REVIEW ARTICLE

Efficacy, Safety and Clinical Applicability of PCSK9 Inhibitors

Eficacia, seguridad y aplicabilidad clínica de los inhibidores de la PCSK9

WALTER MASSON[1,2], MARIANO GIORGI[2,3,4,5]

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a new group of lipid-lowering drugs, which have generated a substantial change in lipid management. In a few years, a large number of studies have evaluated the lipid-lowering efficacy and safety of these drugs. More recently, large randomized clinical trials have demonstrated that the decrease in LDL-C levels achieved with these agents were associated with lower incidence of cardiovascular events. This evidence led to approval and marketing of PCSK9 inhibitors in many countries. Consequently, several scientific societies and reference healthcare institutions have incorporated these drugs into the therapeutic arsenal for dyslipidemia in order to reduce residual cardiovascular risk. In this review, we will describe the efficacy and safety of these agents, analyze the available evidence about their cardiovascular benefits and discuss in which population their use might be most effective.

Keywords: Dyslipidemia, drug treatment, PCSK9 inhibitors

RESUMEN

Los inhibidores de la proproteína convertasa subtilisina kexina tipo 9 (iPCSK9) representan un nuevo grupo de fármacos hipolipemiantes, que han generado un cambio sustancial en el manejo clínico de los lípidos. En pocos años, una gran cantidad de estudios han evaluado la eficacia antilipídica y la seguridad de estos fármacos. Más recientemente, grandes ensayos clínicos aleatorizados demostraron que el descenso del C-LDL alcanzado con estos fármacos se asoció con una menor incidencia de eventos cardiovasculares. Dicha evidencia dio lugar a la aprobación y comercialización de los iPCSK9 en muchos países. En consecuencia, diversas sociedades científicas y organismos de referencia en salud incorporaron estos fármacos en el arsenal terapéutico de la dislipidemia, con el objetivo de reducir el riesgo cardiovascular residual. En esta revisión describiremos la eficacia y la seguridad de estos fármacos, analizaremos la evidencia disponible acerca del beneficio cardiovascular y discutiremos en qué población podría ser más efectiva su utilización.

Palabras clave: Dislipidemia, tratamiento farmacológico, inhibidores de la PCSK9

INTRODUCTION

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a new group of lipid-lowering drugs which have caused a substantial change in the clinical management of lipids due to their high efficacy to reduce lipid levels and, in consequence, to their recently demonstrated cardiovascular benefit.

Over the past years, PCSK9 inhibitors have been evaluated in many clinical trials including patients with cardiovascular disease, familial hypercholesterolemia, mixed dyslipidemia or intolerance to statins.

In this review, we will briefly describe the history and clinical development of these drugs, discuss their efficacy and safety, and analyze the evidence available about their cardiovascular benefits. We will also discuss the main indications for their use according to the latest clinical practice guidelines and which population could be expected to derive the greatest benefit.

Brief history of the development of PCSK9 inhibitors

The discovery of the LDL-C receptor by Goldstein and Brown in 1973, besides being awarded the Nobel Prize, changed the history of cardiovascular disease. (1) In addition to demonstrating the mechanism of receptor-mediated endocytosis by which the LDL-C receptor incorporates LDL particles into the cells, it was established that these receptors might be recycled after fulfilling their function.

A new discovery identified a mutation favoring gain-of-function in a gene that was associated with the

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Address for reprints: Dr. Walter Masson - E-mail: Walter.masson@hospitalitaliano.org.ar

[1] Department of Cardiology. Hospital Italiano de Buenos Aires
[2] Council on Epidemiology and Cardiovascular Prevention. Argentine Society of Cardiology
[3] Cardiovascular Prevention Unit - Cardiology Section - CEMIC
[4] Department of Pharmacology – Instituto Universitario CEMIC
[5] Health Economics and Sanitary Technologies Unit - Instituto Universitario CEMIC

diagnosis of familial hypercholesterolemia. (2) Later, loss-of-function mutations in the same gene were associated with low plasma levels of LDL-C and lower risk for cardiovascular events. (3) This gene encoded a new protein, PCSK9, which binds to LDL receptors on the surface of liver cells and regulates LDL receptors. (4, 5) In the presence of PCSK9, endocytosis of the LDL-PCSK9 complex occurs. Inside the cell, the lipoprotein is cleaved and broken and PCSK9 diverts the LDL receptor to degradation by lysosomes, preventing its return back to the cell surface to perform its function. In the absence of PCSK9, after endocytosis of the LDL receptor complex, the lipoprotein is similarly broken, but the receptor is recycled and returns to the cell surface to continue fulfilling its function. Thus, inhibition of PCSK9 facilitates LDL receptor recycling and increases the number of receptors in liver cells, thus contributing to lower LDL-C plasma levels. One way to produce PCSK9 inhibition is by monoclonal antibodies, known as PCSK9 inhibitors.

In a few years, several programs with a great number of clinical trials have evaluated the efficacy and safety of PCSK9 inhibitors. These studies have found a significant reduction in LDL-C plasma levels and have positioned these new drugs as additional tools to reduce residual cardiovascular risk. (6, 7) More recently, large clinical trials demonstrated that LDL-C levels achieved with these agents were associated with lower incidence of cardiovascular events. (8, 9)

Based on the available evidence, PCSK9 inhibitors evolocumab (Rephata™, Amgen) and alirocumab (Praluent™, Sanofi), administered subcutaneously every two or four weeks, were approved by the Federal Drug Agency (FDA) and the European Medicines Agency (EMA) in 2015. In our country, the ANMAT approved the use of alirocumab in 2017 and of evolocumab in 2019.

Initial programs. Lipid-lowering efficacy and safety

The PROFICIO program (Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations) included several clinical trials to establish the efficacy and safety of evolocumab in different populations with hypercholesterolemia, including those with familial hypercholesterolemia and statin intolerance. (10-19) In all these groups, PCSK9 inhibitors demonstrated to significantly reduce LDL-C levels by up to 60%, allowing many patients to reach therapeutic targets. The analysis of the trials included in the program showed that mean LDL-C reduction was 65.7% (95% CI, 60.9%-70.9%) with evolocumab 140 mg every two weeks and 65.0% (95% CI: 60.4%-69.5%) with evolocumab 420 mg every four weeks. (20)

In the same sense, the ODYSSEY program included many clinical trials evaluating the efficacy and safety of alirocumab in dyslipidemia patients, including familial hypercholesterolemia, diabetes or history of cardiovascular disease. (21-34) Pooled analysis of patients from various clinical trials of the ODYSSEY program, including subjects with familial hypercholesterolemia or history of cardiovascular disease, demonstrated LDL-C reductions at week 24 ranging between 54.1% and 61.9% for alirocumab 150 mg every two weeks. (35) Similarly, prolonged use of alirocumab (78 weeks), when added to statin therapy at the maximum tolerated dose in patients at high risk for cardiovascular events with LDL-C levels >70 mg/dL, was associated with a reduction in LDL-C levels >50%. (36)

A third drug, bococizumab, has been discontinued for generating autoantibodies that negatively impacted on lipid-lowering efficacy over time. Although the mechanism of action of the three drugs is very similar, a crucial difference exists. There are several types of monoclonal antibodies according to their origin and protein structure: murine, chimeric, humanized and fully human. The capability to induce autoantibodies is maximum in murine monoclonal antibodies and minimum in fully human monoclonal antibodies. (37) Alirocumab and evolocumab are fully human antibodies, while bococizumab is a humanized antibody with murine protein sequence and has a greater capability to produce antidrug antibodies. This effect was demonstrated in the SPIRE-1 and SPIRE-2 trials which included >27,000 patients. (38, 39)

PCSK9 inhibitors also produce significant reduction in the levels of other atherogenic particles. In an analysis using pooled data from many trials of patients with metabolic syndrome, PCSK9 inhibitors reduced triglycerides between 7.1% and 15.9%, non-HDL-C between 38.2% and 54,2% and apolipoprotein B between 35% and 55.1%. (40) Similarly, another publication reported that HDL-C may increase between 4.6% and 8.9%, while Lp(a) levels may decrease between 23% and 48.6%. (41) Regarding this last point, a recent meta-analysis including 27 trials with 11,864 patients showed average Lp(a) reduction of 21.9% (95% CI, 9.5%-24.3%) (42) irrespective of the type of PCSk9 inhibitor used, differences in control treatment, treatment duration, baseline Lp(a) levels or participant characteristics.

Considering that the follow-up period was short in most studies, evolocumab and alirocumab have not shown different adverse effects compared with placebo (43, 44) except for injection site reactions which, although rare, were more frequently observed with the use of monoclonal antibodies.

An analysis of the ODYSSEY program evaluated the safety of these drugs in the subgroup of patients who had reached very low LDL-C levels (<25 mg/dL and <15 mg/dL). There were no significant differences in the incidence of myopathy, liver disease, new cases of diabetes or neurocognitive deficit. (45) Although that analysis suggested an increased risk of cataracts with very low LDL-C levels, a recent meta-analysis including large recently published trials did not confirm this association. (46) Similarly, the EBBINGHAUS trial, specifically designed to assess cogni-

tive status, found no differences between evolocumab and placebo. (47) Finally, an extended follow-up of the recently published OSLER-1 trial (Open Label Study of Long Term Evaluation Against LDL-C Trial) determined the safety of evolocumab, 420 mg every four weeks over a 5-year period in patients with hypercholesterolemia. (48)

Atherosclerosis regression and PCSK9 inhibitors

The GLAGOV trial demonstrated that among 968 patients with coronary artery disease under stable statin treatment, use of evolocumab (420 mg every four weeks) compared with placebo, resulted in atherosclerosis regression estimated by intravascular ultrasonography (IVUS) imaging after 72 weeks of treatment. (49) The primary endpoint (percent atheroma volume) increased 0.05% in the placebo group and decreased 0.95% with evolocumab (difference, −1.0% [95% CI, −1.8% to −0.64%]; p <0.001). An exploratory analysis showed an inverse linear relationship between LDL-C decrease and plaque regression up to levels as low as 20 mg/dl, without finding a cutoff value where the benefit was lost.

Recently, the ODYSSEY J-IVUS trial assessed the effect of alirocumab (75/150 mg every two weeks) on the progression of atherosclerosis compared with standard care in 206 Japanese patients with acute coronary syndrome using IVUS imaging analysis. (50) After 36 weeks, a non-significant reduction of the primary endpoint was observed (change in total atheroma volume −4,8% vs. −3,1%, p = 0.23). The shorter study period and small number of enrolled patients compared with previous studies may have limited the ability to show a significant difference in the results.

Reduction of cardiovascular events with PCSK9 inhibitors: mega-trials

The FOURIER trial included patients with cardiovascular disease and associated cardiovascular risk factors, with LDL-C levels >70 mg/dL despite high-intensity statin therapy with or without ezetimibe. (8) The patients were randomized to evolocumab (140 mg every two weeks or 420 mg every four weeks) or placebo with a mean follow-up of 2.2 years. The primary efficacy endpoint (cardiovascular mortality, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) was observed in 9.8% of the patients treated with evolovumab and 11.3% of those treated with placebo (HR: 0.85; 95% CI, 0.79–0.92; p <0.001). However, there were no significant differences in total mortality or cardiovascular mortality.

In a prespecified secondary analysis of the FOURIER trial, a significant monotonic relationship was observed between LDL-C concentrations reached and the incidence of major cardiovascular events extending to LDL-C concentrations below 0.2 mmol/L. Moreover, no safety issues were observed when very low LDL-C levels were achieved during follow-up. (51)

The ODYSSEY OUTCOMES trial included patients who had presented an acute coronary syndrome one to 12 months before their inclusion in the study and could not control their lipid levels (LDL-C level >70 mg/dL, non−HDL-C level >100 mg/dL, or apolipoprotein B level >80 mg/dL) despite receiving statin therapy at the maximum tolerated dose, associated or not with ezetimibe. (9) Patients were randomly assigned to receive alirocumab at a dose of 75 mg/dL or 150 mg/dL every two weeks or matching placebo to reach a therapeutic target of LDL-C between 25 and 50 mg/dL during a median follow-up of 2.8 years. The primary endpoint (cardiovascular mortality, non-fatal myocardial infarction, fatal or non-fatal stroke or hospitalization for unstable angina) was observed in 9.5% of the patients treated with alirocumab and 11.1% of those treated with placebo (HR: 0.85; 95% CI, 0.78–0.93; p <0.001). The greatest effect of alirocumab was observed in the prespecified subgroup with baseline LDL-C ≥100 mg/dL. Moreover, treatment with alirocumab was associated with lower all-cause mortality compared with placebo (3.5% vs. 4,1%; HR: 0.85; 95% CI, 0.73–0.98; nominal p=0.026), although as the analysis was performed in a hierarchical fashion, it cannot be assured that such association was not by chance.

A prespecified analysis demonstrated that the cardiovascular benefit observed with alirocumab was independent of age. (52) The absolute benefit, but not the rate of severe adverse events, was greater with advanced age.

A recent publication suggests that the benefit of alirocumab on mortality observed in the ODYSSEY OUTCOMES trial would be more significant in patients who received prolonged treatment (>3 years), and those with baseline LDL-C ≥100 mg/dL who achieved very low LDL-C levels with treatment (specifically <30 mg/dL after 4-month treatment). (53)

Also, a sub-analysis of that trial showed that alirocoumab-induced reduction of Lp(a) independently predicted a lower risk of major adverse cardiovascular events after adjustment for baseline concentrations of Lp(a) and patient demographic and clinical characteristics. (54) Similarly, another prespecified analysis of the ODYSSEY OUTCOMES trial reported that the absolute cardiovascular benefit associated with alirocumab was greater in patients with polyvascular disease. (55) In other words, patients with more involved vascular territories (coronary, cerebrovascular and peripheral artery disease) had greater baseline risk and, consequently, the positive impact of PCSK9 inhibition with alirocumab when added to usual statin therapy was more evident.

Although there are no large trials designed to assess the effect of PCSK9 on cardiovascular events in patients with diabetes only, the number of subjects with this disease included in the two largest trials published to date was significant. Thus, the benefit of PCSK9 inhibitors in the population with diabetes

mellitus was demonstrated in two subgroup analyses of the ODYSSEY OUTCOMES and FOURIER trials (56, 57). However, both trials included subjects with diabetes in secondary prevention, without assessing the cardiovascular impact in the population without history of cardiovascular disease.

Finally, a recent meta-analysis including 23 trials (n=60,723) showed that PCSK9 inhibitors reduced major cardiovascular events by 17% (RR 0.83, 95% CI 0.78-0.88), without a significant reduction in mortality (RR 0.93, 95% CI 0.85-1.02). (58)

A comparative analysis of both large trails evaluating cardiovascular morbidity and mortality with PCSK9 inhibitors is shown in Table 1.

Indications according to the most important guidelines

Based on the evidence previously reviewed, PCSK9 inhibitors obtained approval for product marketing in many countries. Therefore, several scientific societies and reference healthcare institutions have incorporated these drugs into the therapeutic arsenal for dyslipidemia in order to reduce cardiovascular events.

Table 2 summarizes the main indications of four reference healthcare institutions: the National Institute for Health and Care Excellence (NICE) (59), which updated its recommendations on the management of dyslipidemia in 2019, the American College of Cardiology (ACC)/American Heart Association (AHA) 2018 task force (60), the European Society of Cardiology (ESC) 2019 guidelines (61) and, finally, the 2017 position paper of the Argentine Society of Cardiology (SAC). (62)

One of the main findings of the cross-sectional comparison of recommendations is that the use of these drugs is limited to patients with statin therapy at maximum tolerated dose and with ezetimibe. Furthermore, the specific clinical conditions and LDL-C levels considered for the use of PCSK9 inhibitors are not homogeneous and the levels of evidence supporting their indication are also different. This finding is frequently observed when the comparative analysis of different guidelines and consensuses is made, and reflects, among other causes, that the process of defining the use of a drug (or any other health technology) considers, besides safety and efficacy evidence, epidemiological aspects (baseline morbidity and mortality) and the structure of health services (including economic and financial aspects) of the country or region where

Table 1. Principal characteristics of the two largest trials with PCSK9 inhibitors.

	FOURIER (n = 27,564)	ODYSSEY OUTCOMES (n = 18,924)
Patients included	Patients (40-85 years) with stable cardiovascular disease and associated cardiovascular risk factors. with LDL-C levels >70 mg/dL (or non-HDL-C >100 mg/dL) treated with statins.	ACS (1 to 12 months before inclusion) with LDL-C level >70 mg/dL (or non–HDL-C level >100 mg/dL or ApoB level >80 mg/dL) with high-intensity statin therapy or at the maximum tolerated dose.
Treatment schedule	Evorocumab 140 mg every two weeks or 420 mg every four weeks vs. placebo#	Alirocumab 75/150 mg every two weeks vs. placebo##
Baseline LDL-C	92 mg/dL	92 mg/dL
LDL-C reduction	59%*	56.3%**
Age	62.5 (± 9.1) years	58.5 (± 9.3) years
Male sex	75.4%	74.7%
Diabetes	36.7%	28.5%
Use of high-intensity statins	69.5%	88.8%
Use of ezetimibe	5.3%	2.8%
Follow-up	2.2 years	2.8 years
Primary endpoint	HR: 0.85 (95% CI. 0.79-0.92)a	HR: 0.85 (95% CI. 0.78-0.93)b
Cardiovascular mortality	HR: 1.05 (95% CI. 0.88-1.25)	HR: 0.88 (95% CI. 0.74-1.05)
Overall mortality	HR: 1.04 (95% CI. 0.91-1.19)	HR: 0.85 (95% CI. 0.73-0.98)###
Severe adverse events	Without difference with the placebo group	Without difference with the placebo group

#Dose was administered according to the patient's preference.
##Dose was titrated to reach LDL-C target between 25 and 50 mg/dL
*Compared with placebo after 48 weeks. LDL-C reached 30 mg/dL.
**Compared with placebo after 52 weeks. Per protocol analysis. LDL-C reached 42 mg/dL.
Cardiovascular mortality, myocardial infarction, stroke, hospitalization due to unstable angina, or coronary artery revascularization.
bMortality due to coronary artery disease, non-fatal myocardial infarction, fatal or non-fatal stroke or hospitalization due to unstable angina.
###Although the associated p value was significant, the analysis was performed in a hierarchical fashion; thus, it cannot be assured that such association was not by chance (nominal p-value).
ACS: acute coronary syndrome: ApoB: apolipoprotein B; HR: hazard ratio; CI: confidence interval.

Table 2. Indications of PCSK9 inhibitors recommended by reference institutions

	Clinical condition	Indication	Comments
NICE	- **Without cardiovascular disease:**		
	a) Primary (non-familial) hypercholesterolemia or mixed dyslipidemia (independent of LDL-C levels).	NO	
	b) Heterozygous familial hypercholesterolemia	If LDL-C >193 mg/dL	If those LDL-C values persist.
	- **With cardiovascular disease:**		
	a) Primary (non-familial) hypercholesterolemia or mixed dyslipidemia and HIGH CARDIOVASCULAR RISK[1]	If LDL-C >155 mg/dL	
	b) Primary (non-familial) hypercholesterolemia or mixed dyslipidemia and VERY HIGH CARDIOVASCULAR RISK[2]	If LDL-C >135 mg/dL	
	c) Heterozygous familial hypercholesterolemia (independently of cardiovascular risk)	If LDL-C >135 mg/dL	
ACC/AHA	- **With clinical atherosclerotic cardiovascular disease and VERY HIGH RISK[3]**	If LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL	Despite use of high-intensity statin therapy or maximum tolerated dose of statins and ezetimibe (class IIa).
	- **Without clinical atherosclerotic cardiovascular disease:**		
	a) Familial hypercholesterolemia		Despite use of maximum tolerated dose
	- **With severe primary hypercholesterolemia:**	If LDL-C ≥100 mg/dL	of statins and ezetimibe (value or use
	a) Severe primary hypercholesterolemia (40 to 75 years, with baseline LDL-C ≥200 mg/dL, independently of the calculated risk)	If LDL-C ≥130 mg/dL	not defined). Despite use of maximum tolerated dose of statins and ezetimibe (class IIb).
	b) Heterozygous familial hypercholesterolemia (30 to 75 years)	If LDL-C ≥100 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class IIb).
ESC	**Secondary prevention:**		
	a) With criteria of VERY HIGH RISK4	If LDL-C is not reduced by ≥ 50% compared with baseline levels and LDL-C ≥55 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class I).
	b) After an acute coronary syndrome (early after the event, during hospitalization).	If LDL-C is not reduced by ≥50% compared with baseline levels and LDL-C ≥55 mg/dL	Despite previous use of maximum tolerated dose of statins and ezetimibe (class IIa).
	c) After an acute coronary syndrome (4-6 weeks after the event)	If LDL-C is not reduced by ≥50% compared with baseline levels and LDL-C ≥55 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class I).
	- **In heterozygous familial hypercholesterolemia and VERY HIGH RISK5**	If LDL-C is not reduced by ≥50% compared with baseline levels and LDL-C ≥55 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class I).

Table 2. Indications of PCSK9 inhibitors recommended by reference institutions

	Clinical condition	Indication	Comments
	- **In primary prevention:**		Despite use of maximum tolerated dose
	a) with criteria of VERY HIGH RISK4 and without familial hypercholesterolemia	If LDL-C is not reduced by ≥50% compared with baseline levels and LDL-C ≥55 mg/dL	of statins and ezetimibe (class IIb).
	- **In patients intolerant to statins**	If According to target LDL-C for the estimated risk	Even after rechallenge and associated with ezetimibe (class IIb).
SAC	- **With established cardiovascular disease**	If LDL-C >100 mg/dL or non-HDL-C >130 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class I).
	- **In heterozygous familial hypercholesterolemia**	If LDL-C >100 mg/dL or non-HDL-C >130 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class I).
	a) associated with any of the following conditions: *Lp(a) > 50 mmol/L* *diabetes mellitus* *hypertension* *family history* *subclinical atherosclerosis*		
	b) with no additional risk factors	If LDL-C >160 mg/dL or non-HDL-C >190 mg/dL	Despite use of maximum tolerated dose of statins and ezetimibe (class I).

[1] NICE - HIGH RISK: history of any of the following: acute coronary syndrome requiring hospitalization, coronary or other arterial revascularization procedures, coronary artery disease, ischemic stroke, peripheral arterial disease.
[2] NICE - VERY HIGH RISK: recurrent cardiovascular events or cardiovascular events in more than one vascular bed (polyvascular disease).
[3] AHA/ACC - VERY HIGH RISK: history of multiple major atherosclerotic cardiovascular disease events or one major atherosclerotic cardiovascular disease event and multiple high-risk conditions: age > 65 years; heterozygous familial hypercholesterolemia; history of prior coronary artery bypass surgery or percutaneous coronary intervention outside major atherosclerotic cardiovascular disease event(s); diabetes mellitus; hypertension; chronic kidney disease (estimated glomerular filtration rate 15-59 mL/min/1.73 m2); current smoking; persistently elevated LDL-C >100 mg/dL despite maximum tolerated statin therapy and ezetimibe; history of congestive heart failure.
[4] ESC - VERY HIGH RISK: Documented atherosclerotic cardiovascular disease, clinical or unequivocal on imaging studies. Includes history of acute coronary syndrome, stable angina, coronary artery revascularization (bypass graft surgery, percutaneous coronary intervention or other arterial revascularization procedures), stroke, transient ischemic attack and peripheral arterial disease. Unequivocally documented cardiovascular disease on imaging studies includes findings that have been shown to be strongly predictors of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel disease with stenosis >50% of two major epicardial coronary arteries) or carotid artery ultrasound. Diabetes mellitus with target organ damage or with at least three risk factors, or early-onset type 1 diabetes lasting > 20 years. Chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m2). A calculated SCORE ≥10% for 10-year risk of fatal cardiovascular disease.
[5] ESC - VERY HIGH RISK IN HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA: patients with atherosclerotic cardiovascular disease or other major risk factor.

the drug will be used. Consequently, what is proposed in other countries should be considered as a reference and not as an endorsement for the indication in our setting. In order to support the medical indication of PSCK9 inhibitors in our country, the most relevant is the recommendation provided by the SAC, since it is a local document that considers the epidemiological and healthcare aspects of our country.

Eligibility: real-world clinical effectiveness and financial impact

The clinical trials and guidelines discussed in the previous sections provide a reference framework on the patients who may obtain the greatest clinical benefit from these drugs. However, the use of medications in everyday healthcare practice raises concerns about safety and effectiveness, to which PCSK9 inhibitors are no exception.

The first item to be reviewed is the "eligibility" of patients who are potential candidates for PCSK9 inhibitors. In line with the previous section, very high-risk patients including those with a coronary artery event, are potentially eligible under certain conditions. Siniawski et al. analyzed 351 patients with

documented coronary artery disease (87.2% with history of acute coronary syndrome). (63) At one-year follow-up, only 0.6% of patients were eligible to receive PCSK9 inhibitors according to SAC recommendations (62), despite 54.7% of patients did not meet the target of 70 mg/dL C-LDL and 95.7% were receiving statins. A priori, the proportion of patients eligible for PCSK9 inhibitors would be expected to be much higher. Among the explanations cited by the authors, only 48.4% were receiving high-intensity statins and 11.4% were treated with ezetimibe, both conditions that are considered mandatory in the process of optimizing lipid-lowering therapy according to current recommendations. Although the AHA/ACC and ESC recommendations do not apply to our country as a standard, if these criteria had been used, the percentage of candidates for PCSK9 inhibitors would have been only 4%. The authors proposed an ideal scenario, in which all patients were receiving high-intensity statins and ezetimibe, and, in that case, the percentage of patients eligible to receive PCSK9 inhibitors rose to 12.8%, following SAC recommendations. Even though there are few publications on this topic, the experiences of other countries are similar to those reported in that local study. A study conducted in two hospitals in the United Kingdom including 596 patients with acute coronary syndrome revealed that according to NICE recommendations, 2.17% of these patients were eligible for PCSK9 inhibitors. (64) The authors found that 29.1% of patients had failed to reach the LDL-C target despite receiving moderate or high-intensity statin therapy. However, as ezetimibe, a mandatory first step in optimizing lipid-lowering therapy, was underprescribed, that option may have influenced the results of the study.

In an Italian multicenter study of 3,074 post-infarction subjects, eligibility for PCSK9 inhibitors according to the ESC/European Atherosclerosis Society (EAS) 2017 guidelines was 9.8%; it was also seen that 61.4% of patients were receiving high-intensity statins and only 18% statins and ezetimibe. (65) Finally, a retrospective analysis of a database, albeit with some methodological limitations, including 942,902 patients in the United States with history of documented coronary artery disease, revealed that only 66.9% were receiving statins (the study does not specify statin intensity used) and 3% were receiving ezetimibe. In that study, the use of PCSK9 inhibitors (which were indicated only to patients who fulfilled the eligibility AHA/ACC criteria) was of only 0.21%. (66)

The other group of patients who are candidates for PCSK9 inhibitors are those with familial hypercholesterolemia. As only 1% of patients with familial hypercholesterolemia are diagnosed, this population is undertreated by definition. (67) At this point, it is important to emphasize that the diagnostic criteria recommended by the SAC are those of the Dutch Lipid Clinics Network. (62) The reports on the use of PCSK9 inhibitors in familial hypercholesterolemia usually come from lipid clinics or analysis of prescription databases. A study of 271 patients with private and public health coverage in the United States reported that 54% of the subjects referred for treatment with PCSK9 inhibitors had familial hypercholesterolemia (half of them in primary prevention). None of the patients reached LDL-C targets and use of high-intensity statins in combination with ezetimibe was around 30%. (68) A Spanish study of five referral centers for evaluation of treatment initiation with PCSK-9 inhibitors reported that use of the association with ezetimibe was also low (22%) in patients with familial hypercholesterolemia in secondary prevention, 77% of which were treated with moderate to high intensity statins. (69)

Therefore, the first conclusion of this section is that patients should receive the best possible treatment before being considered candidates for PCSK9 inhibitors. However, treatment depends not only on the prescription made but also on patient's compliance, persistence and adherence to treatments prescribed. In general, in patients with chronic treatments, persistence ranges from 30% to 50% for lipid-lowering agents and anti-hypertensive drugs, even in our country. (70, 71) This issue is multi-faceted by definition, as it involves accessibility to medications and to the healthcare system, and patients' preferences (72), but we know that it has serious consequences for health because discontinuation of treatment leads to increased morbidity and mortality from cardiovascular causes. (73) The reasons that usually appear for the discontinuation or even limitation of the dose of statins received or prescribed include statin-associated muscle symptoms (SAMS) which, in some cases, determine true intolerance. This is where the definition of intolerance used becomes very important, and for this purpose the SAC recommends the use of scoring systems as a tool for identifying intolerant patients in order to unify the criteria applicable to this heterogeneous subgroup of patients (Table 3). (62, 74)

This adverse effect is so complex that it is even considered that the nocebo effect may be one of its determinants. (75) Eligibility for PCSK9 inhibitors is a complex process reflected by the fact that some studies assume that patients treated only with ezetimibe are intolerant. (65) Bearing these considerations in mind, statin intolerance represents a low percentage of patients eligible for the use of PCSK9 inhibitors in reports on eligibility, ranging from 2.2% to 6.6% in secondary prevention patients. (63, 65) These percentages are much higher in referral centers and lipid clinics. (68, 69)

Therefore, the second conclusion of this discussion is that one must be very strict when categorizing a patient as intolerant, since the mere complaint of muscle or joint pain or discomfort is not a criterion for defining statin intolerance and, consequently, patients are inappropriately excluded from statin treatment and

Table 3. Recommendations of the Argentine Society of Cardiology for the identification of statin intolerance

Is there statin intolerance?		
a)	Test withdrawal and rechallenge, to determine causal relationship with statin administration (avoid rechallenge or manage it carefully in cases of rhabdomyolysis or severe myopathy). Use muscle symptom scores to define causality between statins and muscle symptoms.	Class I recommendation Level of evidence C
b)	Verify the presence of predisposing factors: hypothyroidism, vitamin D deficit, polypharmacy, pharmacological interaction.	Class I recommendation Level of evidence C
c)	Try with a second statin. Consider short half-life statins (simvastatin, fluvastatin, pravastatin).	Class I recommendation Level of evidence C
d)	Only in exceptional cases non-conventional regimes can be indicated (alternate-day regimen), considering that the scientific evidence supports daily use of statins.	Class IIb recommendation Level of evidence C

are forced to use PCSK9 inhibitors.

The other major concern in this section is the financial impact. In this regard, it is important to note that the information available on cost-effectiveness and financial impact from other countries is completely useless in our setting because factors such as the incidence and severity of the diseases, the availability and use of health resources, treatment patterns and prices are different. (76)

However, the information from other countries can provide local estimates that contribute with objective information for our health decision makers, especially to deal with the coverage of new health technology. Pharmacoeconomics analysis deals with this issue in the case of medications. (77) This type of analyses focusses on epidemiological aspects, use of resources, efficacy, safety, effectiveness and costs of treatment of a disease under current conditions compared with the use of a new drug, and combines local, regional and international data through a modelling methodology. (78) In the case of PCSK9 inhibitors, when this review was written, there was only one report that had addressed the potential financial impact of alirocumab on the management of patients with heterozygous familial hypercholesterolemia, with and without prior cardiovascular disease, who had private or social healthcare coverage. Based on local and regional data, this study estimated that for those patients with this clinical condition who did not reach LDL-C targets despite treatment with high-intensity statins and ezetimibe, the budgetary impact was marginal, considering specific cost and price conditions. (79) Healthcare service pricing is one of the most important determinants of accessibility to medicines in general, and specifically in the case of PCSK9 inhibitors, since the magnitude of the relative increase in treatment cost can have a negative financial impact on the healthcare payer (State, workers' health insurance or private coverage) and on patients, turning an adequate therapeutic option into a financial burden that is difficult to sustain for the entire healthcare system.

In conclusion, we must be very accurate when selecting patients eligible for PCSK9 inhibitors in daily practice, maximizing conventional regimens and strictly identifying statin intolerant patients. These measures will most probably contribute, from our role as healthcare providers, to further spread the use of these drugs in the group of patients who obtain the greatest benefit and who are precisely defined in the SAC recommendations.

REFERENCES

1. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009;29:431-8. https://doi.org/10.1161/ATVBAHA.108.179564.
2. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154-6. https://doi.org/10.1038/ng1161
3. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005;37:161-5. https://doi.org/10.1038/ng1509
4. Peterson AS, Fong LG, Young SG. PCSK9 function and physiology. J Lipid Res. 2008;49:1152-6. https://doi.org/10.1194/jlr.E800008-JLR200.
5. Leren TP. Sorting an LDL receptor with bound PCSK9 to intracellular degradation. Atherosclerosis 2014;237:76-81. https://doi.org/10.1016/j.atherosclerosis.2014.08.038.
6. Chowdhury SR, Rees A. Inhibition of PCSK9: is this the way forward for managing residual risk? Curr Opin Lipidol. 2012;23:509-10. https://doi.org/10.1097/MOL.0b013e328358246a.
7. Vogel RA. PCSK9 inhibition: the next statin? J Am Coll Cardiol. 2012;59:2354-5. https://doi.org/10.1016/j.jacc.2012.03.011.
8. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713-22. https://doi.org/10.1056/NEJMoa1615664.
9. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097-2107. https://doi.org10.1056/NEJMoa1801174.
10. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370: 1809-19. https://doi.org/10.1056/NEJMoa1316222.
11. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet. 2012;380:2007-17. https://doi.org/10.1016/S0140-6736(12)61770-X.
12. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F,

Wasserman SM, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study. Circ J 2014;78:1073-82. https://doi.org/10.1253/circj.cj-14-0130.
13. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531-40. https://doi.org/10.1016/j.jacc.2014.03.018.
14. Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2012;380:1995-2006. https://doi.org/10.1016/S0140-6736(12)61771-1.
15. Raal F, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the reduction of LDL-C with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation 2012;126:2408-17. https://doi.org/10.1161/CIRCULATIONAHA.112.144055.
16. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:331-40. https://doi.org/10.1016/S0140-6736(14)61399-4.
17. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 2014;311:1870-82. https://doi.org/10.1001/jama.2014.4030.
18. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014;63:2541-48. https://doi.org/10.1016/j.jacc.2014.03.019.
19. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. JAMA. 2012;308:2497-2506. https://doi.org/10.1001/jama.2012.25790.
20. Stroes E, Robinson JG, Raal FJ, Dufour R, Sullivan D, Kassahun H, et al. Consistent LDL-C response with evolocumab among patient subgroups in PROFICIO: A pooled analysis of 3146 patients from phase 3 studies. Clin Cardiol. 2018;41:1328-35. https://doi.org/10.1002/clc.23049.
21. Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. Future Cardiol. 2015;11:27-37. https://doi.org/10.2217/fca.14.82.
22. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. J Clin Lipidol 2015;9:758-69. https://doi.org/10.1016/j.jacl.2015.08.006.
23. Roth EM, Moriarty PM, Bergeron J, Langslet G, Manvelian G, Zhao J, et al. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Atherosclerosis 2016;254:254-62. https://doi.org/10.1016/j.atherosclerosis.2016.08.043.
24. Stroes E, Guyton JR, Lepor N, Civeira F, Gaudet D, Watts GF, et al. Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study. J Am Heart Assoc 2016;5: e003421. https://doi.org/10.1161/JAHA.116.003421.
25. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J 2015;169:906-915.e913. https://doi.org/10.1016/j.ahj.2015.03.004.
26. El Shahawy M, Cannon CP, Blom DJ, McKenney JM, Cariou B, Lecorps G, et al. Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II). Am J Cardiol 2017;120:931-39. https://doi.org/10.1016/j.amjcard.2017.06.023.
27. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015;36:2996-3003. https://doi.org/10.1093/eurheartj/ehv370.
28. Bays H, Gaudet D, Weiss R, Ruiz JL, Watts GF, Gouni-Berthold I, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. J Clin Endocrinol Metab. 2015;100:3140-48. https://doi.org/10.1210/jc.2015-1520.
29. Farnier M, Jones P, Severance R, Averna M, Steinhagen-Thiessen E, Colhoun HM, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. Atherosclerosis. 2016;244:138-46. https://doi.org/10.1016/j.atherosclerosis.2015.11.010.
30. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Baccara-Dinet MT, Lorenzato C, et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. Cardiovasc Drugs Ther. 2016;30:473-83. https://doi.org/10.1007/s10557-016-6685-y.
31. Teramoto T, Kiyosue A, Ishigaki Y, Harada-Shiba M, Kawabata Y, Ozaki A, et al. Efficacy and safety of alirocumab 150mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON. J Cardiol. 2019;73:218-27. https://doi.org/10.1016/j.jjcc.2018.10.004.
32. Ray KK, Leiter LA, Müller-Wieland D, Cariou B, Colhoun HM, Henry RR, et al. Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: The ODYSSEY DM-DYSLIPIDEMIA randomized trial. Diabetes Obes Metab. 2018;20:1479-89. doi: 10.1111/dom.13257.
33. Moriarty PM, Parhofer KG, Babirak SP, Cornier MA, Duell PB, Hohenstein B, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. Eur Heart J. 2016;37:3588-95. https://doi.org/10.1093/eurheartj/ehw388.
34. Leiter LA, Cariou B, Müller-Wieland D3, Colhoun HM, Del Prato S,Tinahones FJ, et al. Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial. Diabetes Obes Metab. 2017;19:1781-92. https://doi.org/10.1111/dom.13114.
35. McCullough PA, Ballantyne CM, Sanganalmath SK, Langslet G, Baum SJ, Shah PK, et al. Efficacy and Safety of Alirocumab in High-Risk Patients With Clinical Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from 5 Placebo-Controlled ODYSSEY Trials). Am J Cardiol. 2018;121:940-48. https://doi.org/10.1016/j.amjcard.2017.12.040.
36. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489-99. https://doi.org/10.1056/NEJMoa1501031.
37. López-Sendón J, Castro A, Dalmau R. Una historia resumida. La inhibición de la PCSK9 y su desarrollo clínico. Rev Esp Cardiol Supl 2017;17(A):10-15. https://doi.org/10.1016/S1131-3587(19)30011-1.
38. Ridker PM, Tardif JC, Amarenco P, Duggan W, Glynn RJ, Jukema JW, et al. Lipid-Reduction Variability and Antidrug-Antibody Formation with Bococizumab. N Engl J Med. 2017;376:1517-26. https://doi.org/10.1056/NEJMoa1614062.
39. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. N Engl J Med. 2017;376:1527-39. https://doi.org/10.1056/NEJMoa1701488.
40. Henry RR, Müller-Wieland D, Taub PR, Bujas-Bobanovic M, Louie MJ, Letierce A, et al. Effect of alirocumab on lipids and lipoproteins in individuals with metabolic syndrome without diabetes: Pooled data from 10 phase 3 trials. Diabetes Obes Metab 2018;20:1632-41. https://doi.org/10.1111/dom.13273.
41. Filippatos TD, Kei A, Rizos CV, Elisaf MS. Effects of PCSK9 Inhibitors on Other than Low-Density Lipoprotein Cholesterol Lipid Variables. J Cardiovasc Pharmacol Ther. 2018;23:3-12. https://doi.org/10.1177/1074248417724868.
42. Cao YX, Liu HH1, Li S1, Li JJ. A Meta-Analysis of the Effect of

PCSK9-Monoclonal Antibodies on Circulating Lipoprotein (a) Levels. Am J Cardiovasc Drugs. 2019;19:87-97. https://doi.org/10.1007/s40256-018-0303-2.
43. Toth PP, Descamps O, Genest J, Sattar N, Preiss D, Dent R, et al. Pooled Safety Analysis of Evolocumab in Over 6000 Patients From Double-Blind and Open-Label Extension Studies. Circulation. 2017;135:1819-31. https://doi.org/10.1161/CIRCULATIONAHA.116.025233.
44. Strilchuk L, Fogacci F, Cicero AF. Safety and tolerability of injectable lipid-lowering drugs: an update of clinical data. Expert Opin Drug Saf 2019;18:611-21. https://doi.org/10.1080/14740338.2019.1620730.
45. Robinson JG, Rosenson RS, Farnier M, Chaudhari U, Sasiela WJ, Merlet L, et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab: Pooled Data From Randomized Trials. J Am Coll Cardiol. 2017;69:471-82. https://doi.org/10.1016/j.jacc.2016.11.037.
46. Masson W, Lobo M, Huerín M, Molinero G, Lobo L, Nogueira JP. Plasma proprotein convertase subtilisin/kexin type 9 inhibitors and cataract risk: A systematic review and meta-analysis. Arch Soc Esp Oftalmol 2019;94:75-80. https://doi.org/10.1016/j.oftal.2018.11.003.
47. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, et al. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med 2017;377:633-43. https://doi.org/10.1056/NEJMoa1701131.
48. Koren MJ, Sabatine MS, Giugliano RP, Langslet G, Wiviott SD, Ruzza A, et al. Long-Term Efficacy and Safety of Evolocumab in Patients With Hypercholesterolemia. J Am Coll Cardiol. 2019;74:2132-46. https://doi.org/10.1016/j.jacc.2019.08.1024.
49. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA. 2016;316:2373-84. https://doi.org/10.1001/jama.2016.16951.
50. Ako J, Hibi K, Tsujita K, Hiro T, Morino Y, Kozuma K, et al. Effect of Alirocumab on Coronary Atheroma Volume in Japanese Patients With Acute Coronary Syndrome - The ODYSSEY J-IVUS Trial. Circ J 2019;83:2025-33. https://doi.org10.1253/circj.CJ-19-0412.
51. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al.Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial.Lancet. 2017;390:1962-71. https://doi.org/10.1016/S0140-6736(17)32290-0.
52. Sinnaeve PR, Schwartz GG, Wojdyla DM, Alings M, Bhatt DL, Bittner VA, et al.Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: an ODYSSEY OUTCOMES trial analysis.Eur Heart J. 2019 Nov 16. pii: ehz809. https://doi.org/10.1093/eurheartj/ehz809.
53. Steg PG, Szarek M, Bhatt DL, Bittner VA, Brégeault MF, Dalby AJ, et al. Effect of Alirocumab on Mortality After Acute Coronary Syndromes. Circulation 2019;140:103-12. https://doi.org/10.1161/CIRCULATIONAHA.118.038840.
54. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, et al. Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. J Am Coll Cardiol. 2020;75:133-44. https://doi.org/10.1016/j.jacc.2019.10.057.
55. Jukema JW, Szarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, et al. Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol. 2019;74:1167-76. https://doi.org/10.1016/j.jacc.2019.03.013.
56. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7:618-28. https://doi.org/10.1016/S2213-8587(19)30158-5.
57. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5:941-50. https://doi.org/10.1016/S2213-8587(17)30313-3.
58. Turgeon RD, Tsuyuki RT, Gyenes GT, Pearson GJ. Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial. Can J Cardiol. 2018;34:1600-05. doi: 10.1016/j.cjca.2018.04.002.
59. http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention
60. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/AphA/ASPC/ NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American Collegeof Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:e285-e350. https://doi.org/10.1016/j.jacc.2018.11.003.
61. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-88. https://doi.org10.1093/eurheartj/ehz455.
62. https://www.sac.org.ar/wp-content/uploads/2018/06/documento-de-posicion-recomendaciones-para-el-uso-de-inhibidores-de-PCSK9.pdf
63. Siniawski D, Masson W, Rossi E, Damonte J, Halsband A, Pizarro R. Elegibilidad para la indicación de inhibidores de PCSK9 según las recomendaciones de diferentes sociedades científicas. Medicina (B Aires).2019;79:104-10.
64. Elamin AFM, Grafton-Clarke C, Wen Chen K, Obafemi T, Luvai A, Katira R, et al. Potential use of PCSK9 inhibitors as a secondary preventative measure for cardiovascular disease following acute coronary syndrome: a UK real-world study. Postgrad Med J. 2019;95:61-6. https://doi.org/10.1136/postgradmedj-2018-136171.
65. Colivicchi F, Massimo Gulizia M, Arca M, Luigi Temporelli P, Gonzini L, Venturelli V, et al. Lipid Lowering Treatment and Eligibility for PCSK9 Inhibition in Post-Myocardial Infarction Patients in Italy: Insights from Two Contemporary Nationwide Registries. Cardiovasc Ther. 2020 Jan 3;2020:3856242. https://doi.org/10.1155/2020/3856242.
66. Chamberlain AM, Gong Y, Shaw KM, Bian J, Song WL, Linton MF, et al. PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network. J Am Heart Assoc. 2019;8:e011246. https://doi.org/10.1161/JAHA.118.011246.
67. Santos RD, Bourbon M, Alonso R, Cuevas A, Vasques-Cardenas NA, Pereira AC, et al. Clinical and molecular aspects of familial hypercholesterolemia in Ibero-American countries. J Clin Lipidol. 2017;11:160-66. https://doi.org/10.1016/j.jacl.2016.11.004.
68. Kaufman TM, Warden BA, Minnier J, Miles JR, Duell PB, Purnell JQ,et al. Application of PCSK9 Inhibitors in Practice. Circ Res. 2019;124:32-7. https://doi.org/10.1161/CIRCRESAHA.118.314191.
69. Cordero A, Fácila L, Rodríguez-Mañero M, Gómez-Martínez MJ, Bertomeu-Martínez V, González-Juanatey JR. Initial Real-World Experience With PCSK-9 Inhibitors in Current Indications for Reimbursement in Spain. Rev Esp Cardiol. 2019;72:968-70. https://doi.org/10.1016/j.rec.2019.03.008.
70. Chapman FH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid lowering therapy. Arch Intern Med. 2005;165:1147-52. https://doi.org/10.1001/archinte.165.10.1147.
71. Giorgi MA, Volman S, Pereira L, Coca A. Análisis de la persistencia de pacientes bajo tratamiento antihipertensivo en programa de educación administración de medicación. Hipertens Riesgo Vasc. 2011;28:137-42.
72. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy?. Curr Atheroscler Rep. 2013;15:291. https://doi.org/10.1007/s11883-012-0291-7.
73. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J. 2016;37:908-16. https://doi.org/10.1093/eurheartj/ehv641.
74. Rosenson RS, Miller K, Bayliss M, Sanchez RJ, Baccara-Dinet MT, Chibedi-De-Roche D, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): Revision for Clinical Use, Content Validation, and Inter-rater Reliability. Cardiovasc Drugs Ther 2017;31:179-86. https://doi.org/10.1007/s10557-017-6723-4.
75. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind

extension phase. Lancet. 2017;389:2473-81. https://doi.org/10.1016/S0140-6736(17)31075-9.

76. Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, et al. Generalisability in economic evaluation studies in health care: a review and case studies.Health Technol Assess. 2004;8(49):iii-iv, 1-192. https://doi.org/10.3310/hta8490.

77. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force Report. Value Health. 2009;12:409-18. doi: 10.1111/j.1524-4733.2008.00489.x.

78. Giorgi M. Conceptos generales de farmacoeconomía: el caso de los nuevos anticoagulantes orales en la prevención de eventos trombóticos en la fibrilación auricular en Argentina. Revista del CONAREC 2015;(131):228-233.

79. Giorgi MA, Boissonnet CP, Micone PV, Gallo M, Stuart P, Giglio ND.PCV-38 - Budget impact of alirocumab in the management of heterozygous familial hypercholesterolemia patients in Argentina. Value in Health. 2018;21 (suppl 3):S98-S99.