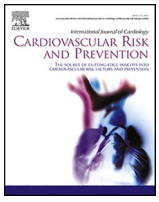
International Journal of Cardiology Cardiovascular Risk and Prevention 21 (2024) 200261

Contents lists available at ScienceDirect

International Journal of Cardiology
Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



Real-world data on treatment patterns in at least high cardiovascular risk patients on dual and triple lipid lowering therapy in a Hellenic nationwide e-prescription database☆

Dimitrios Terentes-Printzios [a,1], Ioanna Dima [a,1], Panorios Benardos [b], Panagiota Mitrou [c], Konstantinos Mathioudakis [d], Anastasios Tsolakidis [d], Fotios Barkas [e], Konstantinos Tsioufis [a], Petros P. Sfikakis [f], Evangelos Liberopoulos [f,2], Charalambos Vlachopoulos [a,*,2]

[a] First Department of Cardiology, Hippokration Hospital, Medical School, National and Kapodistrian University of Athens, Greece
[b] National Technical University of Athens, School of Mechanical Engineering, Section of Manufacturing Technology, Heroon Polytechniou 9, Athens, GR15780, Greece
[c] Independent Department of Therapeutic Protocols and Patient Registries, Hellenic Republic Ministry of Health, Athens, Greece
[d] IDIKA SA - E-Government Center for Social Security Services, Athens, Greece
[e] Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece
[f] First Department of Propaedeutic and Internal Medicine National and Kapodistrian University of Athens Medical School, Athens, 11527, Greece

ARTICLE INFO

Handling editor: D Levy

Keywords:
Dyslipidemia
Familial hypercholesterolaemia
LDL-Cholesterol
Cardiovascular risk
Lipid-lowering therapy' statins
Ezetimibe
PCSK9 inhibitors

ABSTRACT

Background: Despite recent guidelines appropriate lipid-lowering treatment (LLT) remains suboptimal in everyday clinical practice.
Aims: We aimed to describe clinical practice of use of LLT for at least high CV risk populations in a Hellenic real-world setting and assess how this relates to the European Society of Cardiology treatment guidelines.
Methods: We analyzed data from a retrospective cohort study of the National Registry of patients with dyslipidemia between 1/7/2017 and 30/6/2019 who were at least of high CV risk and filled a dual or triple lipid-lowering treatment (dLLT, tLLT) prescription. The primary outcomes of interest of this analysis were to report on the patterns of LLT use in at least high CV risk patients.
Results: A total of 994,255 (45.4% of Greeks on LLT) were of at least high CV risk and 120,490 (5.5%) were on dLLT or tLLT. The percentage of patients with reported statin intolerance ranged from 2 to 10%. While persistence was reported to be satisfactory (>85% for both dLLT or tLLT), adherence was low (ranging between 14 and 34% for dLLT). In 6-month intervals, the percentage of patients achieving a low-density lipoprotein cholesterol (LDL-C) target below 100 md/dL ranged from 20% to 23% for dLLT and 34%–37% for tLLT.
Conclusions: The prevalence of at least high CV risk patients among patients receiving LLT in Greece is substantial. Despite the high persistence and probably due to the low adherence to treatment, LDL-C remains above targets in more than two thirds of patients.

1. Introduction

Over the years, numerous studies have been performed in different populations and regions all over the world to determine characteristics of lipid-lowering therapy (LLT), such as LLT intensity, adherence to LLT, low-density lipoprotein cholesterol (LDL-C) target achievement rate, and the impact of comorbidities [1,2]. Data sources typically include cross-sectional studies and registries. However, these sources are compromised by the fact that they do not include the entire population and do not provide actual prescription filling rates.

The database of the electronic prescription platform of the National Registry of patients with dyslipidemia covers, since June 2015, ~99% of the prescriptions dispensed to the entire Greek population [3]. To our knowledge, only few countries have developed a complete nationwide prescription system that includes their entire population [2]. Such a

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author. Hippokration Hospital, National and Kapodistrian University of Athens, Athens Medical School, Profiti Elia 24, Athens, 14575, Greece.
E-mail address: cvlachop@otenet.gr (C. Vlachopoulos).

[1] The first two authors contributed equally to the manuscript.
[2] The last two authors contributed equally to the manuscript.

https://doi.org/10.1016/j.ijcrp.2024.200261
Received 7 December 2023; Accepted 12 March 2024
Available online 19 March 2024

Nonstandard abbreviations and acronyms

DTP	Dyslipidemia therapeutic protocol
HDIKA	Electronic governance of social insurance
LDL-C	Low-density lipoprotein cholesterol
sLLT	Single lipid-lowering treatment
dLLT	Dual lipid-lowering treatment
tLLT	Triple lipid-lowering treatment
CV	Cardiovascular
TCHOL	Total cholesterol
FH	Familial hypercholesterolemia
PAD	Peripheral arterial disease
DM	Diabetes mellitus
CKD	Chronic kidney disease
SBP	Systolic blood pressure
AAA	Abdominal aortic aneurysm
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
ICH-GCP	International conference on harmonisation-Good clinical practice
ICF	Informed consent form
CAD	Coronary artery disease
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
GP	General practitioners

prescription system (which is called HDIKA system) can provide a valuable data source for obtaining real world big data on current lipid management.

CV deaths remain the leading cause of mortality worldwide, accounting for most of all deaths, with ischemic heart disease and stroke representing the vast majority [4]. Reducing LDL-C with statin therapy has been shown to reduce all-cause and CV mortality, as well as CV outcomes such as non-fatal myocardial infarction (MI), coronary revascularisation procedures, and non-fatal ischemic stroke in populations with prior atherosclerotic CV disease (ASCVD) and in certain primary-prevention populations [4,5]. European guidelines on ASCVDs prevention in clinical practice recommend modulating intensity of pharmacological intervention at the individual level according to the overall CV risk [4,5].

Despite this, appropriate LLT and atherogenic lipid level reduction remain suboptimal in everyday clinical practice, especially in at high and very high CV risk patients [6]. In 2016, as well as in 2019, the European Society of Cardiology (ESC) Clinical Practice Guidelines provided updated recommendations on lipid-lowering therapy (LLT) that emphasized lower LDL-C goals and earlier intensification of LLT in order to reduce CV risk [4,7,8]. However, there are limited real-world data on the implementation of these guidelines and their impact. It follows that there is a great need of such data in European countries in order to ascertain the greatest possible protection at the population level, as well as to shape future health policies by identifying possible shortcomings in the prescription methodology, physician inertia and patient persistence and adherence to LLT. Such valuable information can be used to avoid any increases in morbidity, mortality and eventually health costs related to poor or erroneous implementation of guidelines. Importantly, these data should reflect everyday clinical practice in a detailed manner, as is the case with the HDIKA system, while preferably avoiding any influence by the recent COVID-19 pandemic that could distort the true need for LLT in cardiovascular prevention.

In this study we describe patterns of LLT use in a Hellenic real-world clinical practice setting for at least high CV risk populations.

2. Methods

2.1. Study design and population

This is a population-based study, with patient data collected from the National Registry of patients with dyslipidemia which is part of the Greek digital prescription system. The study population consists of patients in the National Registry that were entitled to pharmaceutical care and received any prescribed lipid modifying therapy between 2017 and 2019. We identified at least high-risk patients on dual LLT with statins plus ezetimibe (dLLT) and triple LLT with statins plus ezetimibe plus proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) (tLLT) from the original 2,176,127 patients in the database, and these patients were selected for further analysis. We used HDIKA database to identify patient characteristics. At least high-risk patients were identified based on their categorization on the HDIKA platform that has incorporated the categories defined in the ESC 2016 Guidelines. Specifically, patients with coronary artery disease, stroke, abdominal aortic aneurysm, peripheral arterial disease, carotid artery disease, diabetes (type 1 and 2), familial hypercholesterolemia and SCORE$\geq$5%) were included.

All observations for patients with dLLT or tLLT age 18 or older entered in the HDIKA between 01/07/2017-31/06/2019 (the study period) were eligible for this study. Patients included in the study had at least one entry in the selected 6-month intervals (01/07/2017-31/12/2017, 01/01/2018-31/06/2018, 01/07/2018-31/12/2018 and 01/01/2019-31/06/2019).

Observations were included if they had available information about LDL-C, prescription of lipid-lowering medications and CV risk. On the other hand, observations were excluded if extreme values of LDL-C were reported (LDL-C <10 mg/dL or LDL-C >500 mg/dL), or if they lacked information on LDL-C, prescription of lipid-lowering medications or CV risk. The study complied with the Declaration of Helsinki and the protocol was approved by our Institutional Research Ethics Committee.

2.2. Study outcomes and definitions

Index visit is defined as the first visit after 1st July 2017. Baseline (before initiation of treatment) LDL-C level was defined as the first entry in the DTP from the beginning of the study. dLLT was defined as someone on a statin was prescribed add-on ezetimibe, while tLLT was defined as someone on dLLT was prescribed a PCSK9i. Pre-existing comorbidities were defined as familial hypercholesterolemia (FH), coronary artery disease (CAD), peripheral arterial disease (PAD), stroke, chronic kidney disease (CKD), diabetes mellitus, or abdominal aortic aneurysm (AAA).

The primary outcomes of interest of this analysis were: (i) to report on the patterns of LLT use (statin + ezetimibe; statin + ezetimibe + PCSK9i) in at least high CV risk patients and (ii) assess measures of persistence and adherence in LLT treatment at 6 months in at least high CV risk patients. Secondary outcomes included: i) evaluation of clinical characteristics and lipid profile, ii) evaluation of pre-existing comorbidities, iii) evaluation of the prevalence of statin intolerance, and iv) reporting on LDL-C target achievement percentages and median difference of LDL-C at 6-months from LDL-C targets (70 and 100 mg/dL) according to the 2016 ESC/EAS Guidelines for patients of at least high CV risk.

The HDIKA platform includes 3 types of intolerance, a) myalgias: muscle symptoms with normal or mildly elevated creatine kinase (CK) levels, b) myopathy: muscle symptoms with CK levels >5 X upper limit of normal (ULN) in 2 measurements, and c) ALT levels >5 X upper limit of normal (ULN) in 2 measurements. Patients should be intolerant to $\geq$2 statins ("totally" intolerant) and other possible causes should have been excluded.

Treatment persistence was defined as the time from the first

prescription until discontinuation of at least one of the index LLT drug classes that was confirmed by pharmacist filling of the prescriptions. Discontinuation was defined as a gap in therapy of 30 days from the run-out date of days' supply. Patients were categorized into 6-month persistent LLT users and non-persistent LLT users (discontinuation of LLT use during the 6 months period). The proportion of days covered (PDC) was used as a proxy for adherence. PDC was calculated by dividing the total number of days covered by prescriptions by the total number of days in the follow-up period, capped at 100%. To calculate days covered, dispensed quantities were used with an assumed intake of one tablet/capsule a day or 1 injection per 2 weeks. Patients were classified as adherent when PDC is $\geq$ 75% and nonadherent when PDC <75%.

Attainment of LDL targets were assessed by reported LDL-C levels at the last visit of the 6 months intervals. Targets were set at 70 mg/dL and 100 mg/dL for patients of at least high CV risk based on 2016 ESC Guidelines. Risk categories are predefined on the HDIKA platform and are provided automatically by the platform. The 2016 ESC Guidelines were in force during the study period (2017–2019).

Single-pill combination dLLT is defined as the use of single-pill formulation of statin and ezetimibe.

2.2.1. Statistical analysis

We calculated patterns of dLLT and tLLT use between 1/7/2017 and 30/6/2019 among patients on the Registry of at least high CV risk based on 2016 ESC Guidelines. Also, we calculated patterns of dLLT and tLLT at 6-month intervals for a 2-year period.

Descriptive statistics are presented as n, % or mean ± SD or median and IQR, as appropriate. All values are expressed as medians and interquartile ranges (IQR) for non-normally distributed continuous variables and as mean and SD for normally distributed variables.

Furthermore, 1) specialty of prescribing physicians and 2) geographical differences in prescription patterns i.e., comparison between urban and rural locations are also presented.

Data analysis was performed with SPSS software, version 24 (Chicago, IL).

3. Results

3.1. Subject baseline characteristics

During the study period (1/7/2017 to 30/6/2019), 2,175,166 unique adult patients were on LLT (Suppl. Fig. 1). Based on the latest census (2011) total population aged over 19 years was 8,693,742, suggesting that 1 out of 4 Greek adults were on LLT. The characteristics of the study population consisting of at least high cardiovascular risk patients (n = 120,940, 5.5% of the patients on LLT and 1.4% of the whole Greek adult population) are shown in Table 1. Median age was 68 (IQR 60–75) years for patients on dLLT (59% males) and 59 (50–66) for patients on tLLT (64% males). Only 1% of study population was on tLLT.

3.2. Patients on dLLT/tLLT of at least high CV risk

Based on the reported data between 1/7/2017 and 30/6/2019 (Table 1), the number of patients at 6-months intervals on dLLT ranged from 74,589 to 88,904, and on tLLT ranged from 351 (at the first 6-month period) to 836 (at the last period) (Fig. 1). Baseline LDL-C level for patients on dLTT was 150 mg/dL and on tLLT 160 mg/dL. Baseline triglycerides ranged from 177 to 180 mg/dL for dLLT, and 175–180 mg/dL for tLLT. Systolic blood pressure was reported at 140 mmHg for both groups. The most common risk factor was diabetes (type 1 and type 2) in approximately one third of patients. Type 2 diabetes was more common in patients on dLLT compared to patients on tLLT. The most common secondary prevention category was CAD (also in one third of patients).

3.3. Statin intolerance, persistence, and adherence to treatment

In 6-months intervals during 1/7/2017-30/6/2019, the percentage

Table 1
Baseline characteristics of study population according to study period at 6-month intervals.

	1/7/2017 - 31/12/2017		1/1/2018–30/6/2018		1/7/2018 - 31/12/2018		1/1/2019–30/6/2019	
	dLLT (n = 76,729)	tLLT (n = 351)	dLLT (n = 74,589)	tLLT (n = 551)	dLLT (n = 75,161)	tLLT (n = 634)	dLLT (n = 88,904)	tLLT (n = 836)
Age (years)	68 (60–75)	57 (49–65)	68 (60–75)	59 (50–66)	68 (60–76)	59 (51–67)	68 (60–75)	59 (51–66)
Males (n, %)	45,438 (59)	225 (64)	44,348 (59)	364 (66)	44,754 (60)	405 (64)	53,186 (60)	520 (62)
Hemodynamic and biochemical measurements								
Baseline LDL-C (mg/dL)	150 (120–178)	160 (126–195)	150 (120–178)	160 (123–190)	150 (120–179)	160 (125–190)	150 (120–180)	160 (126–190)
Baseline total cholesterol (mg/dL)	250 (211–280)	259 (220–300)	250 (213–280)	260 (220–300)	250 (212–280)	260 (220–300)	250 (219–280)	260 (225–300)
Baseline triglycerides (mg/dL)	177 (140–235)	175 (130–230)	177 (140–236)	180 (140–250)	176 (140–236)	175 (132–240)	180 (140–244)	178 (134–240)
Median LDL-C difference[a](mg/dL)	0 (−30 to 16)	−30 (−72 to 0)	0 (−30 to 15)	−25 (−72 to 11)	0 (−30 to 17)	−30 (−77 to 10)	0 (−30 to 16)	−30 (−79 to 16)
SBP (mmHg)	140 (130–151)	140 (121–150)	140 (130–152)	140 (125–150)	140 (130–150)	140 (125–150)	140 (130–151)	140 (125–150)
Cardiovascular risk factors								
Diabetes Mellitus type 1 (n, %)	1018 (1)	3 (1)	1001 (1)	5 (1)	960 (1)	4 (1)	1065 (1)	5 (1)
Diabetes Mellitus type 2 (n, %)	22,962 (30)	30 (9)	21,958 (29)	50 (9)	21,609 (29)	50 (8)	24,261 (27)	67 (8)
Chronic kidney disease (n, %)	3877 (5)	38 (11)	3719 (5)	49 (9)	3841 (5)	57 (9)	5025 (6)	65 (8)
Smoking (n, %)	15,182 (20)	63 (18)	14,716 (20)	112 (20)	15,169 (20)	132 (21)	18,795 (21)	173 (21)
Familial hypercholesterolaemia (n, %)	881 (1)	0 (0)	839 (1)	1 (0.2)	864 (1)	0 (0)	897 (1)	0 (0)
Secondary prevention								
CAD (n, %)	24,520 (32)	127 (36)	23,142 (31)	200 (36)	23,204 (31)	213 (34)	25,290 (28)	276 (33)
Stroke (n, %)	2411 (3)	4 (1)	2324 (3)	9 (2)	2283 (3)	11 (2)	2485 (3)	11 (1)
Abdominal aortic aneurysm (n, %)	455 (1)	2 (1)	408 (1)	2 (0.4)	409 (1)	2 (0.3)	47 (1)	3 (0.4)
PAD (n, %)	4597 (6)	13 (4)	4281 (6)	24 (4)	4286 (6)	21 (3)	5086 (6)	29 (3)

CAD: Coronary artery disease, dLLT: Dual lipid-lowering treatment, LDL-C: Low-density lipoprotein cholesterol, PAD: Peripheral arterial disease, SBP: Systolic blood pressure, tLLT: Triple lipid-lowering treatment.

[a] median LDL difference is defined as the difference between the baseline LDL-C value and the reported as contemporary LDL-C value in the following prescriptions.

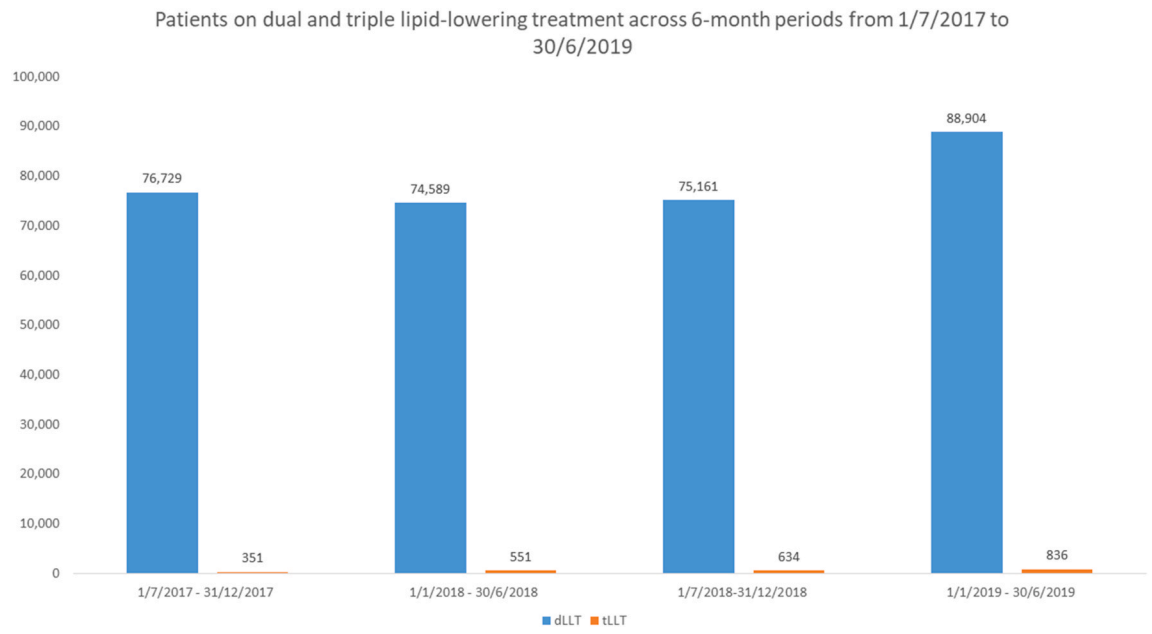


Fig. 1. Number of at least high CV risk patients on dLTT and tLTT by 6-month period.

of patients with statin intolerance ranged from 0.06 to 0.09% for dLLT, and from 2% to 10% for tLLT (Suppl. Fig. 2). While persistence was reported to be satisfactory (more than 85% for either dLLT or tLLT), adherence was low (ranging between 14 and 34% for dLLT and tLLT). Interestingly, adherence increased substantially from 2017 (34%) to 2019 (58%) for tLLT. (Fig. 2).

3.4. Attainment of LDL-C targets based on ESC 2016 and 2019 guidelines

In 6-months intervals during 1/7/2017-30/6/2019, the percentage of patients achieving an LDL-C target below 100 mg/dL ranged from 20 to 23% for dLLT and 34–37% for tLLT, while the percentage of patients achieving an LDL target below 70 mg/dL ranged from 4 to 5% for dLLT and 19–21% for tLLT (Figs. 3 and 4). There was no difference between baseline LDL-C and reported LDL-C values at the time of prescription of patients on dLLT. On the contrary, regarding tLLT the median difference between baseline LDL-C and reported LDL-C values at the time of prescription on ranged from - 25 to −30 mg/dL (Table 1).

3.5. Specialty of prescribing physicians and geographical prescription patterns

The physician specialties with the highest number of prescriptions covering more than 90% of all prescriptions with dLLT were in descending order: 1) internists, 2) general practitioners, 3) cardiologists, 4) endocrinologists, and 5) nephrologists. Similarly, regarding tLLT the order was: 1) cardiologists, 2) internists, 3) endocrinologists, 4) general practitioners, and 5) nephrologists.

Regarding, the place of residence of patients on dLLT or tLLT approximately 40% were from the 2 largest municipalities of Greece (Attica and Thessaloniki), where more than 40% of the Greek population is located.

4. Discussion

To the best of our knowledge, the present study is the first to report on the characteristics of Hellenic patients on dLLT and tLLT that belong to at least high CV risk group. The prevalence of at least high CV risk patients among patients receiving LLT in Greece is substantial. These patients have a very low percentage of LDL-C target achievement (1 out of 3 patients), even when they receive tLLT. Also, despite satisfactory persistence of treatment, adherence remained low for dLLT, whereas it was also low but improved with time for tLLT during the study period.

5. Clinical implications

This is the first time that LLT in Greece, a representative European Country is country is mapped in detail. Strength of our study is the fact that it had the ability to investigate all at least high CV risk patients in a representative European country from a nationwide database with 99% coverage of the Greek population. Therefore, our results reflect the real-world practice of a European country and could be extrapolated, with assumptions, to other European ones. Another strength is that the study period refers to 2017–2019, which does not consist of the COVID-19 pandemic that could have influenced real-world practice due to the change in prescription patterns. Furthermore, our results could be useful in terms of health policy making, especially in the era of introduction of new therapies. In addition, emerging new therapies are being investigated for possible implementation to clinical practice and our results may facilitate an evidence-based adoption of these new therapies as well as creation of more detailed and focused registries in patients at high CV risk [9].

5.1. Attainment of LDL targets, persistence, and adherence

Management of dyslipidemia is the cornerstone of current strategies for primary and secondary CVD prevention. The reduction in risk that can be achieved with LLT is influenced by the absolute reduction in LDL-C achieved, baseline CV risk profile and the duration of LLT. This beneficial effect is largely independent of the mechanism for achieving reduction of LDL-C. Nevertheless, despite the availability of a range of different LLT options, either alone or in combination, optimal control of LDL-C is challenging [10,11], especially in patients at the highest risk for CVD [12–14]. As one might expect, the lower the target in patients at the highest risk, the harder to achieve such a target. Specific goals have been established concerning the optimal LDL-C levels for each cardiovascular risk category. Our results confirm earlier studies highlighting that even patients on dLLT or tLLT do not achieve treatment goals. Indeed, the finding that only 1 out of 3 patients of at least high CV risk achieve the LDL-C target is disappointing and implies gaps in care and clinical

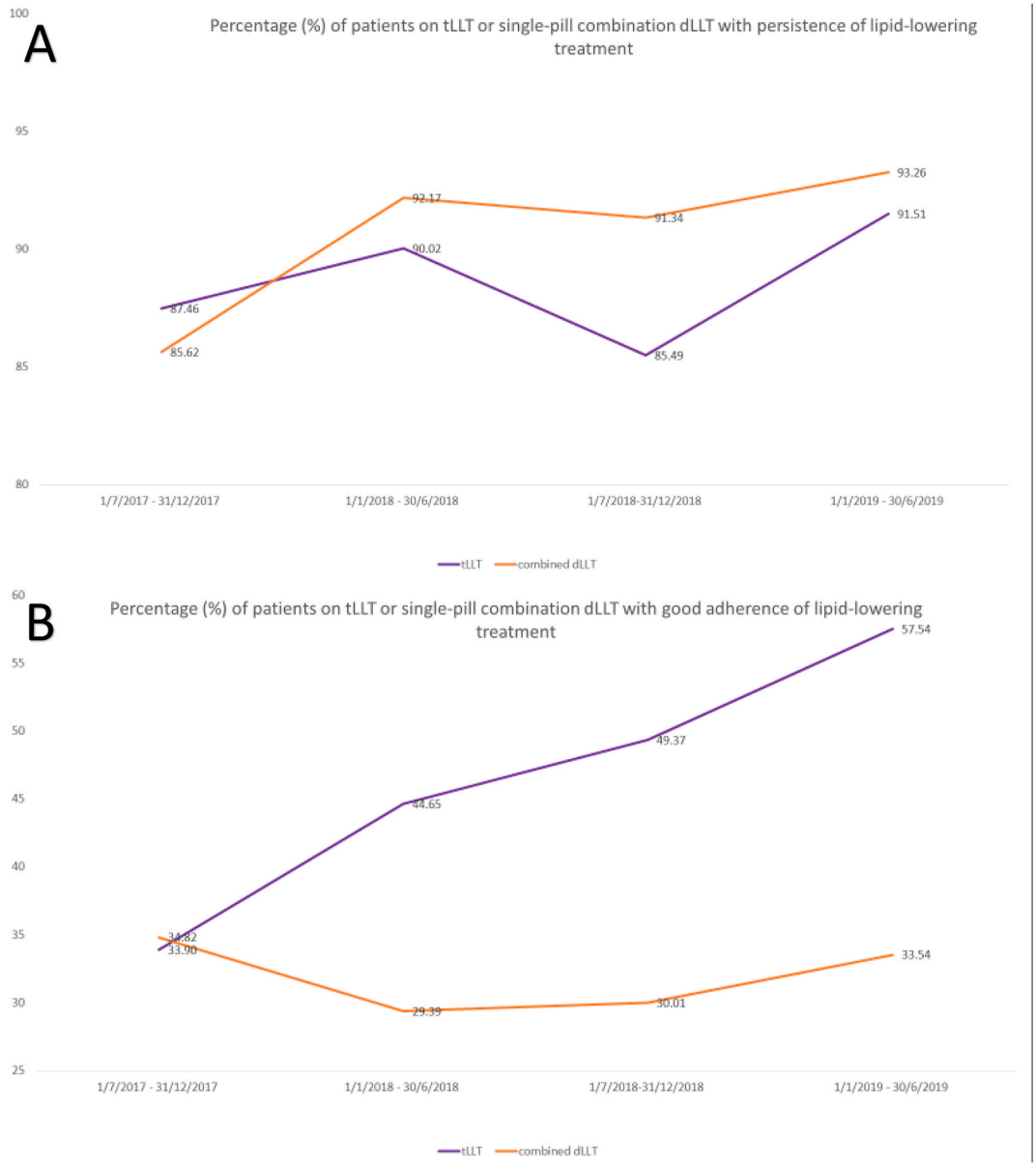


Fig. 2. Percentage of patients on tLLT or single-pill combination dLLT with good persistence (panel A) and good adherence (panel B) to treatment.

inertia of physicians [1,15].

Persistence of therapy was adequate in our study population and comparable to other recent studies [1,16]. On the other hand, adherence was extremely low, and this could potentially have prognostic implications. Multiple factors influencing adherence to LLT have been described, including history of CVD and comorbidities, the setting of LLT, formulation, type, intensity and, therapy changes, frequency of LDL-C monitoring, and patients' experiences of side effects [17]. Furthermore, we cannot differentiate at this point between patients on new and stable LLT. Patients on stable, long-term use of LLT are well known to have higher adherence rates compared to new users [2]. At least as far as statin intolerance is concerned, the reported percentage is low (2–10% of patients on tLLT) and cannot explain these numbers. Although underreporting of statin intolerance is probable [18] numbers are within realistic range [19].

5.2. Study strengths and limitations

The comprehensive material obtained from the HDIKA allowed us to assess guideline adherence over time among at least high CV risk patients. To the best of our knowledge, scarce data exist on such populations in Europe [2,8].

Data reflect what has been entered as prescribed by healthcare providers, so we cannot be sure of whether LLT prescriptions were used or not by the patients. However, we have data on whether the prescription was issued by pharmacists which provides even more reliable data on the adherence of patients compared to other European nationwide databases that rely only on data from the prescriptions of healthcare providers.

Since not all variables were measured at each medical visit, presence of missing data is expected, due to the large number of subjects included in the database we do not expect these missing values to influence our conclusions in a clinically meaningful manner while we expect them to be missing at random.

The bias due to reporting error is also an inherent limitation of all such nationwide prescription databases and it attested by the fact that the changes of LDL-C with time are trivial implying use of repetitive LDL-C values of patients on dLLT. Despite this is a major limitation for

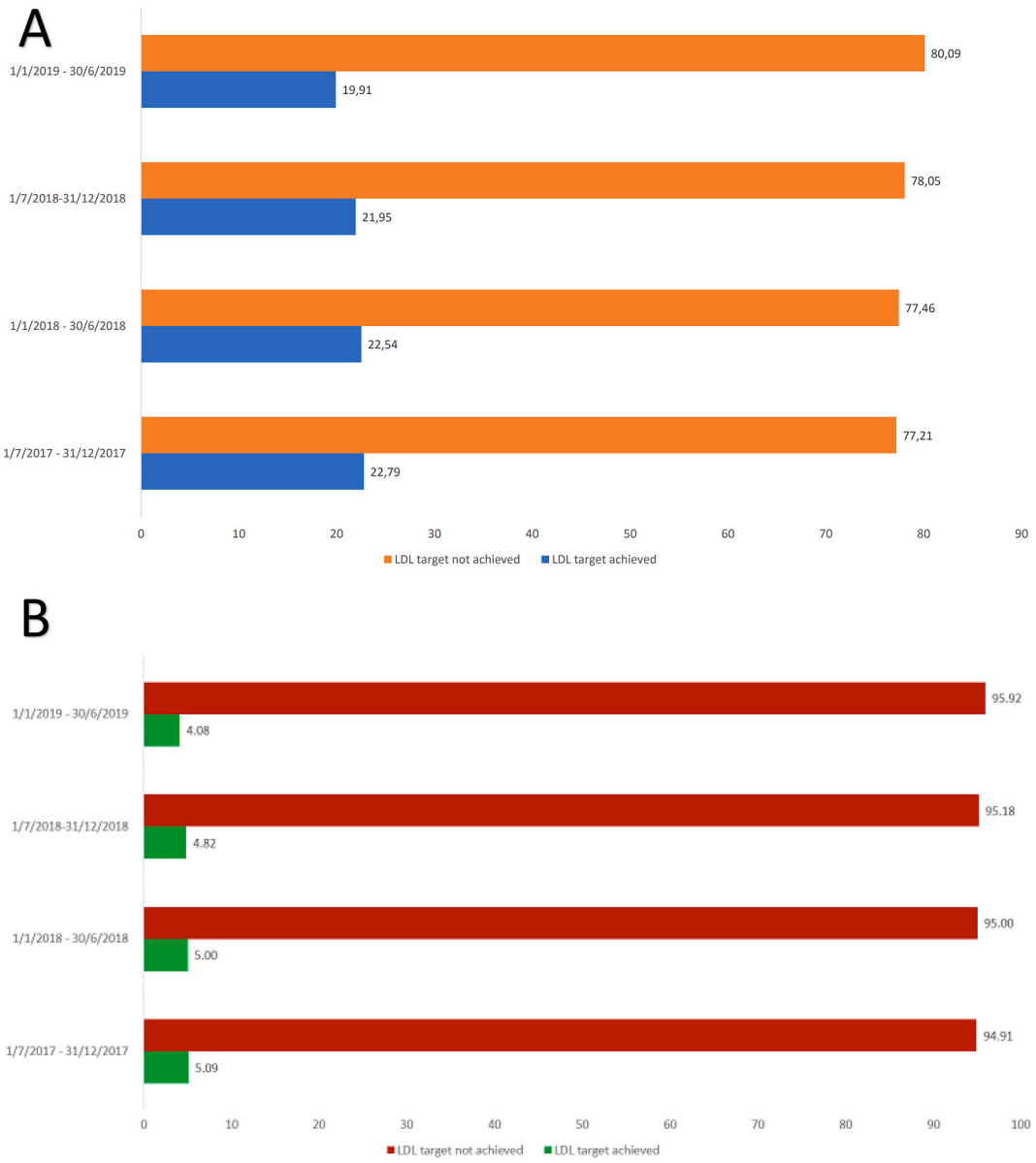


Fig. 3. Percentage of patients on dLLT achieving LDL-C targets based on LDL-C target <100 mg/dL (panel A) and LDL-C target <70 mg/dL (panel B).

specific analysis of specific parameters of the present study (i.e., goal attainment), it does not affect the rest of the analyzed parameters and does not affect patients on tLLT. We strongly believe that this reporting of the specific shortcoming will prompt ways of ensuring input of accurate data in our national prescription system.

6. Conclusions

For the first time, this nationwide real-world data analysis demonstrates that the current prevalence of at least high cardiovascular risk patients among patients receiving LLT in Greece is substantial. Despite the high persistence and probably due to the low adherence in treatment, LDL-C targets are not achieved in more than two thirds of patients irrespective of LLT treatment.

Sources of funding

This work was financially supported by Amgen (Europe) GmbH.

Conflict(s) of interest/Disclosure(s)

C.V. reports research grant(s)/support and fees from Amgen, ELPEN, MSD, Sanofi, and Vianex.

Dr. LIBEROPOULOS reports personal fees and non-financial support from AMGEN, personal fees from SERVIER, personal fees from BOEHRINGER-INGELHEIM, personal fees and non-financial support from ASTRA-ZENECA, personal fees from LILLY, personal fees and non-financial support from BAYER, personal fees from NOVARTIS, personal fees from CHIESI, outside the submitted work.

CRediT authorship contribution statement

Dimitrios Terentes-Printzios: Data curation, Writing – original draft, Writing – review & editing. **Ioanna Dima:** Data curation, Resources. **Panorios Benardos:** Formal analysis, Methodology. **Panagiota Mitrou:** Writing – review & editing. **Konstantinos Mathioudakis:** Data curation. **Anastasios Tsolakidis:** Data curation. **Fotios Barkas:** Investigation, Methodology, Writing – review & editing. **Konstantinos Tsioufis:** Supervision. **Petros P. Sfikakis:** Supervision. **Evangelos**

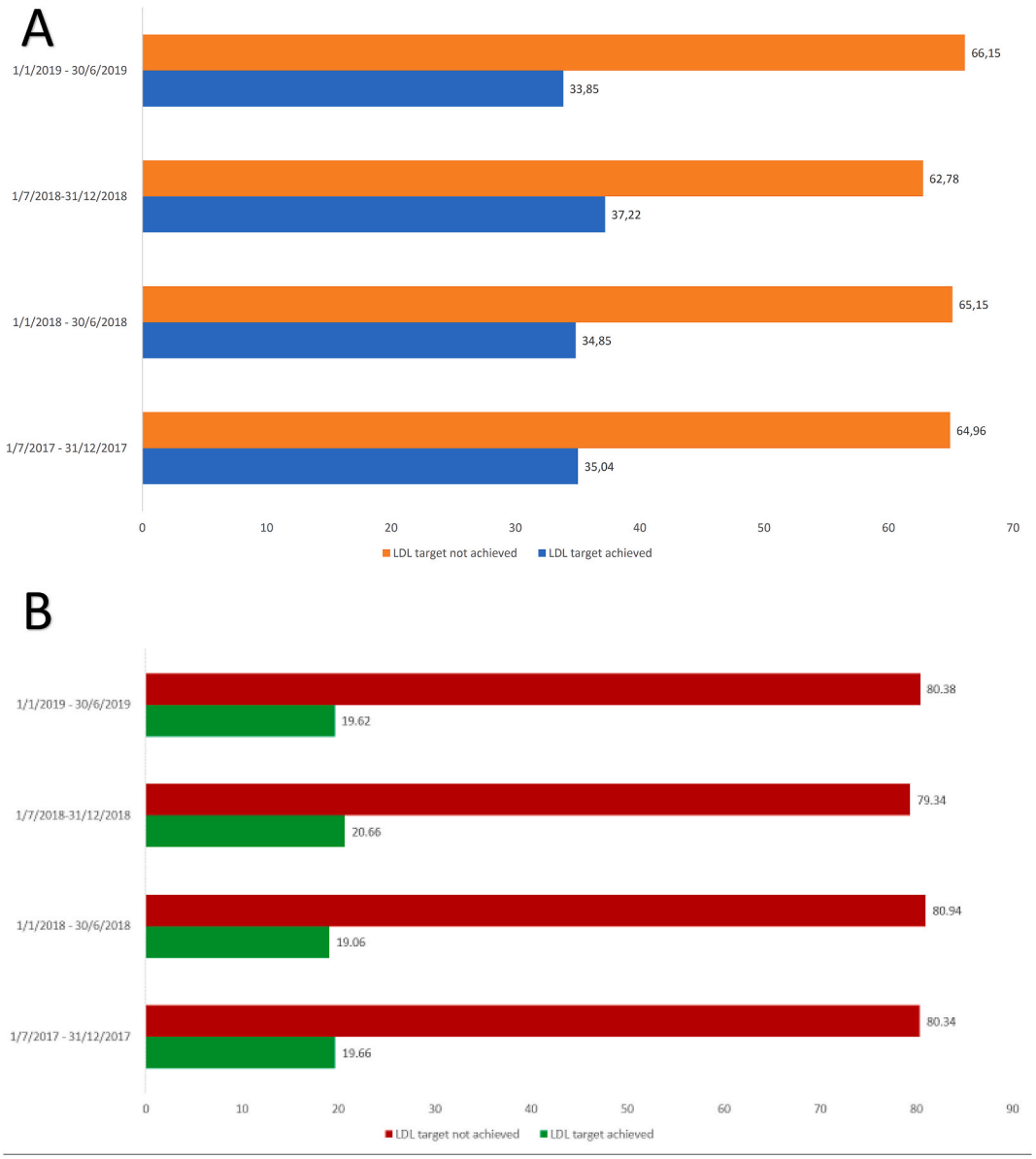


Fig. 4. Percentage of patients on tLLT achieving LDL-C targets based on LDL target <100 mg/dL (panel A) and LDL-C target <70 mg/dL (panel B).

Liberopoulos: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Charalambos Vlachopoulos:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that AI was not employed in the writing process.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200261.

References

[1] K.K. Ray, B. Molemans, W.M. Schoonen, P. Giovas, S. Bray, G. Kiru, J. Murphy, M. Banach, S. De Servi, D. Gaita, I. Gouni-Berthold, G.K. Hovingh, J.J. Jozwiak, J. W. Jukema, R.G. Kiss, S. Kownator, H.K. Iversen, V. Maher, L. Masana, A. Parkhomenko, A. Peeters, P. Clifford, K. Raslova, P. Siostrzonek, S. Romeo, D. Tousoulis, C. Vlachopoulos, M. Vrablik, A.L. Catapano, N.R. Poulter, Study DV. EU-Wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study, Eur J Prev Cardiol 28 (2021) 1279–1289.

[2] V. Barrios, J. Soronen, A.M. Carter, A. Anastassopoulou, Lipid management across Europe in the real-world setting: a rapid evidence review, Curr. Med. Res. Opin. 37 (2021) 2049–2059.

[3] S. Liatis, G.E. Dafoulas, C. Kani, A. Politi, P. Litsa, P.P. Sfikakis, K. Makrilakis, The prevalence and treatment patterns of diabetes in the Greek population based on real-world data from the nation-wide prescription database, Diabetes Res. Clin. Pract. 118 (2016) 162–167.

[4] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, M. J. Chapman, G.G. De Backer, V. Delgado, B.A. Ference, I.M. Graham, A. Halliday, U. Landmesser, B. Mihaylova, T.R. Pedersen, G. Riccardi, D.J. Richter, M. S. Sabatine, M.R. Taskinen, L. Tokgozoglu, O. Wiklund, E.S.C.S.D. Group, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Eur. Heart J. 41 (2020) 111–188.

[5] A.L. Catapano, I. Graham, G. De Backer, O. Wiklund, M.J. Chapman, H. Drexel, A. W. Hoes, C.S. Jennings, U. Landmesser, T.R. Pedersen, Z. Reiner, G. Riccardi, M. R. Taskinen, L. Tokgozoglu, W.M.M. Verschuren, C. Vlachopoulos, D.A. Wood, J. L. Zamorano, M.T. Cooney, E.S.C.S.D. Group, 2016 ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (2016) 2999–3058.

[6] C. Vlachopoulos, G. Andrikopoulos, D. Terentes-Printzios, S. Tzeis, E. K. Iliodromitis, D. Richter, I. Mantas, A. Kartalis, V. Vasilikos, D. Stakos, S. Patsilinakos, S. Lampropoulos, D. Symeonidis, C. Kyrpizidis, N. Marinakis,

N. Nikas, J. Lekakis, D. Tousoulis, P. Vardas, Patients with acute coronary syndrome are at high risk prior to the event and lipid management is underachieved pre- and post- hospitalization, Curr. Vasc. Pharmacol. 16 (2018) 405–413.

[7] M. Averna, A.L. Catapano, One year after the ESC/EAS guidelines on cholesterol control, What's the new evidence? What's missing? Eur. J. Intern. Med. 95 (2022) 1–4.

[8] M. Averna, M. Banach, E. Bruckert, H. Drexel, M. Farnier, D. Gaita, P. Magni, W. Marz, L. Masana, E.S.A. Mello, Z. Reiner, E. Ros, M. Vrablik, A. Zambon, J. L. Zamorano, J.K. Stock, L.S. Tokgozoglu, A.L. Catapano, Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: a statement from a European Atherosclerosis Society Task Force, Atherosclerosis 325 (2021) 99–109.

[9] L.S. Rallidis, D. Tasoulas, I. Leventis, B. Malkots, E. Kladou, D. Zapantiotis, A. Theofilatos, G. Zormpas, P. Kalogeras, C. Betsis, A. Lykoudis, D. Tsamoulis, C. Kalantzis, A. Miliotou, S. Daios, I. Delakis, G. Manolis, K.A. Papathanasiou, C. Vlachopoulos, Rationale and design of the hellenic Registry of clinical events and adherence to lipid LowerINg therapy in aCUte coronary syndrome (CALLINICUS-Hellas Registry), Hellenic J. Cardiol. 66 (2022) 84–86.

[10] L.S. Rallidis, I. Skoumas, E.N. Liberopoulos, C. Vlachopoulos, E. Kiouri, I. Koutagiar, G. Anastasiou, N. Kosmas, M.S. Elisaf, D. Tousoulis, E. Iliodromitis, PCSK9 inhibitors in clinical practice: novel directions and new experiences, Hellenic J. Cardiol. 61 (2020) 241–245.

[11] G.S. Stergiou, A. Ntineri, A. Menti, N. Kalpourtzi, C. Vlachopoulos, E. N. Liberopoulos, L. Rallidis, D. Richter, M. Gavana, A. Vantarakis, G. Chlouverakis, C. Hajichristodoulou, G. Trypsianis, P.V. Voulgari, Y. Alamanos, A. Karakosta, G. Touloumi, Twenty-first century epidemiology of dyslipidemia in Greece: EMENO national epidemiological study, Hellenic J. Cardiol. 69 (2023) 1–8.

[12] L.S. Rallidis, E.N. Liberopoulos, C. Vlachopoulos, I. Skoumas, G. Kolovou, G. Anastasiou, I. Dima, D. Tousoulis, E. Iliodromitis, Very high-risk familial hypercholesterolaemia patients in real life: the remaining gap in achieving the current LDL-C targets despite the use of PCSK9 inhibitors, Atherosclerosis 309 (2020) 67–69.

[13] C. Vlachopoulos, I. Dima, D. Soulis, D. Terentes-Printzios, I. Skoumas, K. Aznaouridis, E. Solomou, D. Richter, D. Tousoulis, Eligibility for PCSK-9 inhibitors treatment in acute coronary syndrome, chronic coronary artery disease and outpatient dyslipidemic patients, Atherosclerosis 303 (2020) 29–35.

[14] C.V. Rizos, I. Skoumas, L. Rallidis, E. Skalidis, K. Tziomalos, A. Garoufi, P. Anagnostis, G. Sfikas, V. Kotsis, M. Doumas, G. Kolovou, V. Lambadiari, I. Dima, E. Kiouri, E. Zacharis, D. Agapakis, A. Attilakos, C. Antza, C. Vlachopoulos, E. N. Liberopoulos, LDL cholesterol target achievement in heterozygous familial hypercholesterolemia patients according to 2019 ESC/EAS lipid guidelines: implications for newer lipid-lowering treatments, Int. J. Cardiol. 345 (2021) 119–124.

[15] Z. Reiner, G. De Backer, Z. Fras, K. Kotseva, L. Tokgozoglu, D. Wood, D. De Bacquer, E. Investigators, Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries–Findings from the EUROASPIRE IV survey, Atherosclerosis 246 (2016) 243–250.

[16] F.J. Penning-van Beest, F. Termorshuizen, W.G. Goettsch, O.H. Klungel, J. J. Kastelein, R.M. Herings, Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study, Eur. Heart J. 28 (2007) 154–159.

[17] S. Deshpande, R.G. Quek, C.A. Forbes, S. de Kock, J. Kleijnen, S.R. Gandra, R. J. Simpson Jr., A systematic review to assess adherence and persistence with statins, Curr. Med. Res. Opin. 33 (2017) 769–778.

[18] E.M. Heintjes, A. Anastassopoulou, J. Kuiper, A. Bilitou, F. Beest, R.M.C. Herings, M.J. Postma, J.W. Jukema, Treatment and low-density lipoprotein cholesterol levels in patients with hypercholesterolaemia or mixed dyslipidaemia at high or very high cardiovascular risk: a population-based cross-sectional study in The Netherlands, Curr. Med. Res. Opin. (2022) 1–11.

[19] L.S. Rallidis, A practical algorithm for the management of patients with statin-associated muscle symptoms, Hellenic J. Cardiol. 61 (2020) 137–140.