Κλινική εφαρμογή των αναστολέων της PCSK9 σε ένα εξειδικευμένο ιατρείο

Φώτιος Μπάρκας

Φώτιος Μπάρκας [1,2], Ευάγγελος Λυμπερόπουλος [1,2], Αναστάζια Κεή [1,2], Ανδρομάχη Μακρή[2], Ευσταθία Μεγαπάνου [1,2], Αδελαϊδα Πανταζή [2], Μωυσής Ελισάφ [1,2], Γεώργιος Λιάμης [1,2]
1 Τομέας Παθολογίας, Ιατρική Σχολή Πανεπιστημίου Ιωαννίνων
2 Β' Παθολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων

Υπεύθυνος επικοινωνίας:
Γεώργιος Λιάμης, MD, PhD
Αναπληρωτής Καθηγητής Παθολογίας
Τομέας Παθολογίας, Ιατρική Σχολή Πανεπιστημίου Ιωαννίνων
Λεωφόρος Σταύρου Νιάρχου, 45110, Ιωάννινα, Ελλάδα
Τηλ.: +302651007509 Φαξ: +302651007016
e-mail: gliamis@cc.uoi.gr

Περίληψη

Σκοπός: Η καταγραφή των ασθενών που είναι υποψήφιοι για αγωγή με αναστολείς της PCSK9 (proprotein convertase subtilisin/kexin type 9).
Μέθοδοι: Πρόκειται για μία αναδρομική μελέτη παρατήρησης στην οποία συμμετείχαν 1,000 ενήλικοι ασθενείς που παρακολουθούνται στο εξωτερικό ιατρείο Λιπιδίων του Πανεπιστημιακού Νοσοκομείου Ιωαννίνων για ≥3 έτη. Οι κατηγορίες των ασθενών που ήταν υποψήφιοι για τη χορήγηση αναστολέων της PCSK9 ορίστηκαν σύμφωνα με τις κατευθυντήριες οδηγίες της Ελληνικής Εταιρείας Αθηροσκλήρωσης. Ως επιθετική αγωγή με στατίνη ορίστηκε εκείνη που αναμένεται να μειώσει τα επίπεδα της χοληστερόλης των χαμηλής πυκνότητας λιποπρωτεϊνών (LDL-C) κατά ≥50%.
Αποτελέσματα: Από το σύνολο των ατόμων που συμμετείχε στη μελέτη, το 17% των ατόμων είχε διαγνωσθεί με CVD, το 6% με σακχαρώδη διαβήτη τύπου 2 και βλάβη οργάνου στόχου, το 11% των ατόμων είχε οικογενή υπερχοληστερολαιμία (FH) και το 4% εμφάνισε δυσανεξία στη στατίνη. Τα επίπεδα της LDL-C για τις 3 κατηγορίες ασθενών που ελάμβαναν επιθετική υπολιπιδαιμική αγωγή ήταν 97 mg/dL (εύρος:46-305), 69mg/dL (εύρος:54-159) και 107 mg/dL (εύρος:45-242), αντίστοιχα, ενώ τα άτομα που εμφάνισαν δυσανεξία στις στατίνες και ελάμβαναν οποιαδήποτε υπολιπιδαιμική αγωγή σε ανεκτή δόση είχαν επίπεδα LDL-C 104 mg/dL (εύρος:32-230). Από τους ασθενείς που ελάμβαναν επιθετική υπολιπιδαιμική αγωγή, 11 από τους 27 ασθενείς με CVD, 1 από τους 5 διαβητικούς ασθενείς με βλάβη οργάνου στόχου και 10 από

τους 51 ασθενείς με FH ήταν υποψήφιοι για αγωγή με αναστολείς της PCSK9. Αντίστοιχα, 12 από τους 41 ασθενείς που εμφάνισαν δυσανεξία στις στατίνες ήταν επίσης υποψήφιος να λάβει αναστολείς της PCSK9.

Συμπεράσματα: Ένα ικανό ποσοστό υπερλιπιδαιμικών ασθενών υψηλού κινδύνου και ιδιαίτερα οι ασθενείς με καρδιαγγειακή νόσο και FH δεν επιτυγχάνουν τους στόχους της αγωγής όσον αφορά τη LDL-C και είναι υποψήφιοι για αγωγή με αναστολείς της PCSK9.

Λέξεις – Κλειδιά: επίτευξη, στόχοι, χοληστερόλη, PCSK9 αναστολείς

Clinical application of PCSK9 inhibitors in a specialized lipid clinic

Fotios Barkas [1,2], Evangelos Liberopoulos [1,2], Anastazia Kei [1,2], Andromachi Makri [2], Efstathia Megapanou [1,2], Adelaida Pantazi [2], Moses Elisaf [1,2], George Liamis [1,2]

1 Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece
2 2nd Department of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece

Summary

Aim: To record how many patients are candidates for treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in the setting of a specialized lipid clinic.

Methods: This was a retrospective observational study including 1,000 adult dyslipidemic patients followed-up for ≥ 3 years in a specialized lipid clinic. The groups of patients being candidates for PCSK9 inhibitors were defined according to the guidelines of Hellenic Atherosclerosis Society. As high intensity statins were considered those expected to reduce low-density lipoprotein cholesterol (LDL-C) levels by ≥50%.

Results: Of the total study participants, 17% of the subjects were diagnosed with cardiovascular disease (CVD), 6% with type 2 diabetes and target organ damage, 11% had familial hypercholesterolemia (FH) and 4% exhibited statin intolerance. LDL-C levels for the first three groups of patients receiving high intensity statin treatment were 97 mg/dL (46-305), 69 mg/dL (54-159) and 107 mg/dL (45-242), respectively. Patients with statin intolerance and receiving any hypolipidemic treatment at any tolerable dose had LDL-C levels of 104 mg/dL (32-230). Of the patients receiving aggressive lipid-lowering treatment, 11 out of 27 CVD patients and one of 5 diabetic patients with target organ damage had LDL-C ≥100 mg/dL, whereas 10 of 51 FH patients had LDL-C ≥130 mg/dL. Correspondingly, 12 out of the 41 patients who had statin intolerance were also candidates for PCSK9 inhibitors.

Conclusions: A considerable proportion of hyperlipidemic patients at high cardiovascular risk and especially those with FH, do not achieve optimal LDL-C levels and are candidates for treatment with PCSK9 inhibitors.

Keywords: target, achievement, attainment, cholesterol, PCSK9 inhibitors

Introduction

Cardiovascular (CV) disease remains the major leading cause of mortality in the developed countries.[1] Although statins are the cornerstone therapy for the primary and secondary CV prevention [2], since the statin-mediated cholesterol reduction reduces CV mortality [3], a considerable proportion of patients remains undertreated in everyday clinical practice.[4-6] In both Greece and the rest European countries a few patients do not receive intensive hypolipidemic therapy and mostly those at very high CV risk do not achieve optimal low-density lipoprotein cholesterol (LDL-C) levels as proposed by the European guidelines.[4-9] Nevertheless, even the prescription of high doses of high-intensity statins do not lead to effective LDL-C reduction. [8, 10-13] On the other hand, combination therapies of a statin with other hypolipidemic drugs, such as ezetimibe or the inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), induce greater LDL-C reduction rather than statin monotherapy.[14, 15] Considering the controversial results of the studies evaluating the cost-effectiveness of the PCSK9 inhibitors [16-22], it would be of great interest to record the patients who would be candidate to take such treatment in clinical practice.

In the present study, we aimed to evaluate the rates of LDL-C target attainment according to the recent guidelines of the Hellenic Atherosclerosis Society (HAS) and to record the proportion of the candidates for treatment with PCSK9 inhibitors according to the Consensus Panel of the Hellenic Atherosclerosis Society.[23, 24]

Methods

As previously described, this was a retrospective study including 1,000 adult dyslipidemic individuals with a follow-up of ≥3 years who attended the Outpatient Lipid Clinic of University Hospital of Ioannina in Greece.[7-9] The study protocol was approved by the institutional Ethics Committee.

Demographic characteristics as well as clinical and laboratory data were recorded. These included age, gender, smoking status and body mass index (BMI) together with history of CV risk factors and concomitant diseases. Prescribed lipid-lowering medications were also recorded, including the name and dose of statins and other lipid-lowering drugs (i.e. ezetimibe, colesevelam, fibrates and ω-3 fatty acids). Study participants were classified into three CV risk categories: very high, high and moderate according to the HAS guidelines.[23] The corresponding LDL-C goals were 50% LDL-C reduction and LDL-C <70 mg/dL, <100 mg/dL and <115 mg/dL, respectively. In our cohort, subjects were stratified in CV risk groups according to the HAS guidelines and ten-year cardiovascular risk was estimated by the Hellenic SCORE.[25] Familial Hypercholesterolemia (FH) was defined according to the diagnostic criteria of Dutch Lipid Clinic Network. Hyperlipidemic individuals fulfilling the criteria of 'definite' or 'probable' FH were considered as heterozygous FH patients in the present study.

The intensity of statin therapy was classified as high, moderate and low on the basis of the average expected LDL-C lowering of 50, 30–50 and <30%, respectively. Daily doses of atorvastatin 40–80 mg and rosuvastatin 20–40 mg were considered as high-intensity statins.

According to the Hellenic Expert Consensus, the eligible patients for administration of monoclonal antibodies against PCSK9 are the following: 1) Adult patients with established atherosclerotic CV disease or diabetic patients with known CV disease or chronic kidney disease (estimated glomerular filtration rate ≤60 mL/min/1.73 m2 and/or albuminuria for at least 3 months) or other target organ damage who have LDL-C ≥100 mg/dl despite being under appropriate health-diet and pharmaceutical treatment with the maximum tolerated dose of a high-intensity statin (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) + ezetimibe 10 mg, 2) adult patients with FH without known atherosclerotic CV disease and LDL-C ≥130 mg/dL despite being under appropriate and pharmaceutical treatment with the maximum tolerated dose of a high-intensity (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) + ezetimibe 10 mg and 3) high- or very high-risk patients (HELLENIC SCORE >5% or >10%, respectively) who are intolerant to statins and have LDL-C ≥130 or ≥100 mg/dL, respectively, under any tolerated lipid-lowering treatment.[24]

For the purposes of the present analysis we report: 1) the rates of LDL-C goal achievement and 2) the proportion of the candidates for administration of monoclonal antibodies against PCSK9.

Statistical analysis

Analysis of efficacy parameters was performed descriptively. Continuous numeric variables were expressed as mean ± standard deviation and median (interquartile range; IQR) if Gaussian or non-Gaussian distributed, respectively. For categorical values, frequency counts and percentages were applied. Chi-square tests were performed for interactions between categorical values. The difference of variables between 2 or more groups was assessed by analysis of variance (ANOVA) and post-hoc least significant difference (LSD) tests were used for the comparison of variables or ratios of interest between two groups. Two-tailed significance was defined as $p < 0.05$. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) 23.0 software (SPSS IBM Corporation, Armong, NY, USA).

Results

Study population

A total of 1,000 subjects were included and followed up for a median of 6 years (4-10). Demographic and clinical characteristics of the study population are shown in Table 1. Subjects' median age was 64 years and 45% of those were males. Of note, 17% of the study participants were diagnosed with CV disease, 6% had diabetes with target organ damage and 11% fulfilled the criteria for FH.

Ninety four percent of subjects were on lipid-lowering therapy: 91% on statins (68% on statin monotherapy and 32% on combined therapy). In 25% of subjects statins were combined with ezetimibe, 5% with ω-3 fatty acids, 4% with fibrates, and 1% with colesevelam. Some patients were on triple combinations (e.g. statin + ezetimibe + fibrate). Among non-statin treated patients (9% of the whole population), 69% were not on any lipid-lowering medication, 24% were on fibrates, 9% on ezetimibe and 7% on ω-3 fatty acids. Four percent of all patients were unable to tolerate even low-dose statin treatment.

Selected lipid-lowering therapies and LDL-C goal achievement across CV risk groups

Selected lipid-lowering treatment and rates of LDL-C target achievement across CV risk groups are shown in Table 2. Patients at 'very-high' CV risk were more likely to receive 'high-intensity' statin treatment compared with those at 'high' and 'moderate' CV risk, while approximately half of patients in each CV risk group were treated with a 'moderate-intensity' statin therapy (Table 2). A non-significant trend towards a higher rate of a statin + ezetimibe combination treatment was noted in subjects at 'very-high' and 'high' CV risk compared with those at 'moderate' CV risk (Table 2).

Patients at 'very-high' CV risk had the lowest rate of LDL-C target attainment compared with the other 2 groups (16 vs 27 vs 59%, $p < 0.05$) (Table 2). The combination treatment of a statin with ezetimibe achieved higher rates of LDL-C target attainment compared with statin monotherapy (41 vs 27%, $p < 0.05$), whereas the additional use of ezetimibe boosted the anticipated LDL-C reduction ≥50% of high-intensity statin monotherapy (76 vs 47%, $p < 0.05$).

Candidates for administration of monoclonal antibodies against PCSK9

Table 3 presents the median LDL-C levels of patients taking high-intensity statin therapy plus ezetimibe. Of the patients receiving aggressive lipid-lowering treatment, 11 out of 27 patients with CV disease and one of 5 diabetic patients with target organ damage had LDL-C ≥100 mg/dL, whereas 10 of 51 FH patients had LDL-C ≥130 mg/dL. Correspondingly, 12 out of the 41 patients who had statin intolerance were also candidates for PCSK9 inhibitors.

Discussion

The present study shows that LDL-C target attainment remains poor in everyday clinical practice. Although the use of combination statin therapy with ezetimibe boosts LDL-C reduction, a

considerable proportion of high risk patients and especially those with CV disease or FH, remain undertreated and are candidates for therapy with PCSK9 inhibitors.

LDL-C reduction remains the main target of primary and secondary CV prevention.[2] Nevertheless, our results showing that LDL-C goal achievement is far from optimal in everyday clinical practice are in agreement with previously published studies. EUROASPIRE IV, a cross-sectional trial conducted in 24 European countries with a total of 16,426 study participants, showed similar low rates of LDL-C goal achievement, mostly in those with coronary heart disease (19.3%).[6] Furthermore, Dyslipidemia International Study II (DYSIS II) demonstrated that only 29.4% of the enrolled 10,661 patients with coronary heart disease had optimal LDL-C levels.[5] Likewise, additional studies have demonstrated low rates of LDL-C target attainment not only in patients with CV disease [4, 26, 27], but also in other high risk patients, such as those with diabetes and FH.[28-30] Of note, our rates of LDL-C goal achievement were the lowest compared with the aforementioned studies. This could be attributed to the fact that our study adapted the most recent guidelines which additionally require the stringent target of the anticipated 50% LDL-C reduction in high risk individuals.

There are several reasons accounting for poor LDL-C target attainment in clinical practice. First, compliance with treatment should be considered. A previous analysis of ours along with other studies have shown that poor compliers exhibit lower rates of LDL-C attainment compared with good compliers.[9, 31] This issue is relevant since poor adherence to lipid-lowering treatment has been associated with increased CV morbidity and mortality.[32] Some strategies can increase compliance with treatment. For instance, fixed-dose combinations of lipid-lowering medications can improve compliance leading to a long overdue reduction in CV events.[33] In addition, reluctance of physicians to prescribe a more aggressive lipid-lowering therapy plays a detrimental role. Indeed, high doses of statin therapy are avoided in everyday clinical practice due to the fear of potential side effects.[7, 9] In our study, almost half of the patients at high CV risk were taking high-intensity statin and only 25% of those were taking combination therapy of a statin plus ezetimibe. Similarly to ours, previously published studies have demonstrated that statin utilization is low in clinical practice, even in very-high and high risk patients.[11, 34] Thus, more aggressive lipid lowering therapies, such as statin therapy at maximal dose or combination treatment with ezetimibe, are needed in order to increase LDL-C target attainment. Indeed, our results showed that combination statin therapy with ezetimibe achieved higher rates of LDL-C goal achievement compared with statin monotherapy, whereas the additional use of ezetimibe on high intensity statin treatment boosted the anticipated LDL-C reduction ≥50%.[8] Nevertheless, a considerable proportion of patients at high risk, such as those with CV disease or FH, remained undertreated in our study despite their potent lipid-lowering therapy. Indeed, high-intensity statin therapy does not always achieve ≥50% LDL-C reduction [13], whereas optimal LDL-C goal achievement in FH patients remains a challenge in clinical practice. [12, 35] Finally, statin intolerance, which appears more common in real world practice than the randomized trials [36], might be a reason for poor LDL-C target attainment, since such individuals cannot tolerate statin at maximal doses if not at all. This has attracted most attention, given the well-established consequences of increased cardiovascular events and mortality associated with statin discontinuation.[37] In this context, new treatment modalities are needed in order to overcome the issue of poor LDL-C target attainment in everyday clinical practice.

Several trial and meta-analyses have endorsed the effectiveness of PCSK9 inhibitors in LDL-C reduction.[15, 38, 39] Considering the recent results of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial showing that the use of evolocumab on a background of statin therapy reduced the risk of CV events by 15% [40], current guidelines propose the use of PCSK9 inhibitors in certain patient groups. [24] Nevertheless, there is a debate whether these drugs should be widely used in the market

because of their neural effect on mortality and their cost.[18] Several analyses argue that PCSK9 inhibitor use even in patients with FH or CV disease does not meet generally acceptable incremental cost-effectiveness thresholds and they have reached the conclusion that significant discounts are necessary to meet conventional cost-effectiveness standards.[17, 41, 42] Considering this debate, there is an urgent need for trials identifying the proportion of patients being candidates for PCSK9 inhibitors in everyday clinical practice. To the best of our knowledge, our trial was the first to evaluate the applicability of PCSK9 inhibitors in the setting of a lipid clinic. Our results showed that a considerable proportion of patients diagnosed with either CV disease or FH are candidates for treatment with PCSK9 inhibitors (40 and 20%, respectively), despite taking aggressive lipid-lowering therapy. Thus, our study highlights the need for future policies reducing the cost of PCSK9 inhibitors therapies, whereas physicians should be alarmed to identify those patients who remain undertreated and are candidates for such treatment.

Conclusion

Despite the available lipid-lowering drugs, the majority of patients at high CV risk are either mistreated or undertreated. Although the additional use of ezetimibe on high-intensity statin therapy boosts LDL-C reduction, a considerable proportion of patients with CV disease or FH remain undertreated and are candidates for administration of monoclonal antibodies against PCSK9.

Table 1 Demographic and clinical characteristics of the study population.

Variable	Total study participants (n=1000)
Age, years	64 (55-72)
Male sex, %	45
Smoking, %	15
Family history of premature coronary heart disease, %	23
Metabolic syndrome, %	55
Hypertension, %	73
Body mass index, kg/m2	28.3 (25.7-31.1)
Systolic blood pressure, mmHg	130 (120-136)
Diastolic blood pressure, mmHg	78 (72-84)
Total cholesterol, mg/dL	178 (154-200)
Triglycerides, mg/dL	112 (84-150)
High-density lipoprotein cholesterol, mg/dL	53 (45-62)
Low-density lipoprotein cholesterol, mg/dL	98 (79-117)
Lipid-lowering treatment, % ¥	94
Statin treatment, %	91
Cardiovascular risk, %	
Very-high	47
High	41
Moderate	12
Morbidities, %	
Diabetes	21

Diabetes with target organ damage	6
Chronic kidney disease	18
Cardiovascular disease	17
Familial hypercholesterolemia	11
Statin intolerance	4

Values are expressed as median (range).

Table 2. Lipid-lowering treatment and LDL-C target attainment across the CV risk groups.

Variable	**Cardiovascular risk groups**		
	'Moderate' risk (n=115)	'High' risk (n=408)	'Very-high' risk (n=477)
Intensity of statin treatment			
'High-intensity', %	17*	27*	40
'Moderate-intensity', %	55	57	53
'Low-intensity', %	7*	4*	1
No statin treatment, %	21*	12*	6
Statin plus ezetimibe, %	19	24	24
High intensity statin plus ezetimibe, %	6	11	13
LDL-C target attainment, %	59*	27*	16

ANOVA analysis was performed across cardiovascular risk groups

* p <0.05 for the post-hoc LSD comparison with individuals at 'very-high' cardiovascular risk

Abbreviations: LDL-C: low-density lipoprotein cholesterol; ANOVA: Analysis of variance; LSD: least significant difference

Table 3. LDL-C levels of patients taking high-intensity statin therapy with ezetimibe.					
Variable		LDL-C levels (mg/dL)			
	Median (range)	<70 mg/dL (n)	70-100 mg/dL (n)	100-130 mg/dL (n)	>130 mg/dL (n)
Adult patients with established CV disease (n=27)	97 (46-305)	7	9	5	6
Diabetic patients with target organ damage (n=5)	69 (54-159)	4	0	1	0
FH patients without CV disease (n=51)	107 (45-242)	6	14	20	10
Patients with statin intolerance (n=41)	104 (32-230)	4	17	8	12

Abbreviations: LDL-C = low-density lipoprotein cholesterol, CV = cardiovascular, FH = familial hypercholesterolemia

Βιβλιογραφία

1. Atlas Writing, G., et al., European Society of Cardiology: Cardiovascular Disease Statistics 2017. Eur Heart J, 2018. 39(7): p. 508-579.
2. Catapano, A.L., et al., 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J, 2016. 37(39): p. 2999-3058.
3. Baigent, C., et al., Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet, 2005. 366(9493): p. 1267-78.
4. Elisaf, M.S. and N. Nikas, Centralized Pan-European survey on the undertreatment of hypercholesterolemia in patients using lipid lowering drugs--the CEPHEUS-Greece survey. Angiology, 2010. 61(5): p. 465-74.
5. Gitt, A.K., et al., Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. Atherosclerosis, 2017. 266: p. 158-166.
6. Kotseva, K., et al., EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol, 2016. 23(6): p. 636-48.
7. Barkas, F., et al., Attainment of multifactorial treatment targets among the elderly in a lipid clinic. J Geriatr Cardiol, 2015. 12(3): p. 239-45.
8. Barkas, F., et al., How effective are the ESC/EAS and 2013 ACC/AHA guidelines in treating dyslipidemia? Lessons from a lipid clinic. Curr Med Res Opin, 2015. 31(2): p. 221-8.
9. Barkas, F., et al., Lipid target achievement among patients with very high and high cardiovascular risk in a lipid clinic. Angiology, 2015. 66(4): p. 346-53.
10. Arca, M., et al., Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: Insights from Italian general practice. Atherosclerosis, 2018. 271: p. 120-127.
11. Fox, K.M., et al., Treatment patterns and low-density lipoprotein cholesterol (LDL-C) goal attainment among patients receiving high- or moderate-intensity statins. Clin Res Cardiol, 2017.
12. Oh, J., et al., Target achievement with maximal statin-based lipid-lowering therapy in Korean patients with familial hypercholesterolemia: A study supported by the Korean Society of Lipid and Atherosclerosis. Clin Cardiol, 2017. 40(12): p. 1291-1296.
13. Ridker, P.M., et al., Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J, 2016. 37(17): p. 1373-9.
14. Cannon, C.P., et al., Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med, 2015. 372(25): p. 2387-97.
15. Toth, P.P., et al., Systematic Review and Network Meta-Analysis on the Efficacy of Evolocumab and Other Therapies for the Management of Lipid Levels in Hyperlipidemia. J Am Heart Assoc, 2017. 6(10).
16. Stam-Slob, M.C., et al., Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease. Int J Cardiol, 2018. 253: p. 148-154.
17. Kazi, D.S., et al., Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. JAMA, 2016. 316(7): p. 743-53.
18. Schmidt, A.F., et al., PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev, 2017. 4: p. CD011748.
19. Villa, G., et al., Cost-effectiveness of Evolocumab in Patients With High Cardiovascular Risk in Spain. Clin Ther, 2017. 39(4): p. 771-786 e3.
20. Arrieta, A., et al., Economic Evaluation of PCSK9 Inhibitors in Reducing Cardiovascular Risk from Health System and Private Payer Perspectives. PLoS One, 2017. 12(1): p. e0169761.
21. Everett, B.M., R.J. Smith, and W.R. Hiatt, Reducing LDL with PCSK9 Inhibitors--The Clinical Benefit of Lipid Drugs. N Engl J Med, 2015. 373(17): p. 1588-91.
22. Tice, J.A., D.S. Kazi, and S.D. Pearson, Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors for Treatment of High Cholesterol Levels: Effectiveness and Value. JAMA Intern Med,

2016. 176(1): p. 107-8.
23. Elisaf, M., et al., Updated guidelines of the Hellenic Society of Atherosclerosis for the diagnosis and treatment of dyslipidemia-2014. Hellenic Journal of Atherosclerosis, 2014. 5(3): p. 151-163.
24. Achimastos, A., et al., Expert consensus on the rational clinical use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Hormones, 2016. 15(1): p. 8-14.
25. Panagiotakos, D.B., et al., Statistical modelling of 10-year fatal cardiovascular disease risk in Greece: the HellenicSCORE (a calibration of the ESC SCORE project). Hellenic J Cardiol, 2007. 48(2): p. 55-63.
26. Wang, Y., et al., Real-world study of low-density lipoprotein cholesterol levels and cardiovascular outcomes in Chinese: A retrospective cohort study in post-percutaneous coronary intervention acute coronary syndrome patients. Int J Cardiol, 2017. 249: p. 18-24.
27. Xanthopoulou, I., et al., First-line treatment patterns and lipid target levels attainment in very high cardiovascular risk outpatients. Lipids Health Dis, 2013. 12: p. 170.
28. Khunti, K., et al., Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: A meta-analysis. Diabetes Res Clin Pract, 2018. 137: p. 137-148.
29. Bogsrud, M.P., et al., Treatment goal attainment in children with familial hypercholesterolemia: A cohort study of 302 children in Norway. J Clin Lipidol, 2018. 12(2): p. 375-382.
30. Tsimihodimos, V., et al., Effects of benchmarking on the quality of type 2 diabetes care: results of the OPTIMISE (Optimal Type 2 Diabetes Management Including Benchmarking and Standard Treatment) study in Greece. Ther Adv Endocrinol Metab, 2015. 6(5): p. 199-209.
31. Guglielmi, V., et al., Effectiveness of adherence to lipid lowering therapy on LDL-cholesterol in patients with very high cardiovascular risk: A real-world evidence study in primary care. Atherosclerosis, 2017. 263: p. 36-41.
32. Liberopoulos, E.N., et al., Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. Expert Opin Drug Saf, 2008. 7(6): p. 717-25.
33. Barkas, F., E. Liberopoulos, and M. Elisaf, Impact of compliance withantihypertensive and lipid-lowering treatment on cardiocascular risk – Benefits of fixed-dose combinations.
. Hellenic J Atherosclerosis. , 2013. 4(1): p. 31-39.
34. Marz, W., et al., Utilization of lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients at high and very-high cardiovascular risk: Real-world evidence from Germany. Atherosclerosis, 2018. 268: p. 99-107.
35. Arca, M., Old challenges and new opportunities in the clinical management of heterozygous familial hypercholesterolemia (HeFH): The promises of PCSK9 inhibitors. Atherosclerosis, 2017. 256: p. 134-145.
36. Stroes, E.S., et al., Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J, 2015. 36(17): p. 1012-22.
37. Kim, M.C., et al., Impact of postdischarge statin withdrawal on long-term outcomes in patients with acute myocardial infarction. Am J Cardiol, 2015. 115(1): p. 1-7.
38. Descamps, O.S., et al., Anti-PCSK9 antibodies for hypercholesterolaemia: Overview of clinical data and implications for primary care. Int J Clin Pract, 2017. 71(8).
39. Gouni-Berthold, I., et al., Systematic review of published Phase 3 data on anti-PCSK9 monoclonal antibodies in patients with hypercholesterolaemia. Br J Clin Pharmacol, 2016. 82(6): p. 1412-1443.
40. Sabatine, M.S., et al., Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med, 2017. 376(18): p. 1713-1722.
41. Arrieta, A., et al., Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial. JAMA Cardiol, 2017. 2(12): p. 1369-1374.
42. Hlatky, M.A. and D.S. Kazi, PCSK9 Inhibitors: Economics and Policy. J Am Coll Cardiol, 2017. 70(21): p. 2677-2687.