3.0 mmol/L)[14].

Treatment with PCSK-9 inhibitors is recommended in patients with high-risk familial hypercholesterolemia, in whom target LDL-C levels have not been achieved despite maximal therapy with Statins/Ezetimibe. In patients with Acute Coronary Syndrome (ACS), if the LDL-C target has not been reached after 4-6 weeks of maximal therapy with a statin and ezetimibe, the addition of a PCSK-9 inhibitor is recommended.

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If at the time of ACS the patient is already on optimal therapy with Statin/Ezetimibe, therapy with PCSK-9 inhibitors can be started during the hospital stay. From what has been said so far, the need for therapies other than those based on statins emerges that, with different mechanisms of action, they can contribute to achieving the recommended targets. The new generation drugs present completely different pharmacodynamic characteristics from HMG-CoA reductase inhibitors and are represented by oligonucleotides aimed at blocking the transcription of the mRNA for apolipoprotein B (ApoB, Mipomersen), by inhibitors of microsomal proteins that transfer triglycerides and are involved in the formation of ApoB at the liver and intestinal level (Lomitapide) and by PCSK9 inhibitors[15].

As it always happens with new drugs, it is advisable to monitor their use in daily "Real World" clinical practice, especially for special populations, such as the elderly, or individuals suffering from concomitant pathologies, categories excluded from clinical trials and on which no the risk/benefit ratio of the drug is predictable, if not in actual therapeutic use. For these reasons, it is important to implement the so-called post-marketing phase (phase IV) of the clinical trial, Pharmacovigilance, which allows the identification of everything that was not possible to detect, during the clinical trial itself, due to issues of time, number of subjects enrolled in the various phases, inclusion/exclusion criteria and protected environment The aim of our work was to carry out a retrospective observational analysis of a cohort of patients treated with anti-PCSK9 antibodies, also evaluating the change in percentage terms in LDL-C levels at the first possible re-evaluation.

Method

Sampling and Eligibility

A retrospective observational study was conducted by consulting the registers of drugs subjected to AIFA monitoring and the related AIFA therapeutic plans drawn up by the Simple Departmental Hemodynamics Operating Unit of the "Barone I. Romeo" Hospital of Patti, Messina, and received at the Simple Pharmacy Operational Unit of the same P.O. from 01/01/2021 to 06/30/2023. The data were collected by researchers and processed for research purposes only. To ensure confidentiality, each patient was assigned a number. During the considered period, one ADR was found from the under-study drugs. It was not necessary to request the opinion of the ethics committee for this type of study.

Tools

The data were collected and processed by the researchers in aggregate form for exclusive research use only. The researchers who took part in this observational study are Cardiologists specializing in Hemodynamics and Hospital Pharmacists, some of whom have over 20 years of service. For each patient the following data were extrapolated: sex, age, PCSK-9 drug and related dosage prescribed, any combinations of drugs for the treatment of hypercholesterolemia, any ADRs, percentage of adherence to treatment, C-LDL values before treatment and at the first reassessment, concomitant conditions such as smoking, diabetes, hypertension, heart attack, peripheral arterial disease, hyperuricemia and previous cerebrovascular disease; pathology from which they are affected (mixed dyslipidemia; non-familial hypercholesterolemia; heterozygous familial hypercholesterolemia). All data were reported on a spreadsheet and processed with the aid of the Apache Open Office Calc v. 4.1.14.

Statistical Analysis

The p value of the LDL-C values at baseline and after 24 weeks of treatment was calculated to highlight statistically significant differences certifying the effectiveness of the anti-PCSK9 treatments.

Result and Discussion

Alirocumab and Evolocumab are human monoclonal antibodies, they are administered subcutaneously, every two weeks or once a month, at different doses depending on the drug used. The possibility of interaction with drugs taken orally is absent, as they do not interfere either from a pharmacokinetic or pharmacodynamic point of view. Among the most frequent adverse effects reported are itching at the injection site and flu-like symptoms[16]. An increase in neurocognitive effects has been described in some studies[17]. Furthermore, a potential problem of long-term treatment with antibodies is the formation of auto-antibodies. Evolocumab and Alirocumab are human antibodies, theoretically less prone to the phenomenon of immunogenicity and therefore loss of effect. To date, the formation of antidrug antibodies without reduction of LDL cholesterol has been reported in only a few cases. In any case, long-term use must be monitored. The development of a third monoclonal antibody, PCSK9 inhibitor, Bococizumab, was interrupted due to an increase in neutralizing antibodies, which resulted in an attenuation of the lowering of LDL cholesterol levels over time, as well as a greater speed in establishing of reactions at the injection site[18].

Over the considered time period, the AIFA therapeutic plans of PCSK-9 inhibitors of 329 patients were examined; of these, 215 (65.3%) are being treated with Evolocumab and 114 (34.7%) with Alirocumab. Of the patients treated with Evolocumab only 155 (72.1%) had at least one reassessment. Of these, 33 (21.3%) are treated in primary prevention, 122 (78.7%) in secondary prevention. The duration of the treatment cycle was 24 weeks, 146 patients (94.2%) were compliant with the treatment.

The average age of the patients is 65 years (min. 35 max. 87). 122 patients (78.7%) were male and 33 (17.42%) were female. 128 (82.5%) are affected by non-familial hypercholesterolemia and 27 (17.5%) by familial hypercholesterolemia. As regards cardiovascular risk factors, 37 (23.9%) are smokers, 27 (17.42%) suffer from diabetes mellitus, 143 (92.25%) are hypertensive, 121 (78%) have cardiovascular diseases. 47 (30.3%) associate statins with Evolocumab therapy, 107 (69%) associate, 1 patient (0.65%) associates other therapies.

For patients treated with Alirocumab, 69 (60.5%) have at least one reassessment. Of these, 7 (10.15%) are treated in primary prevention and 62 (89.85%) are treated in secondary prevention. 54 patients (78.26%) take the 75 mg dosage, 15 (21.74%) take the 150 mg dosage. The duration of treatment is 24 weeks. The percentage of patients who adhered to the treatment was 91.3% (63 patients).

The average age of patients treated with Alirocumab is 63 years (min. 30 max. 80 years). 56 patients (81.15%) are male, 13 patients (18.85%) are female. 61 patients (88.4%) are affected by non-familial hypercholesterolemia, 8 patients (11.6%) by familial hypercholesterolemia. For cardiovascular risk factors it emerged that 17 patients (24.6%) are smokers, 23 patients (33.3%) have diabetes mellitus, 63 patients (91.3%) have hypertension, 61 patients (88.4%) have cardiovascular disease. 23 patients (33.3%) combine statins with Alirocumab, 44

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(63.8%) ezetimibe, 2 (2.9%) other therapies. The effectiveness of therapies with PCSK9 inhibitors was evaluated by analyzing LDL-C values before starting treatment and after a first therapeutic cycle.

For patients treated with Evolocumab, at baseline no patient had LDL-C values <70mg/dL, 1 (0.64%) values between 70-100 mg/dL, 13 (8.38%) values between 100-129 mg /dL, 27 (17.42%) values between 130-159 mg/dL, 51 (32.9%) values between 160-189 mg/dL, 63 (40.64%) values > 190 mg/dL. At the first re-evaluation, 82 (52.9%) patients were found to have values <70mg/dL; 53 (34.2%) with values between 70-100 mg/dL, 15 (9.67%) with values between 100-129 mg/dL, 2 (1.3%) with values between 130-159 mg/dL, 3 patients (1.93%) with values between 160-189 mg/dL, no patient was found to have LDL-C values > 190 mg/dL.

For patients treated with Alirocumab, at baseline no patient had LDL-C values <70 mg/dL, after the first 24-week therapeutic cycle 55 (79.71%) had LDL-C values <70 mg/dL; at baseline 2 patients (2.89%) had values in the range 70-100 mg/dL, which became 3 (4.34%) after the first cycle; 17 (24.63%) patients had, at baseline, values between 100-129 mg/dL, which rose to 6 (8.7%); 26 patients, at baseline, (37.7%) presented values between 130-159 mg/dL which became 3 (4.34%), 7 patients presented, at baseline, values between 160-189 mg/dL (10.14%) which then became 2 (2.89%); 17 patients (24.63%) had values >190 mg/dL at baseline, which became 0 at the first re-evaluation. (Tables 2, 3, 4, 5 and 6). Finally, the p value was calculated, which demonstrated statistically significant differences for the LDL-C values at baseline and after 24 weeks of treatment, with p value <0.001 in both the Alirocumab and Evolocumab groups. (Table 7).

The retrospective observational analysis conducted highlighted that in patients for whom treatment re-evaluation is available to date, the average percentage change (reduction) in pre-treatment LDL cholesterol values available at the first re-evaluation is equal to 59.8%, thus as also found in the ODISSEY and FOURIER studies[19,20], with consequent reduction in cardiovascular events, a condition that convinced the prescriber to continue with the prescribed therapy. Furthermore, the p value values obtained demonstrated statistically significant differences between C-LDL values at baseline and after 24 weeks of treatment, confirming the effectiveness of anti-PCSK9-based treatments.

The majority of patients evaluated took Evolocumab with biweekly administration, were male and were over 60 years of age. Among the concomitant/predisposing conditions, the highest percentage found concerns hypertension and cardiovascular diseases, followed by smoking and diabetes mellitus.

Conclusion

Evolocumab and Alirocumab have been evaluated in a series of clinical studies including FOURIER and ODYSSEY. The results obtained from our analysis proved to be in line with the results observed in the studies cited, in terms of percentage change (reduction) in LDL cholesterol values.

Despite the scientific evidence and recommendations from clinicians on the importance of keeping LDL cholesterol levels under control, the results of this study have demonstrated that in real daily clinical practice the majority of patients at high cardiovascular risk present high levels of LDL-C, in some cases attributable to inadequate adherence to lipid-lowering treatment with statins.

For these reasons, monitoring the lipid profile of hypercholesterolemic patients becomes crucial to drawing up prescriptions that are appropriate for the individual patient, improving therapeutic adherence, and resulting in clinical benefits. Precisely the close collaboration between the professional figures involved, Clinician, Pharmacist and Nurse, allowed prompt intervention in the management of all those patients who presented adverse reactions to treatment with statins, in order to direct them as quickly as possible to new biological therapies with PCSK9 inhibitors. Each figure had their specific role, the Clinician was responsible for the diagnosis, establishing the pharmacological therapy and intervening in the event of complications arising; the pharmacist took care of advising the patient on how to use the drug and reporting any adverse effects that occurred following taking the drugs; the Nurse was the professional figure who was closest to the patient and advised/directed him to obtain the maximum possible compliance using communication as a key tool, making him feel an active part of the therapeutic process.

This cooperation had as its ultimate aim the protection of patients' health, demonstrated by the maximum adherence found and the therapeutic success achieved. Furthermore, the compilation and constant updating of the AIFA monitoring registers has made it possible not only to evaluate the effectiveness, i.e. the effectiveness in real daily clinical practice, of anti-PCSK9-based therapies, but has also proven to be a tool guarantor of prescriptive appropriateness.

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Conflict of Interest
The authors report no conflicts of interest.

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Table 1. 2019 ESC/EAS guidelines include 4 categories of cardiovascular risk

Very high risk:
Atherosclerotic cardiovascular disease (ASCVD) clinical/imaging Score ≥ 10%
Familial hypercholesterolemia (FH) with ASCVD or another major risk factor
Severe chronic kidney disease (CKD) with eGFR values less than 30 mL/minute
Diabetes Mellitus with target organ damage or at least 3 of the major risk factors or early onset of long-lasting (>20 years) T1DM (Type 1 Diabetes Mellitus)
High Risk:
Score ≥ 5% and <10%
Individual markedly elevated risk factors, in particular TC>8mmol/L (310mg/dl) or LDL -C >4.9mmol/L (190mg/dL) or BP >180/110mmHg
Familial hypercholesterolemia without other major risk factors
Moderate chronic kidney disease (eGFR 30-59 mL/min)
Diabetes mellitus with organ damage, with diabetes lasting ≥10 years or other additional risk factors
Moderate risk:
SCORE ≥1% and <5%
Young patients (T1DM<35 years; T2DM <50 years) with duration <10 years without other risk factors
Low risk:
Score <1%

Table 2. General Data of the Study

Parameters	N	(%)
Alirocumab		
Patients with aifa register	114	/
Patients with no reassessment	45	39,50%
Patients with at least one reassessment	69	60,50%
Patients in primary prevention	7	10,15%
Patients in secondary prevention	62	89,85%
Dosage used during treatment 75 mg	54	78,26%
Dosage used during treatment 150 mg	15	21,74%
Duration of the therapeutic cycle (weeks)	24	/
Average % of adherence to the treatment	63	91,30%
Evolocumab		
Patients with aifa register	215	/
Patients with no reassessment	60	27,90%
Patients with at least one reassessment	155	72,10%
Patients in primary prevention	33	21,30%
Patients in secondary prevention	122	78,70%
Duration of the therapeutic cycle (weeks)	24	/
Average % of adherence to the treatment	146	94,20%

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Table 3. General Data of the Study

Characteristics	Alirocumab (n=69)		Evolocumab (n=155)	
	Number	(%)	Number	(%)
Age				
Average	63	/	65	/
Range	30-80	/	35-87	/
Sex				
Males	56	81,15%	122	78,70%
Females	13	18,85%	33	21,30%
Type of Hypercholesterolemia				
Non-familial hypercholesterolemia	61	88,40%	128	82,50%
Familial hypercholesterolemia	8	11,60%	27	17,50%
Cardiovascular risk factors				
Smokers	17	24,60%	37	23,90%
Diabetes mellitus	23	33,30%	27	17,42%
Hypertension	63	91,30%	143	92,25%
Cardiovascular disease (ischemic heart disease, acute myocardial infarction (ami), coronary artery bypass grafting, coronary artery disease)	61	88,40%	121	78%
Associated hypolipidemic therapies				
Statins	23	33,30%	47	30,30%
Ezetimibe	44	63,80%	107	69%
Other therapies	2	2,90%	1	0,65%

Table 4. Change in lipid levels from baseline in the Alirocumab group.

Alirocumab (n=69)				
Parameters	Basal lipid levels	Lipid levels after first cycle with alirocumab (24 weeks)	Average variation in absolute terms	Average variation in %
LDL cholesterol	175,80 mg/dl	72,65 mg/dl	-103,15 mg/dl	-58,67%
HDL cholesterol	47,32 mg/dl	52,63 mg/dl	5,31 mg/dl	11,22%
Total cholesterol	265,27 mg/dl	163,84 mg/dl	-101,43 mg/dl	-38,23%
Triglycerides	156,75 mg/dl	123,12 mg/dl	-33,63 mg/dl	-21,45%

Alirocumab (n=69)				
Parameters	Patient at baseline		Patients after the first cycle of treatment with alirocumab (24 weeks)	
	Number	%	Number	%
LDL cholesterol < 70mg/dl	0	0,00%	55	79,71%
LDL cholesterol 70-100 mg/dl	2	2,89%	3	4,34%
LDL cholesterol normal 100-129 mg/dl	17	24,63%	6	8,70%
Excess LDL cholesterol 130-159 mg/dl	26	37,70%	3	4,34%
High LDL cholesterol 160-189mg/dl	7	10,14%	2	2,89%
Very high LDL cholesterol >190 mg/dl	17	24,63%	0	0,00%

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Table 5. Change in lipid levels from baseline in the Evolocumab group

Evolocumab (n=155)				
Parameters	Basal lipid levels	Lipid levels after first cycle with evalocumab (24 weeks)	Average variation in absolute terms	Average variation in %
LDL cholesterol	178,26 mg/dl	65,72mg/dl	-112,54mg/dl	-63,13%
HDL cholesterol	49,56mg/dl	53,47mg/dl	3,91mg/dl	7,90%
Total cholesterol	210,89mg/dl	139,55mg/dl	-71,34mg/dl	-33,82%
Triglycerides	163,54mg/dl	122,76mg/dl	-40,78 mg/dl	-25%

Evolocumab (n=155)				
Parameters	Patient at baseline		Patients after the first cycle of treatment with alirocumab (24 weeks)	
	Number	%	Number	%
LDL cholesterol < 70mg/dl	0	0,00%	82	52,90%
LDL cholesterol 70-100 mg/dl	1	0,64%	53	34,20%
LDL cholesterol normal 100-129 mg/dl	13	8,38%	15	9,67%
Excess LDL cholesterol 130-159 mg/dl	27	17,42%	2	1,30%
High LDL cholesterol 160-189mg/dl	51	32,90%	3	1,93%
Very high LDL cholesterol >190 mg/dl	63	40,64%	0	0,00%

Table 6. Change in lipid levels compared to baseline in all patients treated with a PCSK9i

Parameters	Categories (n. of patients)	Basic LDL-C levels	Average LDL-C levels during treatment	%Change in LDL-C compared to basic	Number patients (%) with LDL-C <70mg/dl
PCSK9i	alirocumab (69)	175,80 mg/dl	69,47 mg/dl	-60,50%	55 (79,71%)
	evolocumab (155)	178,26 mg/dl	70,63 mg/dl	-60,37%	82 (46%)
Sex	male (178)	186,72 mg/dl	76,27 mg/dl	-59,15%	102 (57,3%)
	female (46)	165,63 mg/dl	65,64 mg/dl	-60,36%	35 (76%)
Age	< 65 (150)	175,36 mg/dl	71,13 mg/dl	-59,43%	108 (72%)
	≥65 (74)	167,23 mg/dl	64,66 mg/dl	-61,33%	19 (57,57%)
Basal LDL-C levels	≤150mg/dl (33)	122,88 mg/dl	62,59 mg/dl	-49,06%	27 (81,81%)
	151-199mg/dl (111)	180,93 mg/dl	65,44 mg/dl	-63,83%	77 (69,36%)
	≥200 mg/dl (80)	225,43 mg/dl	68,10 mg/dl	-69,79%	33 (41,25%)
Heterozygous familial hypercholesterolemia	yes (77)	206,63 mg/dl	81,22 mg/dl	-60,7%	40 (52%)
	no (147)	168,58 mg/dl	66,01 mg/dl	-60,84%	97 (66%)
Statin therapy	yes (70)	150,27 mg/dl	65,06 mg/dl	-56,70%	46 (64,28%)
	no (150)	189,63 mg/dl	73,02 mg/dl	-61,50%	91 (60,66)
Adherence %	≤ 90% (56)	161,40 mg/dl	77,1 mg/dl	-52,23%	18 (32,14%)
	≥ 90% (168)	175,32 mg/dl	68,56 mg/dl	-61%	119 (71%)

Table 7. Significance level at 24 weeks of therapy

Drug	Basic LDL-C levels	LDL-C levels after 24 weeks	P-value
Alirocumab	175.80 mg/dl	69.47 mg/dl	P< 0.001
Evolocumab	178.26 mg/dl	70.63 mg/dl	P< 0.001
Average-baseline LDL-C	176.41 mg/dl	65,37mg/dl	P< 0.001