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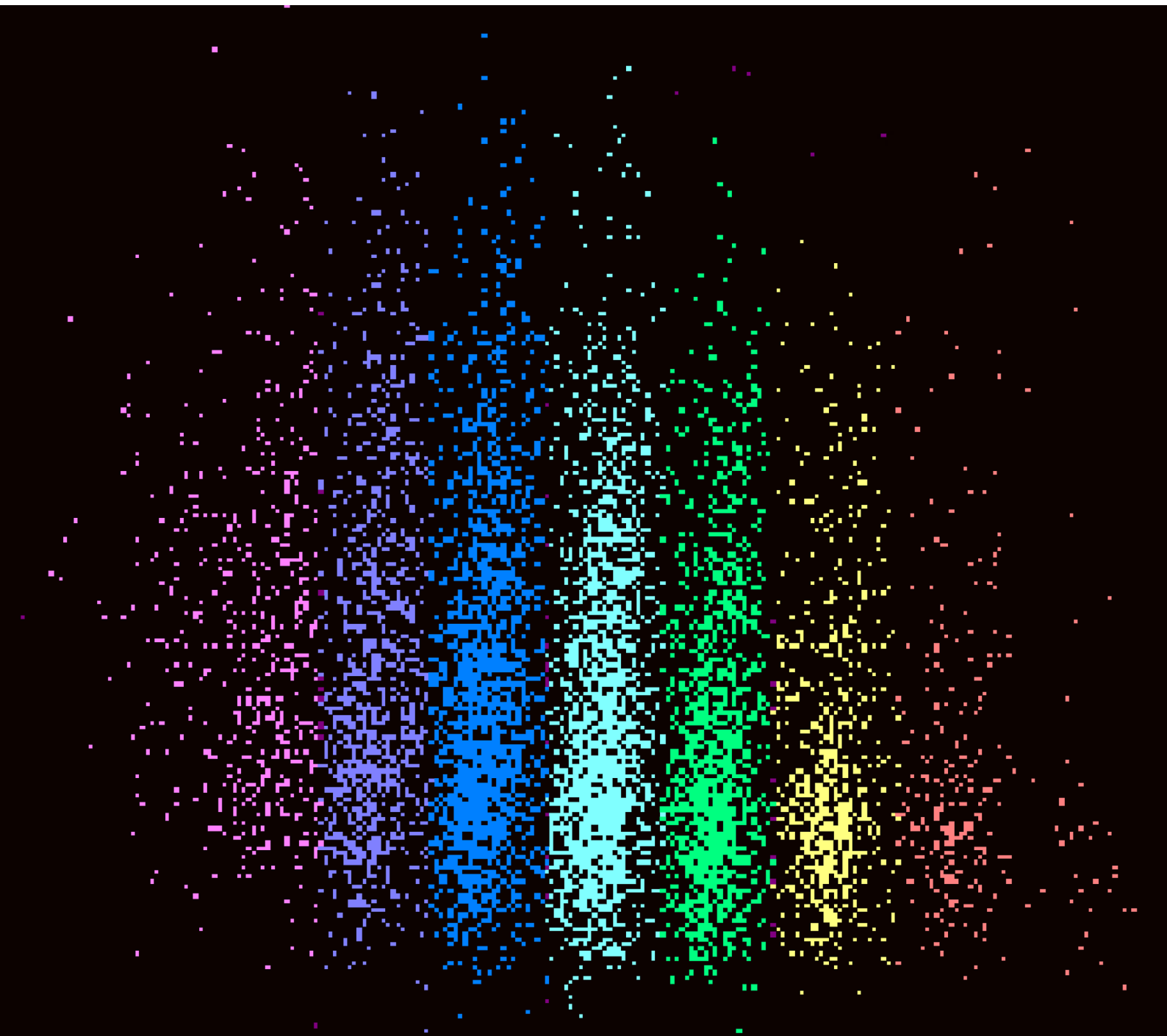

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Contents

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LDL-cholesterol goal attainment with ezetimibe and bempedoic acid in patients at high and very-high cardiovascular risk: A simulation study in the Italian cohort of the SANTORINI study

Marcello Arca[1], Angela Pirillo[2], Rosanna Gambacurta[3], Christian Becker[4], Françoise Diamand[4], Kausik K. Ray[5], Alberico L. Catapano[6]

[1]Department of Translational and Precision Medicine, "Sapienza", University of Rome, Rome, Italy
[2]Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy
[3]Daiichi Sankyo Italia S.p.A., Medical Affairs, Rome, Italy
[4]Daiichi Sankyo Europe GmbH, Munich, Germany
[5]Imperial Centre for Cardiovascular Disease Prevention, ICTU-Global, Imperial College London, London, United Kingdom
[6]IRCCS MultiMedica, Milan, Italy, and Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

Keywords
Lipid-lowering therapy; combination therapy; ezetimibe; bempedoic acid; high cardiovascular risk; very-high cardiovascular risk; simulation

ABSTRACT

Aims: Data from the Italian cohort of the SANTORINI study, a European observational study focusing on lipid management in patients at high or very-high cardiovascular risk, were used to simulate the effect of sequential addition of ezetimibe and bempedoic acid in patients not at LDL-C goal with their current lipid-lowering therapy (LLT).
Methods: Eligible patients were selected based on criteria including LDL-C levels and LLT status. Patients who were not at LDL-C goal at baseline and had not received PCSK9 inhibitors (PCSK9i) or bempedoic acid underwent sequentially 1) simulation of adding ezetimibe in patients who had not previously received this drug, and 2) simulation of the effect of adding bempedoic acid in patients who did not achieve the LDL-C goal after treatment with ezetimibe (actual or simulated). Mean LDL-C after each simulation step and the proportion of patients achieving LDL-C goal were calculated at each stage and overall.
Results: In the overall population, the simulation resulted in a significant increase in patients achieving the LDL-C goal after each step (from 25.9% to 37.6% after ezetimibe and 55.4% after ezetimibe+bempedoic acid). Among very high risk patients, the proportion of individuals at goal increased from 26.1% at baseline to 37.9% after simulating the addition of ezetimibe and to 55.8% after simulating the addition of ezetimibe+bempedoic acid. Similar results were observed in the high risk subgroup.
Conclusions: The simulation of SANTORINI data shows that goal attainment in patients at high-risk and very-high-risk can be substantially increased by optimizing oral LLT with the addition of ezetimibe and bempedoic acid.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of death and disability worldwide, responsible for more than 18.5 million deaths in 2019, with ischemic heart disease accounting for half of global CVD deaths [1]. This trend is also observed in Europe. Recent data from the Global Burden of Disease Study clearly showed that in 2022 age-standardised CVD mortality rates in Western European countries ranged from 80.2 to 199.9 per 100,000, indicating significant differences between countries in the same world region [2]. Although mortality from CVD decreased by 60% from 1990 to 2022, ischemic heart disease remains the leading cause of CVD in this re-

Corresponding Author
Alberico L. Catapano: alberico.catapano@unimi.it

gion, with a death rate and a disability-adjusted life year rate of 49.5 and 957.8 per 100,000, respectively [2].

Low-density lipoprotein (LDL) level is a major causal factor in atherosclerotic CVD (ASCVD) [3, 4] and numerous clinical trials have shown that lowering LDL-cholesterol (LDL-C) is a crucial step to reduce the risk of ASCVD. Current European guidelines for the management of dyslipidaemia recommend lowering LDL-C based on the individual cardiovascular risk [5]. An LDL-C reduction of ≥50% from baseline is also recommended for both very-high-risk patients (either in primary or secondary prevention) and high-risk patients, together with an LDL-C goal of <55 mg/dL (<1.4 mmol/L) for those at very-high risk and <70 mg/dL (<1.8 mmol/L) for those at high risk [5]. The recommended LDL-C levels are lower compared to those of the 2016 guidelines [6], due to the availability of compelling data demonstrating that cardiovascular risk decreases continuously with the decrease of LDL-C levels.

On the other hand, several studies have made clear that LDL-C goal achievement is far from being optimal in clinical practice. This observation is of utmost relevance in patients having high or very-high CV risk. Several studies have highlighted significant gaps between guideline recommendations and clinical practice, with very low rates of goal attainment in high/very-high-risk patients (7-9). The current guidelines have further reduced the LDL-C level goals for high-risk and very-high-risk patients [5] and new lipid-lowering drugs have since become available. The SANTORINI study was designed to evaluate whether these gaps still exist. This observational study, conducted in 14 European countries, enrolled approximately 9,000 patients at high and very-high cardiovascular risk between March 2020 and February 2021 [10]. It showed that 1) at the time of enrolment, 80% of patients at high and very-high risk were not at the LDL-C goals recommended by 2019 ESC/EAS guidelines, 2) about one in five patients were not taking lipid-lowering therapies (LLT), and 3) those who were on therapy were mainly receiving a monotherapy [10]. Of note, Italy was among the countries with the highest use of combination therapies (33%) [10, 11].

Despite this observation, it appears that control of LDL-C levels in high-risk and very-high-risk patients is still far from optimal.

The treatment algorithm proposed by the current European guidelines follows a stepwise approach. Statins are always the first choice for lowering LDL-C levels, and ezetimibe is often given in combination when the recommended LDL-C goal is not achieved with statin monotherapy [5]. The combination with inhibitors of PCSK9 (PCSK9i), which reduce LDL-C levels by up to a further 60% on top of statins, is recommended in very-high-risk and high-risk patients who do not achieve their LDL-C goal despite the maximum tolerated dose of a statin and ezetimibe [5]. Although this stepwise approach appears to be effective in increasing the proportion of patients achieving the LDL-C goal, we must emphasise that each step takes at least 4-6 weeks (which can extend to 12 weeks in the case of statin intolerance) to be implemented.

Bempedoic acid is the first oral ATP citrate lyase (ACL) inhibitor that specifically targets the hepatic biosynthesis of cholesterol. Phase 3 studies have shown that bempedoic acid lowers LDL-C levels by 17.4-18.1% (placebo-corrected) in hypercholesterolaemic patients on maximally tolerated statin therapy and by 21.4-28.5% (placebo-corrected) in statin-intolerant patients [2]. The CLEAR Outcomes trial showed that treatment with bempedoic acid significantly lowered LDL-C levels (–21.1% after 6 months) and the risk of major adverse cardiovascular events (–13.0%) versus placebo after a median follow-up period of 40.6 months in statin-intolerant patients [3]. Although the value of bempedoic acid in LDL-C lowering is widely recognised by clinicians, it is not yet included in the ESC/EAS guidelines. Therefore, this simulation study aims to evaluate the impact of implementing the use of ezetimibe and adding bempedoic acid in the treatment pathway in the Italian setting. Data from high-risk and very-high-risk patients from the Italian cohort of the SANTORINI study were used for this purpose.

Methods

SANTORINI patient cohort

The SANTORINI study (NCT04271280) is a European multinational observational study that aimed to describe the pharmacological approach to lipid management in patients at high or very-high CV risk [10]. For this simulation study, we used baseline data from the Italian cohort of the SANTORINI study. The baseline characteristics of the entire Italian cohort have already been published [11].

Patients from the Italian SANTORINI cohort were eligible for the simulation study if they were receiving LLT, were taking a statin of known intensity (for statin users), had a non-missing baseline LDL-C value (recorded directly or calculated using the Friedewald formula) and had a non-missing ESC risk classification at baseline. The classification into high and very-high CV risk was based on the 2019 ESC/EAS guidelines [5]. This study did not require ethical approval, as only anonymised data were obtained and analysed.

Simulation of the lipid-lowering treatment pathway and LDL-C reduction

In this study, we used a Monte Carlo simulation to mimic the sequential addition of ezetimibe and bempedoic acid in the Italian SANTORINI cohort. First, we determined whether or not the selected patients were at goal with their current LLT based on their CV risk (<70 mg/dL for high-risk patients and <55 mg/dL for very-high-risk patients). Patients who were at goal and patients taking a PCSK9i were not included in the treatment optimisation. The algorithm se quentially simulated the effect of adding

1) ezetimibe (10 mg) on LDL-C in patients who were not at goal at baseline with their current treatments (i.e. statin) and had not previously received ezetimibe, and
2) bempedoic acid (180 mg) in patients who were either taking ezetimibe at baseline and were not at goal or who did not achieve LDL-C goals after the simulated add-on of ezetimibe.

The same simulation study was performed applying national LDL-C goals, which refer to the 2016 ESC/EAS guidelines (<100 mg/dL for high-risk patients and <70 mg/dL for very-high-risk patients) [6].

Ezetimibe simulation

The percent LDL-C reduction by ezetimibe was simulated using a beta distribution similar to that used by Cannon et al. [14], derived from literature for modelling the effect of ezetimibe. The beta distribution was based on a mean of 22.7% [15] and an SD of 16.5% [16]. The alpha and beta parameters of the distribution used were not reported in the publication. In the present simulation, a beta distribution with alpha=1.6 and beta=5.4 was used, resulting in a mean and SD in the range of the referenced effects (mean 22.9%, SD 14.8%). As no patient-level data on the efficacy of ezetimibe were available, the parameters were derived from published data.

Bempedoic acid simulation

The parameters of the distributions used to simulate the effect of bempedoic acid on LDL-C levels were derived from the effects observed in the CLEAR trials for which patient-level data were available.

The data were split into two pools: 1) Pool 1 (Wisdom and Harmony CLEAR studies) [17, 18], consisting of patients treated with moderate- or high-dose statins, and 2) Pool 2 (Serenity and Tranquility CLEAR studies) [19, 20], consisting of patients treated with low-dose statins or no statin.

Each pool of data was used separately to calculate the distribution parameters that were applied for the simulation to the corresponding patients depending on their background statin intensity at baseline.

In pool 1, where data from 1922 patients were used for the analysis, the mean LDL-C reduction was 16.7% with an SD of 20.9%; in pool 2, where data from 399 patients were used, the mean LDL-C reduction was 24.1% with an SD of 22.3%.

No individual patient-level data were available for the effect of ezetimibe; therefore, the distribution was defined according to the information provided in two publications [15, 16] and only a decreasing effect of ezetimibe was simulated due to the choice of a beta distribution. In contrast, in the bempedoic acid treatment arm of the CLEAR trials, increases in LDL-C were observed in some patients between baseline and 12-week visits. For this reason, we also included the percentage increases in LDL-C and chose a distribution that allowed for a wider range of measurements compared to the distribution chosen for ezetimibe (the beta distribution is restricted to [0,1]). Indeed, the use of a log-normal distribution made it possible to simulate both a decrease (simulated percentage less than 1) and an increase (simulated percentage greater than 1) in LDL-C levels.

Outline of the simulation

Patients who were not at LDL-C goal at baseline and had not received PCSK9i or bempedoic acid participated in the simulation sequentially, as detailed below:

1) Simulation of the effect of ezetimibe on LDL-C in patients who had not previously received ezetimibe;
2) Simulation of the effect of bempedoic acid on LDL-C in patients not at LDL-C goal after ezetimibe (received or simulated).

No simulation of statin intensification was performed, as it was assumed that this medication was taken at the maximum tolerated regimen at baseline (95.9% of patients were on moderate or high-intensity statin).

The probabilistic sampling was run 10,000 times on the complete set of patients. The mean LDL-C value and the number of patients at goal on each of the 10,000 simulated cohorts were calculated after ezetimibe simulation and after bempedoic acid simulation. The median (2.5%-97.5% quantiles) of these 10,000 mean LDL-C values and the median (2.5%-97.5% quantiles) of these 10,000 numbers at goal were then calculated for both time points.

All simulations were performed using R version 4.0.3 (2020)

Results

Characteristics of the cohort used for the simulation

Patients for whom relevant information was missing (including LDL-C level, ESC risk classification, intensity of statin therapy for statin users, or no LLT documented) were not included in this simulation (**Table 1**). The baseline characteristics of the Italian cohort participating in the SANTORINI study and selected for the simulation are shown in **Table 2**. The eligible cohort consisted of 1344 patients with a mean age of 66 years and a mean LDL-C level of 82.1±42.9 mg/dL and comprised 1234 very-high-risk patients (mean LDL-C 79.7±41.3 mg/dL) and 110 high-risk patients (mean LDL-C 108.6±50.3 mg/dL). Of the very-high-risk patients, 87.5% were in secondary prevention. The detailed description of relevant cardiovascular events at baseline and risk classification based on

Table 1 | Patient selection for the simulation.

Cohort selection	Number of patients (%)		
	Whole cohort	*Very-high-risk cohort*	*High-risk cohort*
Overall cohort with cleaned baseline data	2095 (100%)	1857 (100%)	166 (100%)
With non-missing baseline LDL-C or recalculated with Friedewald formula	2076 (99.1%)	1845 (99.4%)	166 (100%)
With non-missing ESC classification of risk	2011 (96%)	1845 (99.4%)	166 (100%)
With non-missing intensity for statin users	1993 (95.1%)	1827 (98.4%)	166 (100%)
Excluding patients with no LLT documented	*1344 (64.2%)*	*1234 (66.5%)*	*110 (66.3%)*

LDL-C: low-density lipoprotein cholesterol; ESC: European Society of Cardiology; LLT: lipid-lowering therapy.

Table 2 | Baseline characteristics of the Italian SANTORINI cohort selected for the simulation.

Baseline characteristics	Italy (N=1344) Whole cohort	Italy (N=1234) Very-high-risk cohort	Italy (N=110) High-risk cohort
Age (years), mean (SD)	65.7 (10.5)	66.3 (10.0)	59.6 (13.7)
Female, N (%)	354 (26.3)	306 (24.8)	48 (43.6)
Diabetic, N (%)	458 (34.1)	447 (36.2)	11 (10.0)
BMI, mean (SD)	27.43 (4.3)	27.6 (4.3)	25.0 (3.4)
Mean LDL-C (mg/dL), mean (SD)	*82.1 (42.9)*	*79.7 (41.3)*	*108.6 (50.3)*
Patients in secondary prevention (%)	1080 (80.4)	1080 (87.5)	0 (0)
Patients in primary prevention (%)	264 (19.6)	154 (12.5)	110 (100)

SD: standard deviation; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol.

ESC/EAS 2019 guidelines is shown in **Table S1**. At baseline 25.9% of the entire cohort was at LDL-C goal, based on the ESC/EAS 2019 guidelines [5]; this percentage was similar between the very-high-risk cohort (26.1%) and the high-risk cohort (23.6%) (**Table 3**). Most patients were taking a statin (85.2%), with 95.9% taking a moderate/high-intensity statin. Ezetimibe was used by 44.2% of patients, while PCSK9i were used by 17.3% of patients. Of note, the use of PCSK9i was greater in the high-risk cohort than in the very-high-risk cohort (23.6% and 16.8%, respectively) (**Table 3**). No patients were taking bempedoic acid as it was not approved in Europe at the time of inclusion in the study.

Simulation in the whole cohort

The mean LDL-C value in the entire cohort (N=1344) was 82.1±42.9 mg/dL at baseline. Among them, 348 patients were at goal (25.9%), with a mean LDL-C value of 42.0±10.6 mg/dL. For patients who were not at goal and were not receiving ezetimibe already (and were not receiving a PCSK9i) an LLT intensifying algorithm was applied consisting of a simulated sequential addition of ezetimibe 10 mg/day and bempedoic acid 180 mg/day. After excluding patients at goal or receiving a PCSK9i, 864 patients (mean LDL-C 95.8±39.0 mg/dL) were included in the simulation study (**Figure 1**). For those not receiving ezetimibe (N=545, mean LDL-C 95.0±34.5 mg/dL), the

Table 3 | Lipid-lowering therapies at baseline in the Italian SANTORINI cohort selected for the simulation.

Baseline LLT	Italy (N=1344) Whole cohort		Italy (N=1234) Very-high-risk cohort		Italy (N=110) High-risk cohort	
	N	%	N	%	N	%
At LDL-C goal	*348*	*25.9%*	*322*	*26.1%*	*26*	*23.6%*
No statin users	199	14.8%	181	14.7%	18	16.4%
Statin users	1145	85.2%	1053	85.3%	92	83.6%
Low intensity	47	4.1%	37	3.5%	10	10.9%
Moderate/high intensity	1098	95.9%	1016	96.5%	82	89.1%
No ezetimibe use	750	55.8%	693	56.2%	57	51.8%
Ezetimibe use	594	44.2%	541	43.8%	53	48.2%
BA use	0	0%	0	0%	0	0%
PCSK9i use	233	17.3%	207	16.8%	26	23.6%

LDL-C: low-density lipoprotein cholesterol; BA: bempedoic acid; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitors.

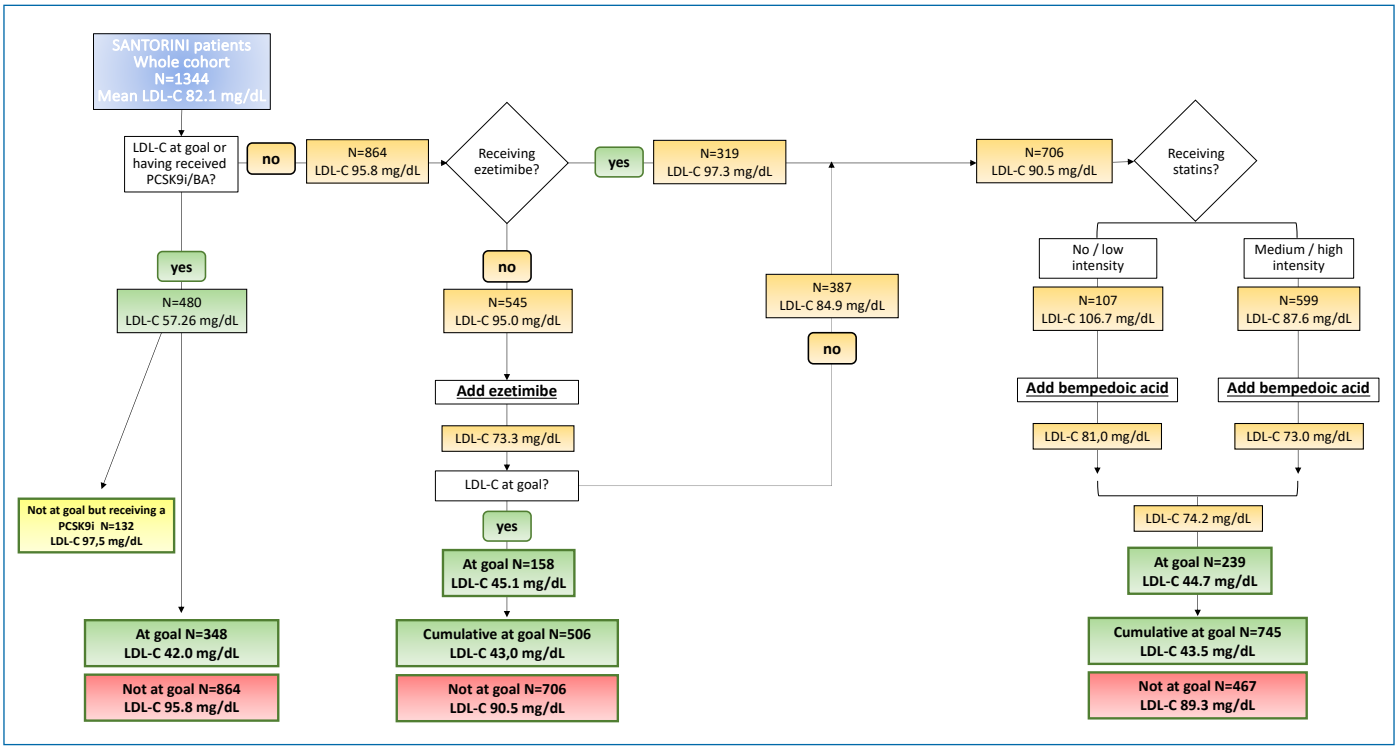

Figure 1 | Application of the simulation algorithm in eligible patients (N=1344) of the Italian cohort of the SANTORINI study; results were obtained based on the LDL-C goals recommended by the 2019 ESC/EAS guidelines.

simulated addition of ezetimibe allowed 158 (29%) of them to reach the LDL-C goal (mean LDL-C 45.1 mg/dL, 95% CI 43.7-46.4).

The combination of patients who did not reach the LDL-C goal after the simulated addition of ezetimibe (N=387, mean LDL-C 84.9 mg/dL, 95% CI 83.3-86.5) with those who were already taking ezetimibe at baseline but were not at goal (N=319, mean LDL-C 97.3±45.6 mg/dL) generated a cohort of 706 patients with a mean LDL-C of 90.5 mg/dL (95% CI 89.5-91.4). The addition of bempedoic acid was simulated in this cohort. For this part of the simulation, patients were divided into two groups based on their background statin therapy. This allowed the application of the LDL-C-lowering efficacy of bempedoic acid observed in the CLEAR Serenity/Tranquility trials in those receiving no/low-intensity statin (N=107, mean LDL-C 106.7 mg/dL, 95% CI 104.2-109.1) and that observed in the CLEAR Wisdom/Harmony trials in those receiving medium/high-intensity statin (N=599, mean LDL-C 87.6 mg/dL, 95% CI 86.6-88.6) [12]. Based on this calculation, the mean LDL-C level after simulating the addition of bempedoic acid was 74.2 mg/dL (95% CI 72.5-76.0) for the whole cohort. Patients with no/low-intensity background statin reached a mean simulated LDL-C of 81.0 mg/dL (95% CI 75.7-86.7) and those with medium/high-intensity background statin achieved a mean simulated LDL-C of 73.0 mg/dL (95% CI 71.2-74.8). Of the 706 patients who participated in the simulation of bempedoic acid addition, 239 (34%) reached the goal, with a mean LDL-C of 44.7 mg/dL (95% CI 43.8-45.7).

A total of 745 subjects had reached the LDL-C goal at the end of the simulation (mean LDL-C 43.5 mg/dL, 95% CI 43.1-44.0). This number was the sum of those who were at goal at baseline (N=348), those who reached the goal after the simulation of ezetimibe addition (N=158) and those who reached the goal after the simulation of bempedoic acid addition (N=239). The percentage of patients at goal thus increased from 25.9% before the simulation to 37.6% after the simulated addition of ezetimibe and to 55.4% after the simulated addition of bempedoic acid (**Figure 2**).

The distribution of LDL-C levels at baseline and at the end of the simulation is presented in **Figure 3**. The proportion of patients with LDL-C <55 mg/dL was significantly increased after the simulation (from 24.9% to 53.8%) (**Figure 3, panels A and B**). Of note, before the simulation 53.5% of patients had LDL-C ≥70 mg/dL; after the simulation, this percentage was largely reduced to 28.6% (**Figure 3, panels A and B**). When analysed according to the intensity of background statin therapy, patients taking a medium/high-intensity statin had the greatest improvement, with 57.0% of patients achieving LDL-C <55 mg/dL (versus 25.3% at baseline) and 74.0% achieving LDL-C <70 mg/dL (versus 47.4% at baseline) (**Figure 3, panels C and D**). Also, patients taking no/low-intensity statin showed improvement, although to a lesser extent (**Figure 3, panels E and F**).

The mean LDL-C for the whole cohort was reduced from 82.1 mg/dL at baseline to 73.3 mg/dL and 64.72 mg/dL, after the sequential simulation of ezetimibe and bempedoic acid, respectively, corresponding to 10.7% and 21.1% reductions, respectively (**Figure 2**).

Simulation in the very-high-risk and the high-risk sub-cohorts

Since the entire cohort used for the simulation comprised both very-high-risk patients and high-risk patients, we repeated the simulation in the two subgroups to assess the algorithm's performance.

The mean LDL-C level in the very-high-risk cohort (1234 patients) was 79.7±41.3 mg/dL at baseline. Of them, 322 were at goal (26.1%), with a mean LDL-C level of 41.2±9.9 mg/dL. After excluding those at goal or already receiving a PCSK9i, 793 patients with a mean LDL-C of 93.0±37.2 mg/dL entered the simulation (**Figure 4**). The 498 patients who were not taking ezetimibe (mean LDL-C 92.8±33.3 mg/

Figure 2 | Percentage of patients at goal before and after the simulated addition of ezetimibe and bempedoic acid in the whole cohort (A), very-high-risk (B) and high-risk subjects (C) of the Italian cohort of the SANTORINI study.

dL) were simulated to receive ezetimibe and achieved a mean LDL-C of 71.6 mg/dL (95% CI 70.2-72.8); of these, 146 reached the goal (mean LDL-C 44.1 mg/dL, 95% CI 42.7-45.3). The remaining 352 patients who did not reach the goal (mean LDL-C 83.0 mg/dL, 95% CI 81.3-84.6) were simulated to receive bempedoic acid, along with those who were already receiving ezetimibe but were not at goal (295 patients, mean LDL-C 93.5±43.1 mg/dL), for a total of 647 patients (mean LDL-C 87.7 mg/dL, 95% CI 86.8-88.7). After the simulated addition of bempedoic acid, the mean LDL-C level was 72.0 mg/dL (95% CI 70.2-73.8). More in detail, in patients with no/low-intensity background therapy, the mean LDL-C level was reduced from 102.8 mg/dL (95% CI 100.3-105.2) to 78.0 mg/dL (95% CI 72.7-83.6) and

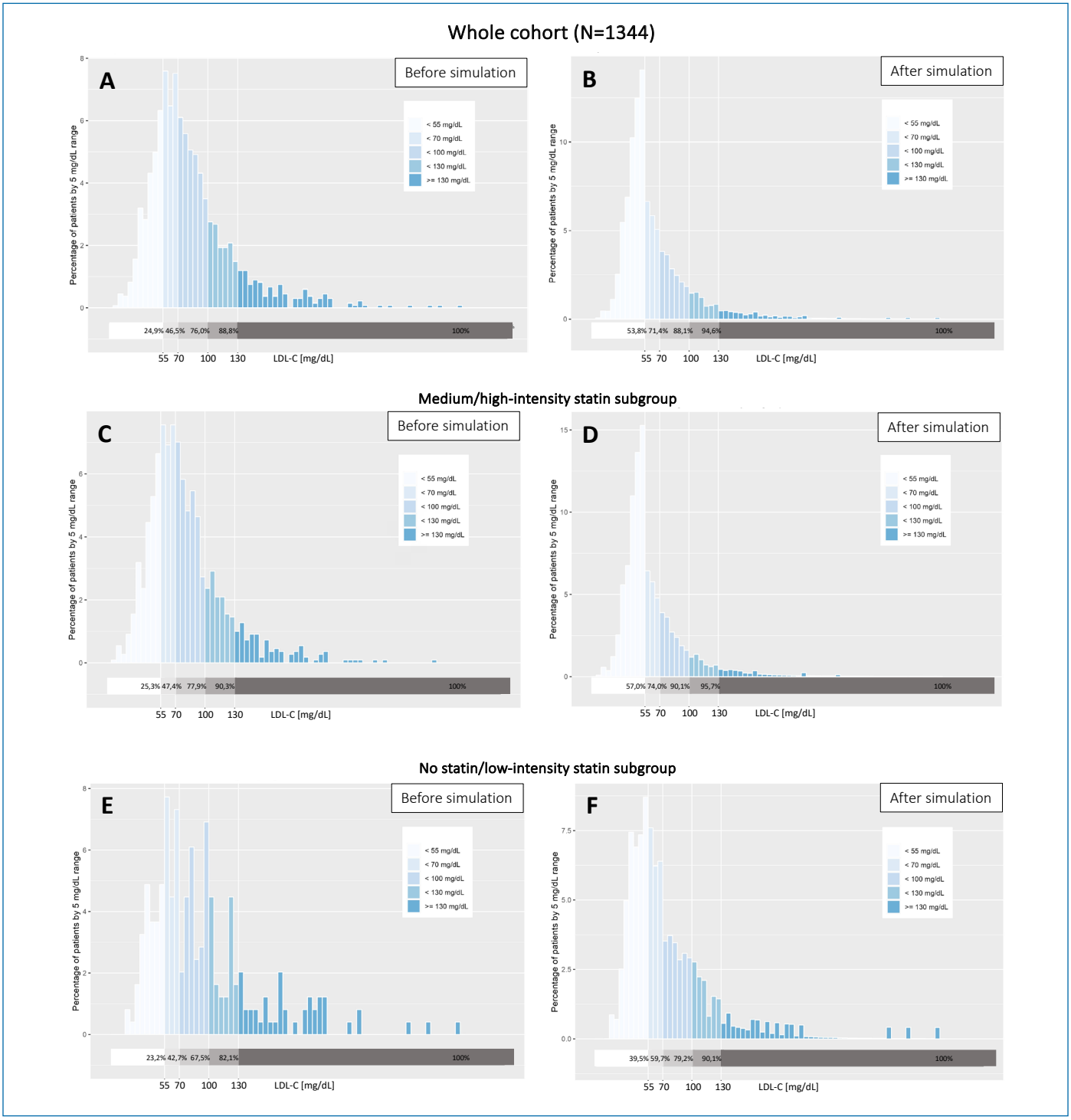

Figure 3 | LDL-C distribution before and after the simulation in the whole cohort (A, B), in the subgroup with no/low-dose statin (C, D) and in the subgroup with medium/high-dose statin (E, F).

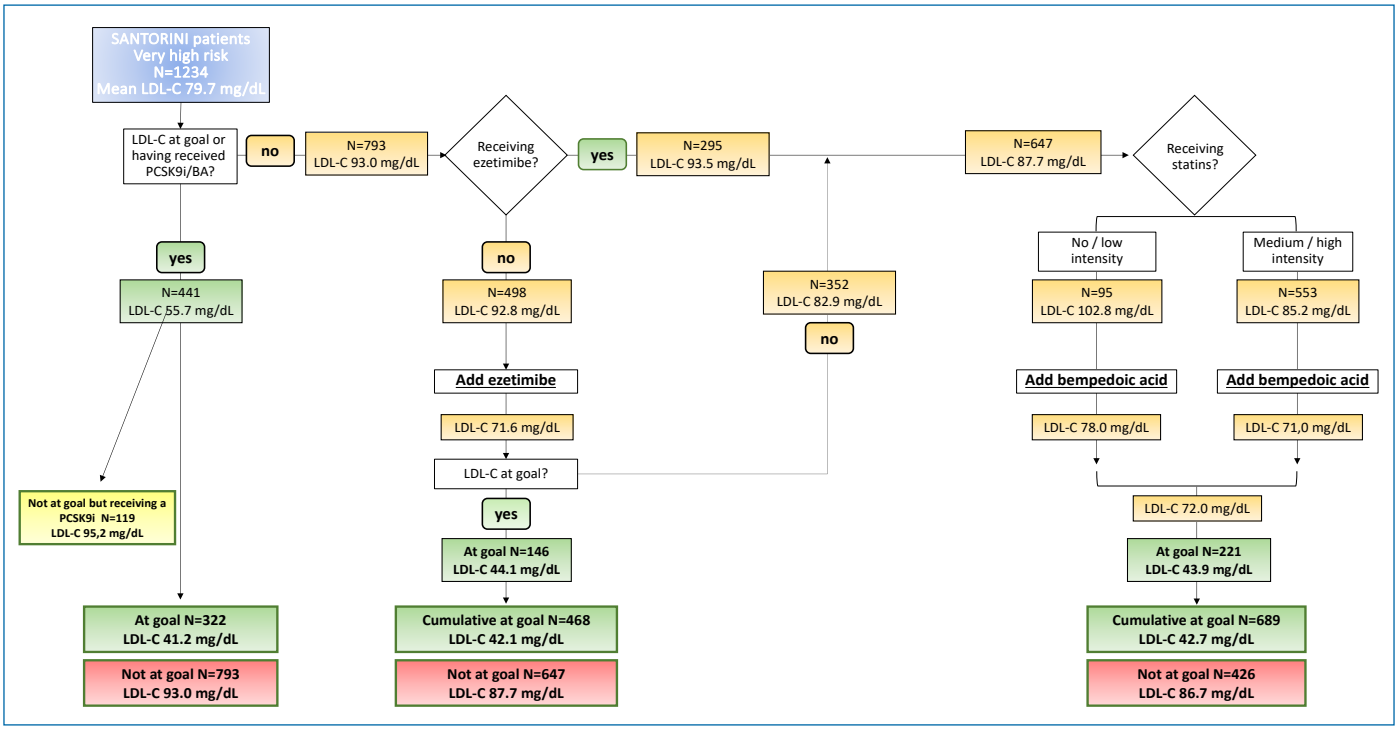

Figure 4 | Application of the simulation algorithm in the very-high-risk subgroup (N=1234) of the Italian cohort of the SANTORINI study; results were obtained based on the LDL-C goals recommended by the 2019 ESC/EAS guidelines.

in patients with medium/high-intensity statin background therapy, the mean LDL-C level was reduced from 85.2 mg/dL (95% CI 84.2-86.2) to 71.0 mg/dL (95% CI 69.2-72.8). After the simulated addition of bempedoic acid, 221 patients reached the goal with a mean LDL-C level of 43.9 mg/dL (95% CI 42.9-44.7). A total of 689 out of 1234 patients (55.8%) reached the goal at the end of the simulation (mean LDL-C 42.7 mg/dL, 95% CI 42.2-43.0). At baseline, 26.1% of the very-high-risk patients were at goal; after the simulation, this percentage had more than doubled (**Figure 2B and Figure S1, panels A and B**). Of note, at the end of the simulation, the proportion of patients with LDL-C ≥70 mg/ had fallen from 51% to 27% (**Figure S1, panels A and B**). As observed in the entire cohort, patients on medium/high-intensity statin therapy were most likely to achieve the LDL-C goal, with 27% of them being at goal before the simulation and 60% achieving the goal after the simulation (**Figure S1, panels C and D**).

Considering the entire subgroup of patients at very-high-risk, the simulated LDL-C was reduced from 79.7±41.3 mg/dL to 71.1 mg/dL (95% CI 70.6-71.7) after ezetimibe (-10.7%) and to 62.9 mg/dL (95% CI 62.0-63.8) after bempedoic acid (overall reduction -21.1%) (**Figure 2B**).

Similar results were obtained in the subgroup of high-risk patients, for whom the current ESC/EAS guidelines recommend an LDL-C goal of <70 mg/dL. At baseline, only 23.6% of patients were at goal (mean LDL-C 52.3±13.6 mg/dL); after the simulation with ezetimibe this percentage increased to 35.5% and after bempedoic acid to 50.9% (**Figure 2 and Figure 5**). LDL-C levels were reduced by 10.3% and 21.6% after simulating the addition of ezetimibe and bempedoic acid, respectively, with absolute reductions larger than those observed in the very-high-risk patient subgroup (-11.2 mg/dL and -23.4 mg/dL). **Figure S2** shows the LDL-C level distribution in high-risk subjects before and after the simulation.

Simulation study in high-risk and very-high risk individuals: application of national LDL-C goals and reimbursement criteria in Italy

We performed the simulation in high-risk and very-high-risk subjects to verify how many could reach the goal during the different simulation steps according to the guidelines applied in Italy (which set a goal of LDL-C <70 mg/dL for very-high-risk subjects and <100 mg/dL for high-risk subjects) and Italian reimbursement criteria [21, 22].

Of the 1234 very-high-risk subjects, 598 were at goal (mean LDL-C 50.7±13.0 mg/dL). The 562 subjects who were not at goal (mean LDL-C 105.7±37.3 mg/dL) and were not taking a PCSK9i participated in the simulation (**Figure S3**). After simulating the addition of ezetimibe in those who were not taking ezetimibe (N=373, mean LDL-C 103.1±32.4 mg/dL), the mean LDL-C decreased to 79.5 mg/dL (95% CI 77.9-81.1) and 159 subjects reached the goal (mean LDL-C 56.2 mg/dL, 95% CI 54.6-57.7). The remaining subjects who did not reach the LDL-C goal (N=214, mean LDL-C 96.8 mg/dL, 95% CI 94.7-99.0) and those who were already taking ezetimibe but were not at goal (N=189, mean LDL-C 111,0±45.2 mg/dL) were analysed together (403 subjects, mean LDL-C 103.4 mg/dL (95% CI 102.2-104.7)). This cohort was simulated to receive bempedoic acid, using the same criteria as described above. The mean LDL-C was lowered to 84.7 mg/dL (95% CI 82.2-87.3) and 166 subjects achieved the goal (mean LDL-C 55.8 mg/dL, 95% CI 54.4-57.1). To summarise this part of the study the cumulative number of subjects who achieved the goal was 923, with a mean LDL-C of 52.6 mg/dL (95% CI 52.2-53.0).

After simulating the addition of ezetimibe, 403 subjects (32.7% of the very-high-risk cohort, mean LDL-C 103.5 mg/dL) would have been eligible for PCSK9i therapy; however, after the simulated addi-

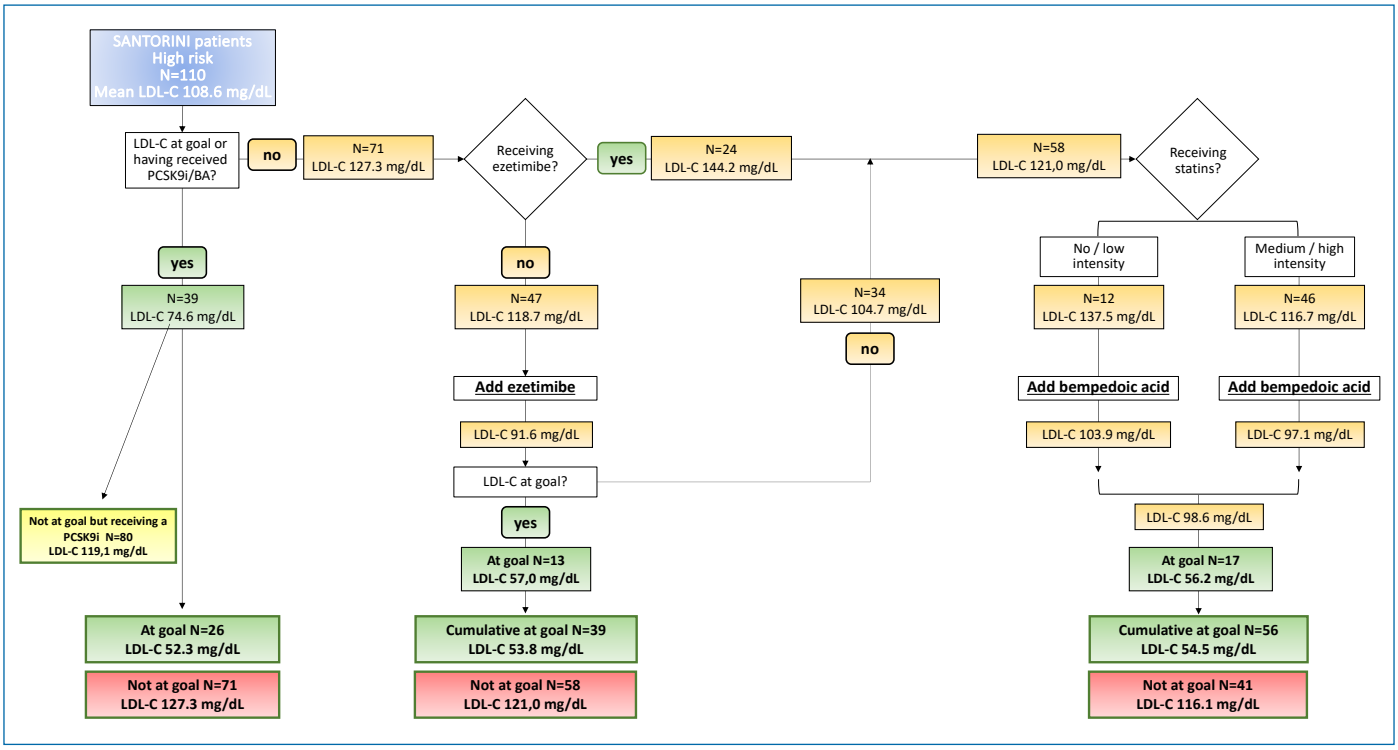

Figure 5 | Application of the simulation algorithm in the high-risk subgroup (N=110) of the Italian cohort of the SANTORINI study; results were obtained based on the LDL-C goals recommended by the 2019 ESC/EAS guidelines.

tion of bempedoic acid, this number decreased to 237 (19.2% of the very-high-risk cohort, mean LDL-C 104.9 mg/dL).

When the simulation was applied to 110 high-risk subjects, the number of subjects at goal increased from 56 (50.9%; mean LDL-C 70.7±20.6 mg/dL) to 71 (64.5%; mean LDL-C 72.9 mg/dL, 95% CI 71.1-74.5) after ezetimibe and to 83 (75.5%; mean LDL-C 74.0 mg/dL, 95% CI 72.2-75.8) after bempedoic acid (**Figure S4**). After the simulated addition of ezetimibe, 33 subjects (30%) (mean LDL-C 149.0 mg/dL) would have been eligible for PCSK9i therapy, while this number decreased to 22 subjects (20%) (mean LDL-C 145.3 mg/dL) after the simulated addition of bempedoic acid.

Discussion

In this simulation study, we showed that LDL-C goal attainment in patients at high and very-high-risk can be substantially increased by optimising oral LLT with the addition of ezetimibe and bempedoic acid. The availability of an increasing number of lipid-lowering drugs has significantly reduced cardiovascular disease mortality in Western Europe [2]. Nevertheless, several observations have shown that, despite the availability of a large variety of treatment options, the management of patients at high and very-high cardiovascular risk is far from optimal.

Several approved LDL-C-lowering drugs utilise complementary mechanisms of action and can be used in combination to achieve greater LDL-C lowering on a background of statin therapy. Ezetimibe can be used in addition to statin therapy, providing further LDL-C-lowering and additional clinical benefit compared with statin alone [15]. Adding ezetimibe to statin therapy is more effective in lowering LDL-C than doubling the statin dose [23, 24]. Based on the results of the IMPROVE-IT trial [15], the current European guidelines for the treatment of dyslipidaemia recommend the addition of ezetimibe to ongoing statin therapy in patients who do not achieve the recommended LDL-C goals with maximally tolerated statins in monotherapy [5]. Despite the observations that combining a statin with ezetimibe can increase the chance of achieving the recommended LDL-C goals, the use of ezetimibe is still inadequate, with only 44.2% of individuals at high/very-high risk taking ezetimibe in the Italian cohort of the SANTORINI trial.

More recently, bempedoic acid has been developed as an oral LDL-C-lowering drug and approved for use in patients with primary hypercholesterolaemia or mixed dyslipidaemia, either as monotherapy or in a fixed-dose combination with ezetimibe. In the pivotal trial programme, bempedoic acid was shown to reduce LDL-C levels by ~17-18% in patients on statin therapy [17, 18] and by ~21-28% in patients intolerant to statins [19, 20]. In addition, the results of the CLEAR Outcomes trial support the use of bempedoic acid to reduce cardiovascular events in statin-intolerant patients at high CV risk [13]. Of note, none of the individuals enrolled in this study was taking bempedoic acid at baseline, as it was not approved at the time of enrolment.

The LDL-C goals adopted in the current European guidelines have further emphasised the need for drugs (or combinations of drugs) that can significantly lower LDL-C levels to achieve recommended LDL-C goals, particularly in individuals at high or very-high cardiovascular risk [5]. In this context, PCSK9i play an important role for patients at high/very-high risk who cannot achieve goals simply with a statin in combination with ezetimibe, as recommended by the treatment algorithm [5]. However, as of today PCSK9i (either monoclonal antibodies or inclisiran) are costly, can only be administered by injection and can only be prescribed to selected patients based on reimbursement criteria imposed in many European coun-

tries. Therefore, an approach that results in more patients achieving their LDL-C goals with less demanding oral therapies is needed.

A simulation study using data from participants in the iASPIRE study showed that 86.3% of patients were not at LDL-C goal at baseline and were therefore eligible for treatment intensification. Optimisation of statin therapy or the addition of ezetimibe and bempedoic acid resulted in most patients achieving their LDL-C goals, leaving a smaller number of patients with unmet goals and thus eligible for a PCSK9i [25]. Another simulation study showed that the sequential addition of ezetimibe and bempedoic acid increased LDL-C goal attainment [26]. In addition, simulated treatment with bempedoic acid halved the percentage of individuals requiring a PCSK9i in the same study which would significantly reduce costs [26]. In our simulation study, which is based on an Italian cohort, we observed that the sequential addition of ezetimibe and bempedoic acid significantly lowered the mean LDL-C of the entire cohort and significantly increased the proportion of patients achieving the LDL-C goals recommended by current European guidelines. This reduces the proportion of patients who would be in need of PCSK9i therapy.

These last observations could play a role when considering the impact of lipid-lowering therapies on the healthcare system. Indeed, PCSK9i, either monoclonal antibodies or siRNA, play an important role in reducing LDL-C and cardiovascular risk (although we are still waiting for the results of the outcome trial with inclisiran). However, reimbursement criteria limit their use in selected patients who have a very-high cardiovascular risk and need a large reduction in LDL-C. In Italy, reimbursement of injectable therapies targeting PCSK9 (i.e. monoclonal antibodies and siRNA) has recently become available for very-high-risk patients with LDL-C levels >70 mg/dl who are already receiving the combination statin+ezetimibe or are intolerant to statins. When we ran the simulation taking into account the LDL-C goals currently in place in Italy, there was a significant reduction in the number of individuals who would have been in need of PCSK9i therapy by adding ezetimibe and bempedoic acid. This effect appears particularly relevant in very-high-risk patients with a background medium/high-intensity statin therapy, in whom the simulated addition of the two oral agents would approximately halve the proportion of patients requiring an additional drug such as a PCSK9i.

Limitations of the study

We must acknowledge some limitations of the present study.

1) Lack of information on LLT use at baseline led to the exclusion of some patients, such as those in whom no LLT was documented and who were taking a statin but lacked information on the intensity of the statin, as this would prevent the definition of the expected efficacy of bempedoic acid.
2) Only the effect of ezetimibe and bempedoic acid was simulated, while the increase in statin intensity was not simulated, as it was assumed that patients were taking their maximum tolerated statin dose. However, the effect of increasing the statin dose is likely to be small, as most patients were already taking moderate/high-dose statins.
3) The simulation pathway depends only on LLT intake at baseline, independent of previous treatment.
4) The achievement of the LDL-C goal is based only on absolute values (the percent change recommended by guidelines is not taken into account).
5) We lack patient level data for the ezetimibe simulation.
6) Efficacy is based on data from RCTs for ezetimibe and bempedoic acid, using the theoretical effect, which may be somewhat different in a real-world population.

Conclusions

The SANTORINI analysis has shown that many Italian patients at high and very-high cardiovascular risk do not achieve the LDL-C goals required in Italy due to a sub-optimal use of combination therapy. With the simulated addition of ezetimibe and bempedoic acid, the number of patients reaching the goals could be significantly increased. With these oral therapies, the number of patients requiring PCSK9i therapy to achieve the LDL-C goals would have been halved, resulting in significant cost savings for the Italian healthcare system.

Author contributions

MA, KKR and ALC contributed to the conception and design of the work; AP and RG contributed to the analysis and interpretation of data and drafted the manuscript; all authors critically revised the manuscript, gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Disclosures

MA received research grant support and lecturing fees from Alfasigma, Amgen, Amryt, Daiichi Sankyo, Ionis Pharmaceuticals/Akcea Therapeutics, Novartis,Pfizer, Regeneron Pharmaceuticals, Sanofi, Sobi, Viatris, and Ultragenyx. AP has nothing to disclose. RG is an employee in Medical Affairs at Daiichi Sankyo Italia. CB and FD are employees of Daiichi Sankyo. KKR has received honoraria for consulting, lectures from Abbott Laboratories, Amgen, Astra Zeneca, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Cargene, CRISPR, Daiichi Sankyo, Eli Lilly Company, Emendobio, Esperion, Kowa, New Amsterdam Pharma, Novartis Corporation, Nodthera, GSK, Novo Nordisk, Pfizer, Regeneron, Sanofi, SCRIBE, Silence Therapeutics, and VAXXINITY. In addition, he has received research grant support to his institution from Amgen, Daiichi Sankyo, Sanofi, Regeneron and Ultragenix, plus stock options New Amsterdam Pharma, Scribe, Pemi 31. ALC has received honoraria, lecture fees or research grants from Aegerion, Amarin, Amgen, Amryt Pharma, AstraZeneca, Daiichi Sankyo, Esperion, Ionis Pharmaceutical, Medscape Education, Menarini, MSD, New Amsterdam Pharma, Novartis, Novo Nordisk, PeerVoice, Pfizer, Recordati, Regeneron, Sanofi, The Corpus, Ultragenyx, Viatris.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Atherosclerotic cardiovascular disease and measurement of lipoprotein(a) levels in Italy

Elena Olmastroni[1,2], Manuela Casula[1,2], Sining Xie[1], Alberico L. Catapano[1,2]

[1]*Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy*
[2]*IRCCS MultiMedica, Sesto San Giovanni (MI), Italy*

ABSTRACT

Background: Lipoprotein(a) [Lp(a)] is a relatively new but underutilized biomarker in the context of atherosclerotic cardiovascular disease (ASCVD).
Objectives: To explore the clinical implementation of Lp(a) measurement and current practices in hospital and specialised settings in Italy.
Methods: An anonymous online questionnaire was distributed to Italian physicians to examine the habits of Italian clinicians regarding Lp(a) measurement. The survey covered three topics: 1) information on the clinical setting of the physicians, 2) questions for physicians who reported not measuring Lp(a), to understand the reasons for not requesting the test, and 3) questions for physicians who measure Lp(a), to investigate its use in patient management.
Results: A total of 978 responses were received. Overall, 63.1% of physicians reported working in a hospital; 12.2% reported being a territorial specialist. Regular Lp(a) measurement was reported by 32.1% of clinicians. Among those who do not measure Lp(a), the main barriers to implementation include high cost and limited availability of the test. The threshold value for defining elevated Lp(a) levels varies significantly among professionals, with 36.7% considering levels above 30 mg/dL to be elevated and 32.7% considering levels above 50 mg/dL to be elevated. Clinical management of patients with elevated Lp(a) primarily includes intensification of lipid-lowering therapy (69.2%), management of cardiovascular risk factors (48.7%), and lifestyle recommendations (37.4%).
Conclusions: The survey highlights the heterogeneity in the approach to managing elevated Lp(a) levels among Italian clinicians, underscoring the importance of clear guidelines and greater accessibility to the test to optimize cardiovascular risk stratification and improve clinical outcomes.

Keywords
Lipoprotein(a); atherosclerotic cardiovascular disease; clinicians; cardiovascular risk management; patient communication simulation

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) represents one of the main global health challenges within the landscape of chronic diseases. Characterized by the formation and progression of atherosclerotic plaques in the arteries, ASCVD is a multifactorial condition mostly involving the deposition of lipids and inflammatory cells within the arterial wall [1]. This pathological process can impede blood flow, compromise arterial distensibility, and, in severe cases, lead to complications such as myocardial infarction, stroke, and other cardiovascular conditions.

Understanding the risk factors, prevention methods, and effective management of ASCVD is crucial for promoting cardiovascular health and reducing related morbidity and mortality.

The role of lipoprotein(a) [Lp(a)] in cardiovascular risk assessment has been and continues to be a topic of debate [2]. Lp(a) is a particle similar to low-density lipoprotein (LDL), differing only by the presence of a glycoprotein called apo(a) (which has a high homology with plasminogen) covalently linked to apoB [3]. Unlike other lipoproteins that have a clear biological function as lipid transport molecules in plasma, the function of Lp(a), after more than 50 years of research, remains practically unknown [4].

Corresponding Author
Elena Olmastroni: elena.olmastroni@unimi.it

On the other hand, the role of Lp(a) as a cardiovascular risk factor is well established. Numerous scientific studies indicate that elevated levels of Lp(a) are associated with an increased risk of adverse cardiovascular events, including stroke and myocardial infarction [5]. Therefore, measuring Lp(a) in clinical practice is becoming increasingly important for cardiovascular risk assessment, enabling targeted and personalized preventive interventions.

Plasma levels of Lp(a) in the general population vary widely, ranging from very low, almost undetectable levels (<0.2 mg/dL) to very high levels (>200 mg/dL). This variability primarily depends on the isoforms of apo(a), which differ in the size of the molecule determined by the number of repeat structures, the kringles, particularly the number of kringle 4 type 2 repeats [6].

The polymorphism of the gene encoding apo(a) size is the major predictor of plasma Lp(a) concentration and accounts for 40-70% of the variation in Lp(a) plasma levels [7]. The strong genetic influence on Lp(a) levels results in its asymmetric distribution in the population, unlike other analytes, complicating the role of Lp(a) in cardiovascular risk assessment.

Some peculiar characteristics of Lp(a), such as its significant heterogeneity, the absence of a clear physiological function, and the current difficulty in measuring it reliably and in a standardised manner, limit its use in routine clinical practice [8].

Therefore, the SISA Foundation has promoted a survey on the themes related to 'Atherosclerotic Cardiovascular Disease and the Importance of Measuring Lp(a) Levels,' targeting physicians operating in Italy.

The project's objective is to gather useful information to improve diagnostic and prognostic approaches in the near future. This includes understanding how often Lp(a) is evaluated in daily practice, the criteria used to decide whether or not to test for Lp(a), and the practical factors considered in the decision to perform the test.

This effort aims to collect essential information to determine the resource, process, infrastructure, and funding requirements needed to make Lp(a) evaluation a common practice.

Methods

The questionnaire, consisting of 23 questions, primarily included multiple-choice responses and was structured into three main areas of investigation:

- Information regarding the background and clinical setting of the physicians;
- Specific questions directed at physicians who reported not regularly measuring Lp(a) in clinical practice, to understand the motivations or practical barriers preventing them from requesting the test;
- Specific questions directed at physicians who reported regularly measuring Lp(a) in clinical practice, to delve into their approach in managing patients at high cardiovascular risk.

Participation in the questionnaire was voluntary. Consent was implied with the return of the completed questionnaire.

All responses were managed anonymously. The results were summarized using frequencies and percentages. Statistical analyses were performed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, NC, USA).

Results

A total of 978 clinicians from various settings responded to the survey: the majority reported working primarily in territorial or university hospitals (24.4% and 22.3%, respectively), and 39.2% and 24.7% of them were cardiologists or internal medicine physicians (**Table 1**). The geographical origin of the clinicians participating in the survey is illustrated in **Figure 1**.

Based on the personal experiences of the participants, the

Table 1 | Clinical settings and specializations of the physicians who participated in the survey.

Number of Clinicians	**978**
Practice Setting, %:	
University Hospital	22.29%
Institute for Treatment and Research (IRCCS)	6.44%
Territorial Hospital	24.44%
Territorial Specialist	12.17%
Specialized Lipidology Center	2.97%
Specialized Diabetology Center	2.56%
Specialized Cardiology Center	5.42%
Other	23.72%
Specialization, %:	
Cardiology (Clinical Cardiology, Hemodynamics, Electrophysiology, Interventional Cardiology)	39.16%
Diabetology	4.19%
Endocrinology	6.24%
Lipidology	1.53%
Internal Medicine	24.74%
Other	24.13%

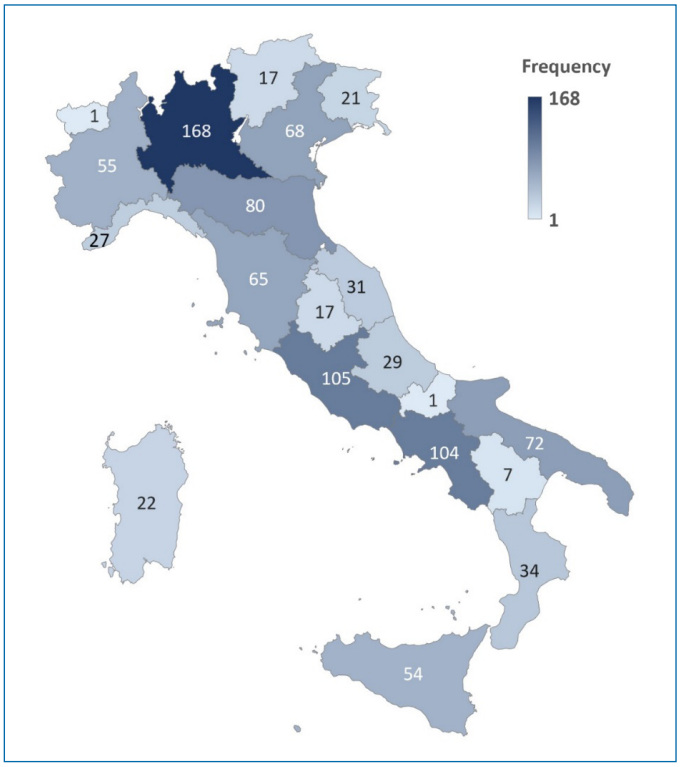

Figure 1 | Geographical distribution of the clinicians participating in the survey.

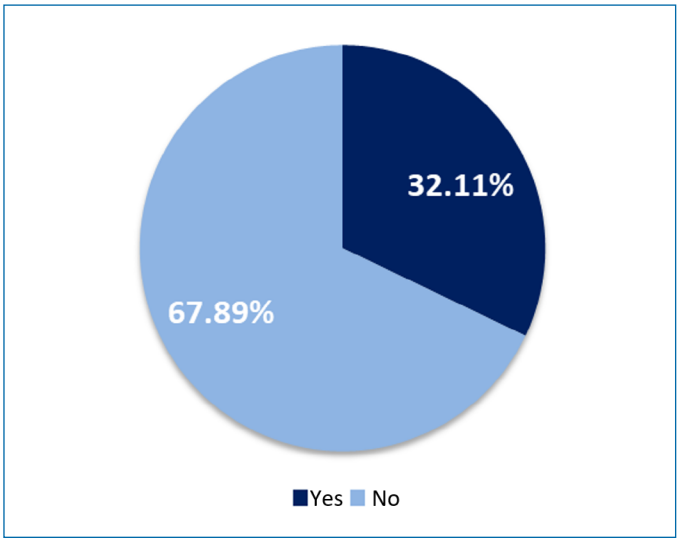

Figure 2 | Proportion of clinicians who regularly measure Lp(a) in clinical practice.

proportion of clinicians who regularly measure Lp(a) in clinical practice was found to be 32.1% (**Figure 2**).

Among the clinicians who do not measure Lp(a) in their clinical practice (N = 664), the most common reasons for not requesting the Lp(a) test were lack of reimbursement by the National Health Service, lack of treatment options for elevated Lp(a) levels, unavailability of the Lp(a) test, and the high cost of the laboratory test (**Figure 3A**). Among these physicians, the availability of specific therapies for the treatment of elevated Lp(a) levels, the availability of the measurement test, and specific recommendations in the guidelines would encourage the inclusion of Lp(a) measurement in their clinical practice (**Figure 3B**).

Among those who regularly measure Lp(a) (N = 314), a high percentage reported requesting the measurement for better cardiovascular risk stratification (**Figure 4**).

The survey shows significant variability among clinicians in the threshold considered for defining high levels of Lp(a) in relation to ASCVD risk (**Figure 5**). Most clinicians (36.7%) consider a value above 30 mg/dL (63 nmol/L) as high, while 32.7% consider a value above 50 mg/dL (105 nmol/L) as high. Only a minority consider higher values as thresholds, with 17.64% indicating 70 mg/dL (150 nmol/L), 8.94% indicating 100 mg/dL (215 nmol/L), and 4.10% considering a value of Lp(a) above 150 mg/dL (325 nmol/L) as high. **Figure 6**, on the other hand, demonstrates that the majority of clinicians adjust their therapeutic approach when Lp(a) levels exceed 50 mg/dL.

Among the categories of patients that clinicians consider eligible for Lp(a) measurement, the majority (67.7%) indicated patients with recurrent cardiovascular events despite LDL cholesterol reduction is important, followed by 64.2% who assess Lp(a) levels in patients with a family history of early cardiovascular events. A significant number of clinicians (48.6%) consider measuring Lp(a) levels important in patients with a history of myocardial infarction, and 45.2% in those with familial hypercholesterolemia. Overall, only 44.2% of clinicians find it useful to measure Lp(a) at least once in the life of every adult patient.

Faced with elevated Lp(a) levels in patients with ASCVD, most clinicians (69.2%) stated that they intensify dyslipidaemia treatment, while 48.7% actively manage other risk factors. Lifestyle

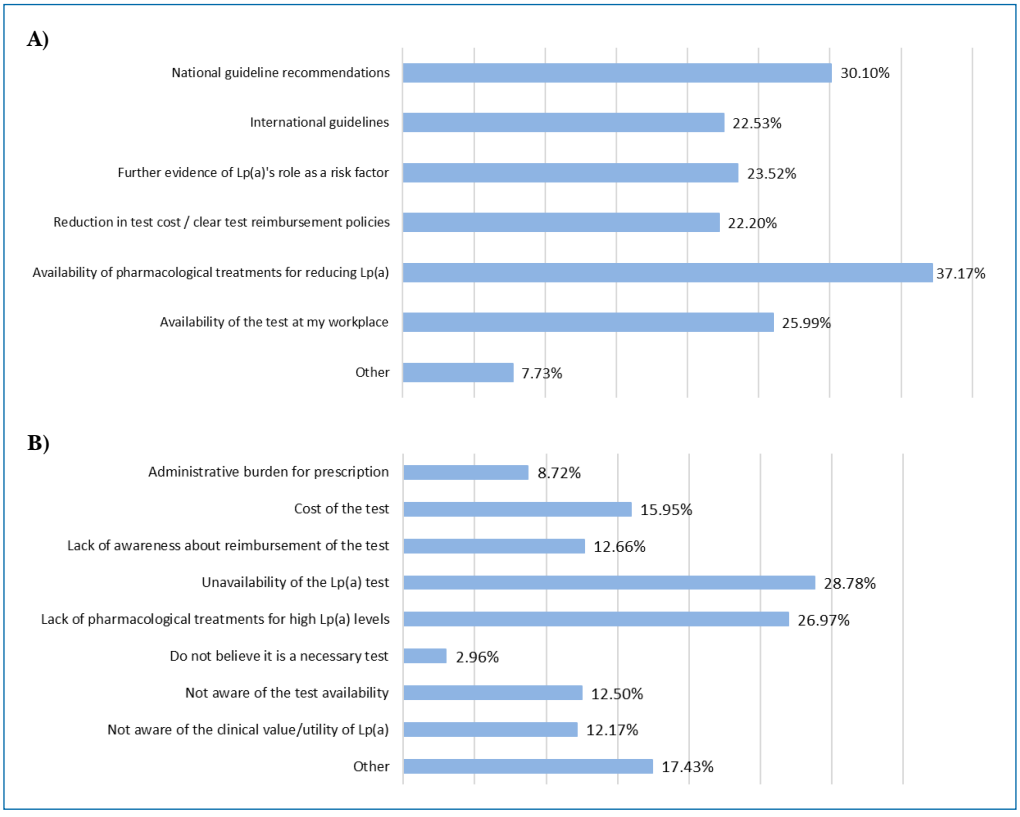

Figure 3 | Among clinicians who do not measure Lp(a) in their clinical practice, panel A shows the reasons for not requesting the Lp(a) test, while panel B shows what clinicians think would be necessary to start testing Lp(a) in clinical practice. Clinicians were allowed to provide multiple answers.

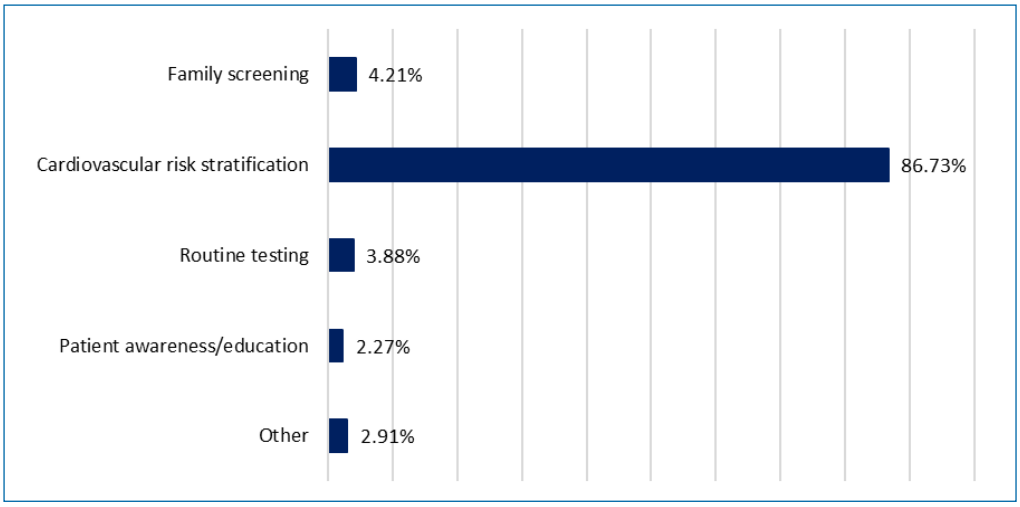

Figure 4 | Additional information for clinicians who regularly measure Lp(a) in their clinical practice. Reasons for requesting an Lp(a) test.

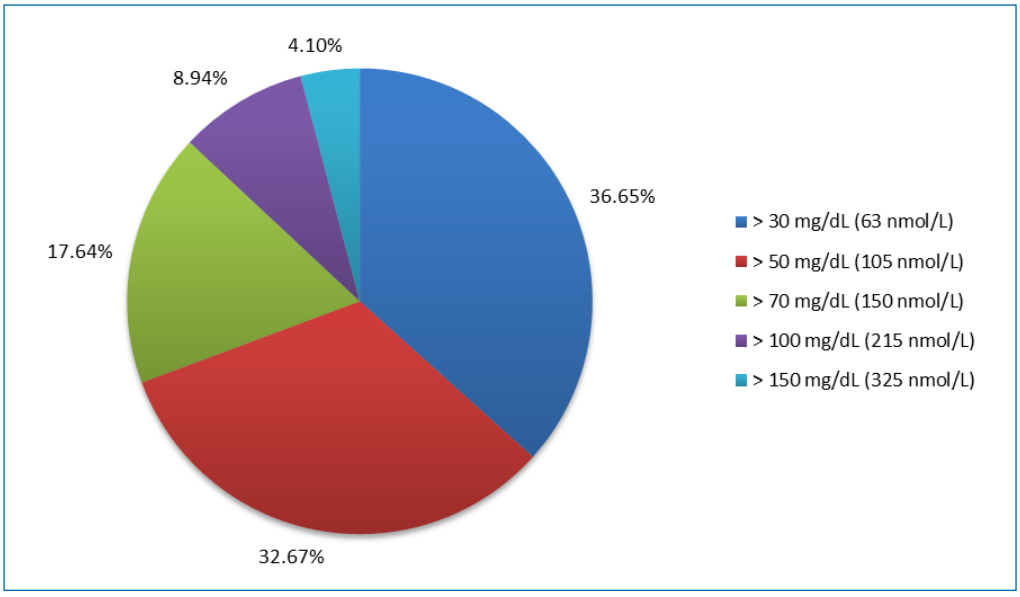

Figure 5 | Proportions of clinicians considering different levels of Lp(a) as high in relation to atherosclerotic cardiovascular disease.

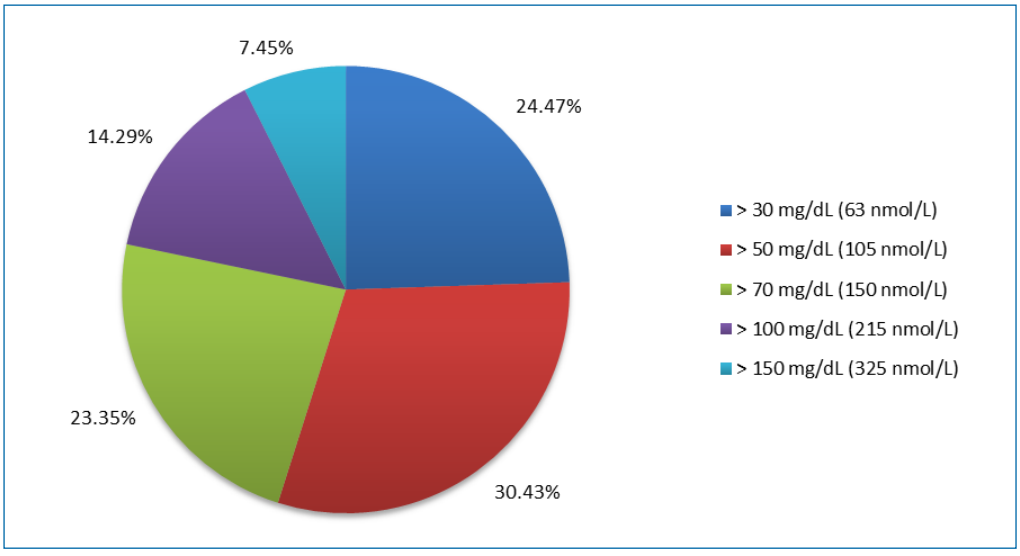

Figure 6 | Proportions of clinicians modifying therapeutic approach based on different levels of Lp(a) in atherosclerotic cardiovascular disease.

recommendations are provided by 37.4% of clinicians. Approximately 20.3% of clinicians refer patients to a colleague specializing in lipid management, and a minority (4.8%) take no action.

Finally, the majority of clinicians (76.4%) reported discussing the Lp(a) test results with the patient, explaining the clinical implications of elevated Lp(a) levels; of these, about 61% also recommend Lp(a) testing for family members. Among clinicians who choose not to discuss these results with patients, one of the most cited reasons is the lack of specific treatment to reduce elevated Lp(a) levels. This concern was highlighted by 40.4% of clinicians, underscoring a significant challenge in managing this biomarker.

Discussion

This survey depicts a detailed overview of clinicians' practices and opinions regarding Lp(a) in the management of ASCVD. The survey involved a broad sample of clinicians from various centres, predominantly those working in territorial and university hospitals. The most common specialization among the participants is cardiology, followed by internal medicine. This reflects a diverse representation of professionals managing patients with cardiovascular diseases, contributing to a comprehensive view of clinical experiences and practices.

One of the key aspects highlighted by the study is the variety of approaches in the measurement and management of Lp(a) among clinicians. While 32.1% of the participants indicated that they regularly measure Lp(a), a significant percentage cited obstacles such as the high cost of tests and the lack of reimbursement as reasons for not regularly performing this test. This evidence confirmed the results of a similar survey on European lipid clinics (12), and underscores the need to improve the accessibility and availability of the Lp(a) test in various clinical settings, especially considering the potential impact of elevated Lp(a) levels on the development of cardiovascular diseases.

Additionally, the variability in thresholds used to define elevated Lp(a) levels among clinicians reflects the lack of clear consensus in clinical guidelines (13). Most of the physicians who participated in this survey tend to consider lower levels (above 30 mg/dL or 50 mg/dL) as indicative of high risk, reflecting greater caution in identifying patients at risk of atherosclerotic cardiovascular disease. This may suggest a growing awareness of the importance of monitoring relatively low levels of Lp(a) as part of cardiovascular risk management and presents an opportunity to develop standardized criteria that can guide a more uniform and evidence-based management of patients with elevated Lp(a) levels.

The survey results on clinicians' management of elevated Lp(a) levels are particularly interesting. These data indicate that the prevailing strategy among clinicians to manage elevated Lp(a) levels involves intensifying lipid-lowering therapy and overall management of cardiovascular risk factors. Lifestyle recommendations are also considered an important component of management. However, a significant portion of clinicians feels the need to consult experts, suggesting that there may be a need for further knowledge or specialist support in this area. The reduced percentage of clinicians who do not take any action suggests a widespread awareness of the importance of addressing elevated Lp(a) levels in the management of cardiovascular diseases (14).

In contemporary medical practice, effective communication of Lp(a) test results plays a crucial role in providing personalized and rational care (15). However, it is interesting to note that some clinicians report not discussing these results with patients primarily due to the lack of a specific treatment to reduce elevated Lp(a) levels. These clinicians likely find it challenging to inform a patient about a risk factor without being able to provide a way to counteract it. This evidence underscores the critical need for medical staff education and updates regarding the currently available alternatives to counteract the increased cardiovascular risk associated with elevated Lp(a) levels. Intensifying the control of other known risk factors is currently the only strategy, and promoting this approach must become an urgent priority for scientific societies to produce and disseminate shared guidelines.

Going forward, integrating Lp(a) measurement into clinical practice is crucial for improving cardiovascular risk stratification and optimizing preventive therapies (16). This study highlights the importance of an integrated and multidisciplinary approach in the management of Lp(a), emphasizing the need for innovations in diagnostic and therapeutic practices to improve the clinical outcomes of patients with cardiovascular diseases. Continuous evolution in research and clinical practice will be essential to effectively address this critical component of cardiovascular pathology.

Authors contributions

EO and ALC were responsible for the study concept and design. SX was responsible for study management and data collection. EO and SX provided methodological knowledge and performed the analysis. MC and ALC contributed to the interpretation of the results. EO and SX wrote the article. ALC and MC critically revised for important intellectual content and approved the final article.

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Conflict of interest disclosures

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Antihypertensive and renal protection effects of lercanidipine and lercanidipine/enalapril

Nicola Ferri[1,2,3], **Alberto Corsini**[3,4], **Roberto Pontremoli**[5]

[1]*Department of Medicine, University of Padua, Padua, Italy*
[2]*Veneto Institute of Molecular Medicine (VIMM), Padova, Italy*
[3]*Centro di Ricerca Coordinata sulle Interazioni Farmacologiche; Milan, Italy*
[4]*Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Milan, Italy*
[5]*Department of Internal Medicine, University of Genoa and IRCCS Ospedale Policlinico San Martino, Genoa, Italy*

Keywords
Hypertension; Calcium channel blocker; lercanidipine; renal protection; combination therapy; angiotensin-converting enzyme inhibitor

ABSTRACT

Systemic arterial hypertension is the second most common cause of end-stage kidney disease (ESKD). Renal protection activity has been demonstrated for angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), gliflozins (dapagliflozin ed empagliflozin) and by the third-generation calcium channel blockers (CCB). Lercanidipine, a third-generation calcium channel blocker, has been shown to have a unique pharmacological and clinical profile, which translates into favorable renal hemodynamic changes. Here we summarized the pharmacological properties of lercanidipine and evaluate its ability to reduce proteinuria and preserve renal function when used as monotherapy or in combination with the angiotensin-converting enzyme (ACE) inhibitor enalapril. The fixed-dose combination lercanidipine/enalapril showed an excellent pharmacological profile with demonstrated clinical efficacy and tolerability in high-risk patients. Lercanidipine can be considered the preferred choice among calcium channel blocker drugs for the treatment of hypertensive patients at risk of renal impairment.

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Introduction

Hypertension is a modifiable risk factor for cardiovascular diseases, including stroke, coronary artery disease, and chronic renal failure [1]. Pharmacologic treatment with several classes of antihypertensive drugs has shown to efficiently reduce the incidence of cardiovascular complications [1]. Despite a clear benefit of treating hypertension, the recent WHO Global report indicated that only 54% of adults with hypertension are diagnosed, 42% receive treatment, and a mere 21% have their hypertension controlled [2]. Low treatment adherence, due to safety profile of drugs and multiple daily prescriptions, certainly contribute to this unmet clinical need [1]. Accordingly, the use of fixed-dose combination therapy has been recommended by the European Society of Hypertension (ESH) Guidelines, also as starting treatment for patients at high cardiovascular risk who are unlikely to be controlled with monotherapy [1].

Combination treatment has at least three potential advantages:

1) additive antihypertensive efficacy due to complementary mechanism of action;
2) lower incidence of side effects thanks to the lower doses of drugs administered;
3) higher adherence because of easier therapeutic schedules. Among the various combinations available, CCBs and angiotensin-converting enzyme (ACE) inhibitors have proven effective and good tolerability [1].

The heart, kidney, brain, and arterial blood vessels are prime targets of uncontrolled hypertension that may result in eventual organ failure and cardiovascular death and disability [3]. Systemic arterial hypertension is the second most common cause of end-stage kidney disease (ESKD) after diabetic nephropathy, and in patients with type 2 diabetes is a major contributor of the progression of kidney damage [4]. Pathophysiological studies suggest that kidney damage results from uncontrolled autoregulatory mechanisms aimed at preventing the transmission of elevated blood pressure (BP) to renal microvascu-

Corresponding Author
Nicola Ferri: nicola.ferri@unipd.it

lature [5, 6]. Indeed, the autoregulatory vasoconstriction of the afferent arteriole prevents the transmission of systemic hypertension to glomerular microvasculature, thus maintaining constant renal blood flow and the intraglomerular pressure. This physiological mechanism preserves the glomerular filtration rate (GFR) and reduces the hypertensive renal damage [7]. However, long-term hemodynamic stress leads to the development of atherosclerotic changes of intrarenal resistance arteries and benign nephrosclerosis which interfere with protective mechanisms of renal protection. This pathological condition is frequently associated with a reduction in renal mass, both in diabetic and nondiabetic patients affected by chronic kidney disease (CKD), that accounts for their increased susceptibility to progressive glomerulosclerosis even with a moderate increase in systemic BP. Controlled BP, with target values depending to the risk profile of the patients, is essential for a proper cardiovascular and renal protection [8].

The renal effects, determined as antiproteinuric action, has been determined to be more potent with ACE inhibitors or angiotensin receptor blockers (ARBs), and more recently by gliflozins [9, 10], compared with first- or second-generation CCBs, likely because these latter agents cause a preferential dilation of the glomerular afferent arteriole, with only modest action on the efferent arteriole [11, 12]. Differently, the third generation CCB seems to act more effectively on both post- and pre-glomerular vessels [13, 14]. Among these, lercanidipine has been shown to protect smaller renal vessels from hypertensive damage by dilating afferent and efferent renal glomerular arteries [11].

To provide optimal blood perfusion to the kidney, the ideal drug should effectively lower systemic BP and positively impact glomerular hemodynamics [15]. The complementary mechanisms of action of CCB and ACE inhibitors provides an effective antihypertensive action with a low rate of side effects. Results from the ACCOMPLISH trial have demonstrated the advantage of the CCB-ACE inhibitor combination in managing cardiovascular (CV) risk in obese and hypertensive patients [16].

The fixed-dose combinations of lercanidipine 10 mg and enalapril 10 or 20 mg have been available in some European countries since 2006 [17].

This review will focus on the pharmacological and clinical profiles of lercanidipine and lercanidipine/enalapril combination and their renal effects on arterial hypertension.

Pharmacological properties of Lercanidipine

Lercanidipine is a third generation dihydropyridine CCB (DHP-CCB) with elevated lipophilicity having a positive value of repartition coefficient (LogP) equal to 6.42 and significantly higher than other CCBs. The lercanidipine has one chiral carbon atom and similarly to other asymmetric DHP the antihypertensive action mainly derives from its (S)-enantiomer (**Figure 1**).

Lercanidipine, like the other CCBs, acts from the inner side of the cell membrane and bind more effectively to L-type calcium channels in depolarized membranes. Binding of the drug reduces the frequency of opening in response to depolarization resulting in a marked decrease in transmembrane calcium current, and thus long-lasting smooth muscle cell relaxation. This vascular effect is responsible for antihypertensive effect of the drug. More in details, the high lipophilicity of lercanidipine facilitate its binding to the membranes phospholipids prolonging its interaction with the L-type calcium channel and the duration of action compared to other DHPs [18, 19]. The high vascular selectivity of lercanidipine determine a minor cardiac negative inotropic effect compared to amlodipine and nifedipine [19]. A second layer of differentiation between lercanidipine and other DHP-CCBs is represented by its blocking activity on both the

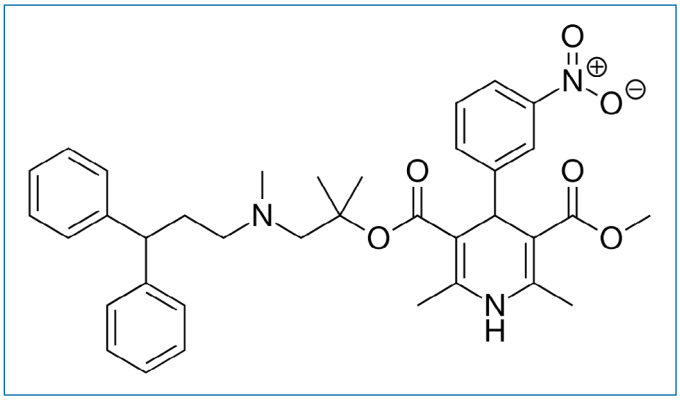

Figure 1 | Chemical structure of lercanidipine.

L-type and T-type calcium channels, with the first mainly expressed in the afferent arterioles and the second on both afferent and efferent arterioles (**Figure 2**). This dual action determines the dilation of both the afferent and the efferent glomerular arteries, with no changes in intraglomerular capillary pressure [20, 21].

Similar to lercanidipine, amlodipine has been shown to inhibit T-type calcium channels in efferent glomerular arteries [22, 23], while lacidipine is more selective on L-type and mibefradil (not more available for clinical use) is a specific T-type blocker (**Figure 3**) [24].

Pharmacokinetic properties

Absorption

Lercanidipine, after oral administration, is completely absorbed by the gastrointestinal tract although its absolute bioavailability is relatively low (10%) due to an extensive first-pass metabolism in the liver. Under fasting condition its oral absorption is reduced to 1/3, thus lercanidipine should be administered in the presence of high-fat meals. The peak of plasma concentration is reached 1.5-3 hours after oral administration at doses of 10-20 mg (T_{max}, **Table 1**). A similar pharmacokinetic profile has been shown for the two enantiomers, although the C_{max} and AUC (area under the curve) are, on average, 1.2-fold higher for the (S) enantiomer [25].

Distribution

Lercanidipine is highly bound to serum proteins (>98%), and the free fraction is rapidly and extensively distributed from plasma to peripheral tissues. In patients with severe renal or hepatic dysfunction it is expected to have a significantly higher concentration of free lercanidipine due to lower plasma protein concentration [26].

Biotransformation

Lercanidipine is mainly metabolized by CYP3A4 to inactive metabolites, and no parent drug is found in the urine or the feces. Approximately 50% of the dose is found in the urine [26].

Elimination

Lercanidipine undergoes to a biphasic elimination phase with the first with a half-life of 3-5 hours and the second of 10.5 hours. Elimination occurs essentially by biotransformation, and the mean terminal elimination half-life has been calculated to be 8-10 hours. Differently, the therapeutical activity lasts for 24 hours due to its high lipophilicity and binding to the cell membrane. No accumulation has been observed after repeated administration [26]. The elimination

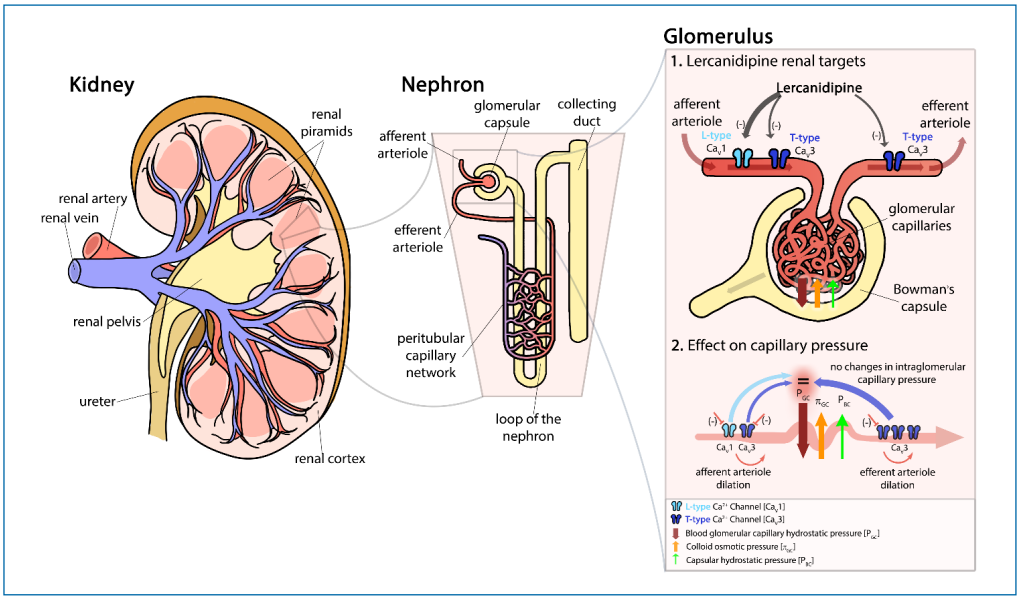

Figure 2 | Schematic representation of the localization of calcium channels (L and T) on afferent and efferent glomerular arterioles. Lercanidipine has shown to block L-type channel expressed on afferent arteriole and T-type channel present on both afferent and efferent arterioles. Source: Marbach *et al.* 2019 [40].

half-lives are superimposable, and no *in vivo* interconversion of enantiomers has been observed.

After oral administration, the plasma levels of lercanidipine are not directly proportional to the dose with a C_{max} ratio equal to 1:3:8 at the doses of 10, 20, or 40 mg, respectively. Even more pronounced saturation of first-pass metabolism was observed on AUC ratios, equal to 1, 4 and 18 for doses of 10, 20 and 40 mg of lercanidipine. Accordingly, the bioavailability increases with the dose (**Table 1**) [26].

Drug-Drug interactions

Preliminary *in vitro* data indicated that lercanidipine may inhibit both CYP3A4 and CYP2D6 activities. However, this effect has been observed at concentrations more than 40-fold higher than those reached in the plasma after administration of 20 mg of the drug.

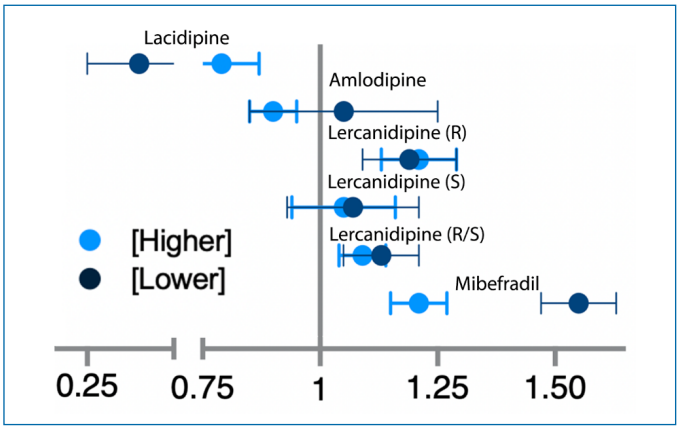

Figure 3 | Ratio of the inhibitory potencies of CCBs on L-type vs. T-type channels. High and low drug concentrations were: 1 or 10 µM for amlodipine and lercanidipine; 0.1 or 1 µM for lacidipine; 3 or 10 µM for mibefradil. Value above 1 (right side of the plot) means that the drug is more selective for T-type than L-type channel. A ratio below1 (left side) indicates selectivity for than L-type channel. Source: Cerbai *et al.* 2018 [24].

Indeed, pharmacokinetic studies in humans demonstrated that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or metoprolol, a substrate of CYP2D6 [27]. Thus, lercanidipine is not predicted to alter the pharmacokinetics of drugs metabolized by CYP3A4 and CYP2D6.

On the other hand, lercanidipine is extensively metabolized by CYP3A4, such that ketoconazole (strong CYP3A4 inhibitor) increased the C_{max} of lercanidipine by eight folds and the AUC by 15 folds [27]. Similarly, ciclosporin, another strong CYP3A4 inhibitor, increased lercanidipine plasma levels by 3-fold when given concomitantly [27]. Thus, other inhibitors of this enzyme, such as itraconazole, erythromycin, and grapefruit juice, are expected to increase plasma concentrations of lercanidipine and thus amplify the antihypertensive effect [27]. Conversely, CYP3A4 inducers, such as carbamazepine, rifampicin, and St John's wort, are expected to lower the exposure and the effectiveness of lercanidipine. Thus, lercanidipine should be avoided with strong CYP3A4 inhibitors and inducers.

Importantly, metoprolol, by reducing the hepatic blood flow, reduced the bioavailability of lercanidipine by 50% [26, 28]. Consequently, lercanidipine may be safely administered with β-adrenoceptor

Table 1 | Pharmacokinetic parameters of lercanidipine.

Parameters	Assessment
Bioavailability	10% (due to first-pass effect)
Gastrointestinal absorption	100%
T_{max}	1.5-3 hours
Protein binding	>98%
Volume distribution	>2 L/kg
Metabolism	Mainly CYP3A4
Elimination half-life	8-10 hours
Duration of action	>24 hours
Excretion	In the urine, 50%

Source: Barchielli *et al.* [26].

blocking drugs, but dose adjustment may be required. On the other hand, lercanidipine does not interact with diuretics and ACE inhibitors.

Differently from other DHP-CCBs, lercanidipine increased the AUC of simvastatin and its active metabolite β-hydroxyacid increased by 56% and 28%, respectively. However, these changes are considered not clinically relevant.

Special Populations

In elderly subjects and patients with mild to moderate renal and hepatic impairment, the pharmacokinetic profile of lercanidipine was similar to that of healthy controls. In patients with severe hepatic impairment, the systemic exposure of lercanidipine is expected to be increased [26]. Patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the drug, and the dosage should be reduced to avoid high plasma concentrations [26].

Importantly, lercanidipine pharmacokinetics is unaffected by carvedilol in hypertensive patients with estimated glomerular filtration rate [eGFR] categories G3b to G5 ranging from 12 to 38 mL/min/1.73 m² (mean 26.5), thus supporting the rationale for its renal protection use [26].

Pharmacodynamic properties

Lercanidipine has a prolonged antihypertensive activity and is devoid of negative inotropic effects due to its high vascular selectivity [19]. The high lipophilicity of lercanidipine provides a slow onset of action, long-lasting smooth muscle relaxation, and peripheral vasodilation [19]. These findings show that lercanidipine is a long-acting CCB allowing for once-daily administration.

Due to the gradual vasodilatation induced by lercanidipine, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients. In addition, differently from verapamil and diltiazem, lercanidipine, like the other DHP-CCB, does not act on calcium channels in the atrioventricular node, and therefore, does not decrease heart rate [29].

Renal protection of lercanidipine: experimental evidence

In a preclinical model of hypertensive rats, the treatment with lercanidipine induced a vasodilation of both afferent and efferent arterioles of the renal microvessels (**Table 2**)[20]. Lercanidipine

Table 2 | Measures of afferent and efferent arterioles in Wistar-Kyoto normotensive and spontaneously hypertensive rats upon different treatments.

Arteriole	WKY untreated	SHR untreated	SHR lercanidipine
Afferent arteriole			
Lumen area, μm²	79.2±5.7	63.6±2.3*	79.1±3.4†
Wall area, μm²	91.6±4.5	96.6±5.1	91.1±5.2
Wall/lumen ratio	1.18±0.04	1.51±0.03*	1.16±0.07†
Efferent arteriole			
Lumen area, μm²	60.2±2.8	50.5±3.1*	60.0±3.3†
Wall area, μm²	121.4±5.1	146.2±6.7*	140.2±5.3*
Wall/lumen ratio	2.03±0.06	2.93±0.08*	2.37±0.12*†

Lumen and wall areas in afferent and efferent glomerular arterioles of Wistar-Kyoto normotensive (WKY) and spontaneously hypertensive (SHR) rats, measured by quantitative image analysis, either exposed to antihypertensive drugs or not exposed.
*p<0.05 vs. WKY, †p<0.05 vs. SHR. Source: Sabbatini et al. [20].

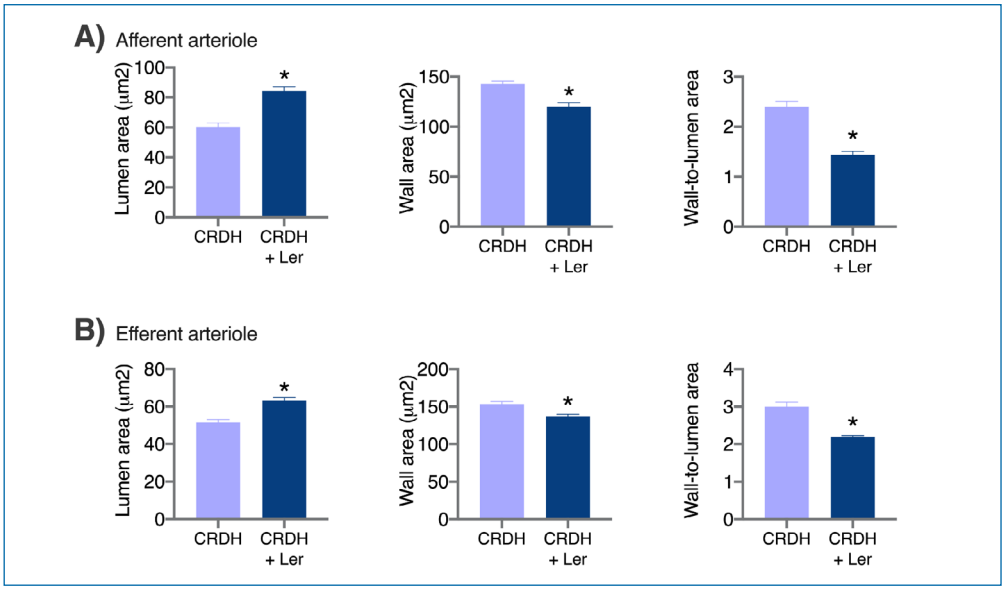

Figure 4 | Effect of lercanidipine on glomerular arterioles morphology in Cohen-Rosenthal Diabetic-Hypertensive Rats. CRDH = Cohen-Rosenthal diabetic-hypertensive rats; LER = lercanidipine. *p<0.05 vs CRDH. Source: Rosenthal *et al.* 2007 [30].

Table 3 | Clinical studies on the renal effects of lercanidipine as monotherapy or as an add-on on ACE inhibitors/ARBs.

Author (Ref.)	Study	Patients (n)	Treatments	Follow-up	Outcome
Dalla Vestra (2004) [34]	DIAL	277	Lercanidipine 10/20 mg *vs.* ramipril 5/10mg	9-12 months	AER: -17.4 *vs.* -19.7 µg/min
Robles (2005) [36]	ZAFRA	203	Lercanidipine 10mg + ACE-inhibitor or ARB	6 months	SBP/DBP: -30.4/-15 mmHg Prot: -0.7 g/die (-20%)
Robles (2010) [37]		68	Lercanidipine 20 mg + ACE-inhibitor or ARB	6 months	SBP/DBP: -17/-9 mmHg Prot: -0.54 g/day (-33%)
Robles (2016) [35]	RED LEVELS	35	Lercanidipine 10-20 mg + ACE-inhibitor vs Amlodipine 5 mg + ACE- inhibitor	12 months	Greater albuminuria reduction -329.0 mg/24 h at 12 months follow-up with Lercanidipine/ enalapril vs. amlodipine/enalapril combo (p=0.0011)

Prot = changes in proteinuria (g/24h); AER = changes in albumin excretion rate (µg/min). ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blocker; AT-II, angiotensin-II. SBP, systolic blood pressure; DBP, diastolic blood pressure (mm/Hg).

administration prevented wall thickening and luminal narrowing in small-sized arteries and glomerular arterioles of Cohen-Rosenthal diabetic hypertensive rats (**Figure 4**) [30].

These results could have relevant clinical implications. It is well established that traditional DHP-CCBs, including amlodipine, act predominantly on L-type calcium channels. The vasodilator response to L-type CCBs is observed only in afferent preglomerular microvessels with no effect on efferent arterioles in the renal vasculature. This determines an increase in glomerular capillary and intraglomerular pressure, proteinuria, and renal damage. Conversely, lercanidipine, by vasodilating both the afferent and the efferent arterioles of the renal microvessels [11], may correct glomerular hypertension and could therefore exert protective actions on the progression of renal injury.

In nephrectomized spontaneously hypertensive rats (SHR), lercanidipine has been shown to reduce BP, prevent renal injury progression, and ameliorate histopathological changes and serum creatinine levels with a significantly reduced significantly proteinuria [23]. A similar renal protection effect by lercanidipine was observed in a double-transgenic rat model overexpressing human renin and angiotensinogen genes associated to a reduction in mortality induced by angiotensin II [31].

Renal Protection with Lercanidipine and Lercanidipine/Enalapril Combination: Clinical Studies

The third generation of CCB decreased glomerular pressure, the filtration fraction and proteinuria, with a nephroprotective effect similar to that exerted by inhibitors of the renin angiotensin-aldosterone system (RAAS) [12]. The combination of these agents should provide complementary effects since CCBs and RAAS inhibitors do not share the same mode of action.

CCBs are potent vasodilators that induce an autonomous activation of the sympathetic system and the RAAS system that can be dampened by ACE inhibitors. Further, CCBs promote a negative sodium balance and an increase in angiotensin II levels, and for this reason, the inhibition of ACE may reinforce the antihypertensive effect. The concomitance of both treatments may reduce the incidence of adverse events, particularly peripheral edema, indeed ACE inhibitors reduce the lower extremity edema caused by CCBs, likely because of their ability to dilate both the arterial vascular bed and the venous capacitance vessels [32]. Thus, lercanidipine in fixed combination with enalapril has a strong rationale for controlling hypertension and hypertension-associated renal damage.

Several clinical studies have investigated the renal protective effect of lercanidipine or lercanidipine/enalapril (**Table 3**). In the DIAL study, patients with type 2 diabetes, mild to moderate hypertension, and persistent microalbuminuria were randomized to receive either lercanidipine (10-20 mg/day) or ramipril (5-10 mg/day) [33]. After a follow-up of 9-12-months, lercanidipine reduced urine albumin excretion rate to the same extent as ramipril (-17.4±65 µg/min, $p<0.05$ and -19.7±52.5 µg/min, $p<0.05$) [33]. The effect of lercanidipine as monotherapy or in combination with RAAS inhibitors has also been investigated in patients with CKD and/or albuminuria [34-36]. Robles *et al.* investigated the renal protective effect of lercanidipine (10 mg/day) in patients with CKD and uncontrolled BP levels already in treatment with either ACE inhibitors or ARB [35]. Overall, 175 patients with CKD and higher than recommended BP were evaluated (63% on ACE inhibitors and 37% on ARB). Over a 6-month follow-up period, lercanidipine further reducing BP (systolic BP from 162 to 132 mm Hg, diastolic BP from 93 to 78 mm Hg) alongside proteinuria (from 3.5 to 2.8 g/

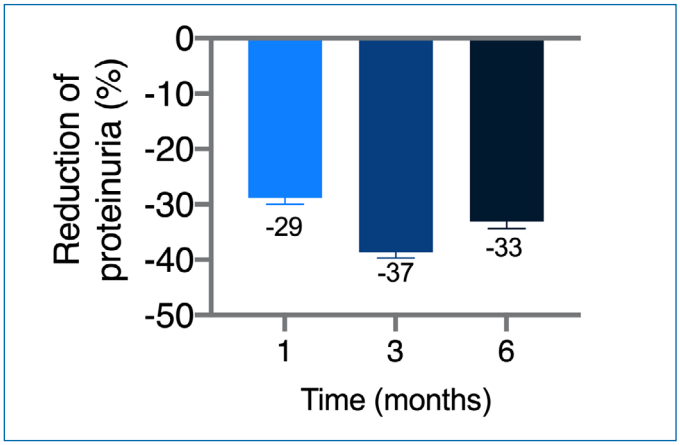

Figure 5 | Percentage reduction in proteinuria after 1, 3 and 6 months of treatment with lercanidipine 20 mg/day, in addition to ACE-inhibitors or ARB, in previously uncontrolled hypertensive patients with CKD. P<0.001 for all values. Source: Robles *et al.* 2010 [36].

day) [35]. Plasma creatinine levels were not affected by the treatment while its clearance increased (41.8±16 at baseline *vs.* 45.8±18 mL/min after 6 months, p=0.019) [35]. The same group reported a similar open label study in 68 hypertensive patients with CKD [36]. Patients already receiving an ARB or an ACE inhibitor without attaining target BP levels were further treated with lercanidipine (20 mg/day) as add-on therapy and followed-up for 6 months. Although systolic and diastolic BP were reduced (from 152/86 mmHg at baseline to 135/77 mmHg after 6 months, with a mean reduction -16.8/-9.3 mmHg) to a lesser extent than in the ZAFRA study [35, 36], proteinuria was reduced by lercanidipine almost twofold, with a dose-response effect, which seems partially to be independent of BP changes [34]. Basal proteinuria was 1.63±1.34 g/day, and it was reduced by 23% in the first month, 37% at 3 months, and 33% at 6 months (p<0.001 at all-time points) (**Figure 5**). In addition, creatinine clearance did not significantly change after lercanidipine treatment (43.5±10.6 *vs* 44.0±1.0 mL/min) [36]. This renoprotective, anti albuminuric could be due to the activity of lercanidipine on glomerular hemodynamics and to other effects, such as inhibition of mesangial cell proliferation and effects mediated by endothelin, antioxidant effects linked to increased nitric oxide synthase activity [36].

Finally, the effects of lercanidipine/enalapril and amlodipine/enalapril combinations were directly compared in a 12-month, prospective, multi-center, randomized, open-label, blinded-endpoint study conducted on hypertensive patients with albuminuria (RED LEVEL and PROBE study) [34, 37]. Over time, albuminuria was significantly reduced, compared with baseline values, only in the lercanidipine/enalapril treated arm [changes from baseline were: -162.5 (p=0.04), -425.8 (p=0.001), -329.0 (p=0.001) mg/24 h, at months 3, 6 and 12, respectively]. However, it was not significantly changed in patients treated with an amlodipine/enalapril combination. Changes in blood hypertension values were significant for both therapy regimens, without differences [34, 37]. Thus, while ACE inhibitors and ARBs remain first-line antihypertensive drugs in CKD patients, as stated by 2021 KDIGO guidelines [38]. We believe that the above-mentioned studies suggest a potential for further renal protection by lercanidipine especially in combination treatment.

Expert Opinion

Beyond BP reduction efficacy of different classes of antihypertensive drugs, their effect on end-organ protective properties (both cardiovascular and renal) can be distinguished. CCBs have traditionally been considered as powerful antihypertensive agents but less effective than RAAS inhibitors and gliflozins in long-term kidney function preservation. Lercanidipine is a third generation CCB that shows a unique pharmacological profile, different from first- and second-generation. This drug shows a prolonged antihypertensive activity and is devoid of negative inotropic effects due to its high vascular selectivity [19]. It is an effective and safe antihypertensive drug and can be used in special populations including elderly, diabetics, and patients at renal damage risk [26]. Lercanidipine is highly lipophilic and inhibits both L and T types of calcium channels eliciting a direct dilation on both afferent and efferent glomerular arteries, preserving the intraglomerular pressure. This activity translates into favourable renal hemodynamic changes, also in monotherapy, and may provide a clinical benefit superior to other CCBs which showed protective effect only when administered in combination with an ACE inhibitor or an ARB.

The effect of lercanidipine on proteinuria seemed to be dose-dependent and was not correlated with the antihypertensive activity [32, 33]. Renal protection with a significant decrease of micro-albuminuria and improvement of creatinine clearance was demonstrated in patients with diabetes and CKD, representing a population at high risk of organ damage. Alone or in combination with ACE inhibitors, lercanidipine has been shown to provide renal vascular protective effects in the experimental setting and reduce proteinuria in clinical studies. The reno-protective and anti-albuminuric effect of lercanidipine could be due to its specific action on glomerular hemodynamics and others, such as the inhibition of mesangial cell proliferation, inhibition of endothelin-mediated renal effects, and increased nitric oxide synthase activity, which has been shown to lead to antioxidant effects [34, 36]. The reduction of oxidative stress obtained by administration of lercanidipine was associated to inhibition of vascular neointimal and smooth muscle cell proliferation and cholesterol accumulation [39]. As lercanidipine is well tolerated and is associated with a low risk of ankle edema, it may be considered a safe tool for hypertension control in subjects with a high risk of kidney damage.

Conclusions

Lercanidipine is an effective and safe antihypertensive treatment and can be used in patients at renal damage risk. Studies in hypertensive patients with diabetes or CKD demonstrated protective effects on the kidneys due to the capability of lercanidipine to dilate the afferent and efferent glomerular arteries and preserving the intraglomerular pressure. Notably, lercanidipine has been shown to reduce proteinuria, a peculiar effect in the CCBs class and a recognized risk factor for CV events in hypertensive patients. This peculiarity was confirmed by a direct comparison trial where proteinuria was reduced by the combination lercanidipine/enalapril but not by amlodipine/enalapril [34]. Indeed, it is possible that the vasodilatory effect of lercanidipine of afferent arteriole may avoid the reduction of filtration fraction due to RAAS blockers because of efferent arteriole vasodilation. However, RED LEVEL represents the only head-to-head comparison study among different CCBs in terms of renal protection [34]. Thus, one should exert great caution when drawing conclusions on long-term renal safety with different CCBs. Nonetheless, based on data discussed in the present manuscript, lercanidipine because of its peculiar intrarenal mechanisms of action, as well as its proven ability to reduce albuminuria, could be the ideal CCB to be used in hypertensive patients at renal risk.

Conflict of Interest

The authors have received a honorarium from Recordati Ireland LTD; A.C. received honoraria from AstraZeneca, AMGEN, Sanofi, Novartis, MSD, Mediolanum, DOC, Mylan and Pfizer. N.F received honoraria from Pfizer, Amgen, Relmada Therapeutics, and Pharmanutra. R.P. received speaker fees and/or advisory boards from AstraZeneca, Boehringer-Ingelheim, Menarini, Eli-Lilly, MSD, Novo- Nordisk, and Alfasigma.

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SMASH: An initiative for equitable access to precision medicine for rare or severe lipid disorders

Miriam Larouche[1], Marianne AbiFadel[2], Alberico L. Catapano[3,4], Marina Cuchel[5], Raul D. Santos[6,7], Frederick J. Raal[8], Daniel Gaudet[1]

[1]*Université de Montréal, Departement of Medicine, Montreal, Canada and ECOGENE-21 Clinical Trial Center, Chicoutimi, Canada*
[2]*Laboratory of Biochemistry and Molecular Therapeutics (LBTM), Faculty of Pharmacy, Pôle Technologie-Santé, Saint Joseph University of Beirut, Beirut, Lebanon*
[3]*IRCCS Multimedica, Milano, Italy*
[4]*University of Milan, Italy*
[5]*Division of Translational Medicine and Human Genetics, University of Pennsylvania, Philadelphia, USA*
[6]*Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil*
[7]*Academic Research Organization, Hospital Israelita Albert Einstein, Sao Paulo, Brazil*
[8]*University of the Witwatersrand, Division of Endocrinology and Metabolism, Faculty of Health Sciences, Johannesburg, South Africa*

Keywords
Access;
equity;
rare diseases;
lipid disorders;
SMASH

ABSTRACT

Background: Despite significant improvements in our knowledge of rare or severe dyslipidemias, barriers to access are gradually emerging. SMASH (System and Molecular Approaches of Severe Hyperlipidemia) is a global initiative with the goal of making precision medicine innovations available without discrimination for patients affected by rare or severe dyslipidemias.

Objectives: SMASH main objective is to facilitate access to accurate diagnosis and optimal treatment for patients affected by rare or severe lipid disorders.

Overview: SMASH is an international initiative comprising five interrelated components: SMASH-Access, -Natural History, -Trials, -e-Share, and -Biorepository. SMASH has selected as templates four severe lipid disorders that have in common the accelerated development of precise diagnosis and the emergence of innovative treatments that represent equity challenges. Access issues are broad and not limited to clinical or socio-economic factors.

Summary: SMASH is developed to conceive and support initiatives that might improve our understanding of rare or severe dyslipidemias and facilitate access to innovation.

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Introduction

Rare diseases are often ignored, and in different parts of the world many patients have little access to accurate diagnosis or effective treatments. There are 25 dyslipoproteinemias listed in the latest European Atherosclerosis Society (EAS) task force consensus statement on rare dyslipidemias [1] to which other rare or severe disorders can be added including elevated Lipoprotein(a) [Lp(a)], lipid storage diseases, primary lipodystrophies (complete or partial), glycerol kinase deficiency, severe causes of MASLD/MASH (metabolic dysfunction-associated steatotic liver disease/steatohepatitis) and non-monogenic persistent chylomicronemia (**Table 1**).

The last decades have been characterized by the Omics era which has led to a huge improvement in our understanding of the biological basis of diseases, the development of genetic testing, and refinement of disease management, with the emergence of new therapeutic targets, biodrugs, and delivery systems covering a wide range of unmet needs in lipidology. Despite their clinical importance, these improvements could lead to multiple equity concerns and barriers to access globally, particularly in low-middle-income countries or remote regions. The issues are diverse and important, covering (among others) access to a precise diagnosis, the challenge of transport and conservation of biodrugs, and issues of

Corresponding Author
Daniel Gaudet: daniel.gaudet@umontreal.ca

Table 1 | Partial List of Rare and Severe Lipid Disorders.

Lipid Disorder	Inheritance	Main Deleterious Consequences	Currently treatable	Emerging Therapies in Development
↑ LDL-cholesterol				
Homozygous familial hypercholesterolemia	ASD	ASCVD	Partly	Yes
Sitosterolemia	AR	ASCVD	Yes	No
Atypical dominant hypercholesterolemia	AD	ASCVD	Yes	Yes
Lysosomal acid lipase deficiency	AR	Multisystemic Liver failure	Partly	Yes
Lysosomal storage diseases (eg. Niemann-Pick)	AR	Multisystemic	Partly	Yes
Extreme Lp(a)	ASD-like	ASCVD Aortic stenosis	No	Yes
↓ LDL-cholesterol or ↓ Triglycerides				
Abetalipoproteinemia	AR	Fat-soluble vitamins deficiency	Yes	No
Homozygous hypobetalipoproteinemia	ASD	None	N/A	No
Chylomicron retention disease (Anderson disease)	AR	Fat-soluble vitamins deficiency	Yes	No
Familial combined hypolipidemia (ANGPTL3 deficiency)	ASD	None	N/A	No Target for drug development
PCSK9 deficiency	ASD	None	N/A	No Target for drug development
Apolipoprotein C-III deficiency	AR	None	N/A	No Target for drug development
↑ Triglycerides				
LPL deficiency	AR	AP Possibly ASCVD	Partly	Yes
Apolipoprotein C-II deficiency	AR	AP Possibly ASCVD	Partly	Yes
Apolipoprotein A-V deficiency	AR	AP Possibly ASCVD	Partly	Yes
Lipase maturation factor 1 deficiency	AR	AP Possibly ASCVD	Partly	Yes
GPIHBP1 deficiency	AR	AP Possibly ASCVD	Partly	Yes
Non-monogenic persistent chylomicronemia	Complex	AP Possibly ASCVD	Partly	Yes
Infantile hypertriglyceridemia, transient	AR	Abdominal pain AP	Yes	No
Dysbetalipoproteinemia	Complex	ASCVD (mainly peripheral)	Yes	Yes
Glycerol kinase deficiency	X-linked	Pseudo-hypertriglyceridemia Glucose intolerance	Comorbidities	No
Primary lipodystrophy (Generalized, partial)	AD or AR	ASCVD AP Multisystemic	Comorbidities	Yes
↓ HDL-cholesterol				
Tangier disease (ABCA1 deficiency)	AR	ASCVD	Partly	No
Apolipoprotein A-I deficiency	AR	ASCVD	Partly	Yes
LCAT deficiency (fish-eye disease)	AR	Multisystemic Corneal opacity	Partly	Yes
Familial LCAT deficiency	AR	Multisystemic Renal disease	Partly	Yes

Lipid Disorder	Inheritance	Main Deleterious Consequences	Currently treatable	Emerging Therapies in Development
↑ HDL-cholesterol				
Genetic cholesteryl ester transfer protein deficiency	ASD	Age-related macular degeneration	Comorbidities	No Target for drug development
Scavenger receptor B1 deficiency	ASD	ASCVD? Female fertility issues?	Comorbidities	Yes
Hepatic lipase deficiency	AR	ASCVD	Partly	No
Others				
Lipid storage diseases (several)	Variable	Multisystemic	Partly	Yes
Metabolic dysfunction-associated steatohepatitis (MASH)	Complex	ASCVD Cirrhosis – hepatocellular carcinoma	Yes Comorbidities	Yes

ABCA1: ATP-binding cassette A1, AD: Autosomal dominant, ANGPTL3: Angiopoietin-like protein 3, AP: Acute pancreatitis, AR: Autosomal recessive, ASCVD: Atherosclerotic cardiovascular disease, ASD: Autosomal semi-dominant, GPIHBP1: Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1, HDL: High density lipoprotein, LCAT: Lecithin-cholesterol acyltransferase, LDL: Low-density lipoprotein, Lp(a): Lipoprotein (a) LPL: Lipoprotein lipase, PCSK9: Proprotein convertase subtilisin/kexin type 9.

reimbursement or insurability [2]. Once approved, novel precision therapies developed through clinical trials are often expensive, and their use is regularly restricted. It is therefore necessary to network efforts to document the clinical expression of rare or severe lipid diseases and facilitate access to accurate diagnosis and effective, safe, and affordable therapies.

SMASH (System and Molecular Approaches of Severe Hyperlipidemia) is a global initiative with the goal of making health and precision medicine innovations available without discrimination for patients affected by rare or severe lipid disorders.

SMASH objectives

Access is the priority of the SMASH initiative, and all activities are patient-centered and community-centered. The main objective is to facilitate access to accurate diagnosis and optimal treatment for patients affected by rare or severe lipid disorders regardless of where they live, their gender, ethnicity, or socioeconomic status by supporting networks, associations, organizations, patients, clinicians, researchers, and other stakeholders concerned by access issues.

Overview of the smash initiative

SMASH is an international philanthropic initiative comprising five interrelated components described below: SMASH-Access, SMASH-Natural History, SMASH-Trials, SMASH e-Share, and SMASH-Biorepository (**Figure 1**).

SMASH-Access

SMASH-Access aims to globally map hurdles to access to diagnosis and treatment of rare or severe lipid disorders including reimbursement, geographical or geopolitical issues, socioeconomic status, mobility difficulties, lack of specialized clinics, etc. Such mapping will facilitate the identification of countries and collectivities where access is an important issue as well as supporting the networking of clinicians, patients, stakeholders and resources regarding access. SMASH will facilitate the development of initiatives favoring access through the principle of equity and will disseminate information through the SMASH website (e-Share component).

SMASH-Natural History

In order to facilitate access, it is essential to improve our understanding of the natural history of rare and severe lipid disorders. The list of rare lipid disorders and subtypes will be dynamically updated, and those requiring efforts in terms of diagnosis or treatment will be highlighted. SMASH-Natural History will map, support, or launch in-

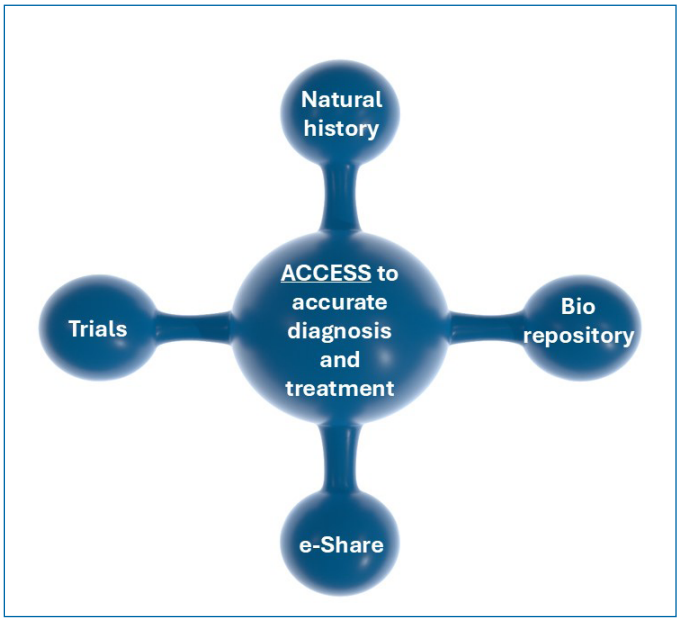

Figure 1 | Description of the components of the SMASH initiative. *SMASH has five components all dedicated to facilitating equitable access to accurate diagnosis and optimal treatment for patients affected by rare or severe lipid disorders. These components are interrelated and cover the needs of better documenting the natural history of lipid disorders, provide access to standardized and decentralized repositories of biosamples, support ongoing initiatives or the conception of investigator initiated clinical studies and disseminate educational material.*

itiatives documenting or targeting the natural history of rare lipid disorders using persistent chylomicronemia, homozygous familial hypercholesterolemia (HoFH), lecithin-cholesterol acyltransferase (LCAT) deficiency and elevated Lp(a) as templates before extending to other diseases. This component also aims to facilitate the acquisition and dissemination of new knowledge acquired via academic research or clinical trials by networking with patients, experts, associations and stakeholders involved in managing rare lipid disorders. Data collected will vary from one disease to another, according to the needs and access issues.

SMASH-Trials

The Trials component conceives, supports, executes, or monitors proof-of-concept, investigator-initiated trials or sub-studies promoting access to innovation and documenting the natural history of diseases or the impacts of interventions. SMASH has the willingness to support inexperienced sites or clinicians in order to manage all aspects of clinical trials, including GCP training, regulatory issues, data management, and remote monitoring. Partnerships with pharma, biotechs, and academic experts will be maintained with the vision of facilitating access to precision treatments where and when needed, based on the principle of equity.

SMASH e-Share

E-Share is a pillar of the SMASH initiative, a virtual platform where all stakeholders can connect. It aims at developing a patient-centered interactive platform connecting key players involved in rare or severe lipid disorders including patients, healthcare providers, researchers, industrial partners, health decision-makers, etc. The platform will also facilitate disseminating existing information and educational material across international networks. SMASH will support the development of new educational material to complement those already available. In order to raise awareness around access to accurate diagnosis and treatments for rare or severe lipid disorders, partners are invited to sign the SMASH declaration (manifesto) on access at www.smash-access.org. Signatures from around the world will be collected and mapped. The declaration will be the voice of patients affected by rare or severe lipid disorders and their relatives, clinicians, researchers, and other stakeholders concerned by access issues. Patients will have the opportunity to participate actively in the SMASH initiative through the e-Share platform which will offer multiple possibilities for patients-driven initiatives. Advocacy groups and patients' associations will also have the opportunity to contribute to a connected knowledge network supporting their efforts in disseminating disease information and awareness.

SMASH Biorepository

SMASH intends to enhance the ability to generate and share new knowledge on rare or severe lipid diseases by supporting national registries and researchers in the development of decentralized biobanking capacities, allowing the standardization and optimization of biosamples storage globally, including in low-middle-income countries and remote regions. The monitoring of storage units and of the samples themselves should be supervised anonymously with high quality standards. A decentralized biobanking approach will foster collaborations between research teams and will help to nurture knowledge acquisition on the natural history and risk trajectory of rare and severe lipid disorders.

Rare disease templates in SMASH

Over the past few decades, the diagnostic and therapeutic offer for rare lipid disorders has evolved rapidly and demand for services has hardly kept pace, which is even more true in remote regions and lower-income economies. Although the issue of equity is becoming increasingly important and central, clinical research has not evolved at the same pace for all diseases, and thus, access issues are not the same for all rare or severe lipid disorders. This is why SMASH has selected as templates four lipid disorders for which there are immediate challenges in terms of access to accurate diagnosis and effective treatments and which also globally represent important equity challenges: HoFH, persistent chylomicronemia, LCAT deficiency, and severely elevated Lp(a). All these severe diseases have in common the accelerated development of precise diagnosis or screening tools and the emergence of innovative treatments. HoFH is a rare condition characterized by the presence of bi-allelic variants in four genes that cause absent or extremely reduced LDL receptor activity (*LDLR, APOB, PCSK9 and LDLRAP1*) and extremely elevated LDL cholesterol (LDL-C) levels, premature atherosclerotic cardiovascular disease (ASCVD), aortic or supra-aortic valve disease, and risk of early death [3]. Persistent chylomicronemia is caused by sustained lipoprotein lipase deficiency (LPLD) or lack of LPL bioavailability. LPLD is associated with the familial chylomicronemia syndrome (FCS), a term that is usually used to describe the monogenic (autosomal recessive) form of LPLD, but this rare disease also has multifactorial causes and is associated with an increased risk of recurrent acute pancreatitis and other morbidities [4]. LCAT deficiency is a rare disease characterized by partial or complete absence of LCAT enzyme activity. LCAT deficiency hampers the maturation of HDL particles and reverse cholesterol transport, thus potentially increasing the risk of ASCVD and can lead to corneal opacification and chronic kidney disease (CKD) in the most severe cases [5]. Elevated Lp(a) is associated with increased risk of ASCVD (including stroke) and aortic valvular disease [6-8]. Many efforts are currently being made to improve the diagnosis and management of these rare and severe diseases.

HoFH. The HoFH International Clinical Collaboration (HICC) is a registry launched in 2016 aiming at creating a formal network of healthcare professionals managing HoFH in order to describe and follow the clinical characteristics of affected patients from around the world. So far, the HICC registry includes nearly 1000 patients from several tens of countries on all continents [9]. LDL receptor independent treatments such as lipoprotein apheresis, evinacumab (ANGPTL3 monoclonal antibody) and lomitapide (MTP inhibitor) have demonstrated great efficacy in reducing LDL-cholesterol in HoFH [10-12]. However, these treatments are expensive and are not available everywhere, and reimbursement can be an issue even in high-income countries. Access to lipoprotein apheresis is often very limited, and many countries do not have the equipment needed [13]. Although genetic testing is still recommended when available and reimbursed, a clinical diagnosis of HoFH is widely accepted and sufficient to prescribe these advanced treatment options, making access to genetic testing a less critical barrier.

Persistent chylomicronemia. Access to accurate diagnosis and effective treatments is also an issue for patients affected by persistent chylomicronemia. All affected patients present sustained lack of LPL bioavailability. However, not all of them carry bi-allelic combination of pathogenic variants in the LPL gene machinery [4]. Since a genetic diagnosis is often required in clinical trials targeting LPLD and FCS, this leads to an equity issue and a dilemma concerning the access to treatment for those with persistent chylomicronemia not carrying bi-allelic combination of pathogenic variants but presenting clinical characteristics of FCS, a term having been specifically used to date to describe patients having a proven pathogenic genetic defect. Clinical diagnosis scoring systems and other strategies can accurately support persistent chylomicronemia diagnosis even in the absence of knowl-

edge of the genetic background [14, 15]. Among emerging or new therapies developed for severe hypertriglyceridemia, apolipoprotein C3 (APOC3) inhibitors (APOC3i) are the most advanced. APOC3i efficiently decreases TG levels even in the absence of available LPL (LPL-independent mechanism). Most APOC3i are sophisticated biodrugs interfering with the APOC3 gene translation, specifically single-stranded antisense oligonucleotides (ASO) or double-stranded small interfering RNA (siRNA) [16, 17]. When approved, these agents might not be easily available or affordable everywhere, particularly in low-middle-income countries [2]. Access might also be initially limited to patients presenting a genetic diagnosis of FCS, although some recent trials include patients presenting clinical features of FCS without carrying bi-allelic pathogenic variants [16]. Access to genetic testing is not evenly distributed across the world and may be limited in many countries. As in the case of HoFH, molecular diagnosis should not be mandatory to make a diagnosis of persistent chylomicronemia or clinical FCS and allow equitable access to treatments for this severe unmet medical need.

LCAT Deficiency. LCAT deficiency is a rare and complex lipid disorder characterized in the most severe cases by chronic kidney disease that progresses to end stage renal disease by the 4th decade of life. Currently, there is no curative treatment, and the management of these patients focuses on controlling the renal symptomatology, with limited success. Some novel agents such as recombinant human LCAT gene, gene therapy and LCAT activators are in development [18, 19]. The biggest regulatory obstacle to the development of novel therapeutic approaches is the poor understanding of the natural history of this condition, that hinders our ability to identify patients that will progress towards CKD or other complications. Access to accurate LCAT deficiency diagnosis and emerging therapies is thus an issue.

Elevated Lp(a). Another SMASH template is severely elevated Lp(a). Strongly genetically determined apo(a) production and plasma concentration of Lp(a) are affected by several factors. The prevalence of elevated Lp(a) (approximately 1 in 5 individuals) varies worldwide and by ethnicity but does not meet rare disease criteria [6]. Patients with elevated Lp(a) values have an increased risk of ASCVD, including coronary artery disease, stroke, and aortic valvular disease [20]. Individuals with Lp(a) levels ≥125 nmol/L are considered at high risk [6], although there is no definite risk threshold or clear cut-off. Extreme values (estimated ≥430 nmol/L) are rarer and have been associated with a 2.5x increased risk of ASCVD independently of LDL-cholesterol in a cross-sectional study [21]. Historically, few agents were effective in decreasing Lp(a), and their efficacy was limited (≤ 25%). This includes niacin, PCSK9, and ANGPTL3 inhibitors among others [22]. Lipoprotein apheresis effectively decreases Lp(a) particle number but is not available everywhere. The emergence of potent apo(a) inhibitors reducing Lp(a) by up to 90% [23-27] will most likely influence medical practice. Although most current guidelines suggest determining Lp(a) at least once in a lifetime, there is a large discrepancy in Lp(a) testing worldwide, and the availability of the test can be an issue in several countries. A recent survey conducted among members of the EAS Lipid Clinic Network in different continents illustrates the lack of consistency in using Lp(a) to assess cardiovascular risk (unpublished data).

Access issues are not limited to clinical or socio-economic factors. Several environmental variables are also contributory. For example, the capacity to optimally store or deliver drugs can be affected by the stability of electricity supply in several low-middle-income countries, as illustrated by the situation in South Africa or in countries at war or armed conflicts. Access to healthcare services is more difficult in remote regions or in some parts of countries that have large sparsely populated territories, for displaced populations or for patients with disabilities.

Conclusion

Identifying and mapping all hurdles to access is only a first step. The second step is to join efforts to facilitate equitable access to accurate diagnosis and optimal treatment for all patients affected by rare or severe lipid disorders. SMASH is developed to conceive, support, or catalyze initiatives that might improve our understanding of rare or severe dyslipidemias and cover the needs of affected patients and healthcare providers from around the world. SMASH will not duplicate ongoing initiatives but will support them when feasible, and promote networking of patients, organizations, healthcare providers, and stakeholders. A system approach and a structured collaborative effort is mandatory to provide fair access to emerging treatments to patients in both developed countries and emerging economies [28].

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The XVIII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS)

Sining Xie[1], Manuela Casula[1,2], Federica Galimberti[2], Alberto Corsini[3], Alberico L. Catapano[1,2]

[1]Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[2]IRCCS MultiMedica, Sesto San Giovanni (MI), Italy
[3]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

CONFERENCE REPORT

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The XVIII National Congress of the Società Italiana di Terapia Clinica e Sperimentale (SITeCS) was held in Milan on October 10-12, 2024. As is now customary, the Congress was organised in collaboration with the Italian Society for the Study of Atherosclerosis (SISA) Lombardy Region. The Congress included the discussion of the most recent evidence or the most topical issues in clinical and pharmacological research as well as presentations of scientific work by young researchers.

The first session on the Pre-Congress Day mainly focused on the new insights from atherosclerotic cardiovascular research. Atherosclerotic plaque formation begins with the accumulation of low-density lipoprotein (LDL) particles in the intima of large arterial blood vessels. Within the intima, LDL particles are oxidatively modified, which renders them immunogenic and triggers an early inflammatory response, including endothelial cell activation. Doctor Lorenzo Da Dalt introduced the role of lysosomes in the interaction between metabolic modulation and immune cell function. Lysosomes are membrane-enclosed organelles that function as metabolic sensors and signalling platforms in the immune-metabolic reprogramming of macrophages and other immune cells in atherosclerosis. Growing evidence indicates that lysosomal dysfunction is one of the hallmarks of lipids accumulation and macrophage activation in the atherosclerotic plaque. He presented the mechanism (restoring lysosomal acidity) and animal experimental data on the use of acidic nanoparticles to treat non-alcoholic fatty liver disease (NAFLD), the impact of lysosomes on adaptive immunity through activating mTORC1 (the mammalian target of rapamycin), as well as the novel pharmacological approaches targeting lysosomes. Next, Doctor Chiara Macchi outlined the effect of mitochondria on driving atherosclerosis. Mitochondria are multifaceted organelles that regulate various important cellular processes including metabolism and ATP generation. Mitochondrial function is required for normal vascular cell growth and function. She began by presenting the results of animal studies, and concluded that mitochondrial dysfunction leads to apoptosis and favours plaque rupture. Then, she explained the role of mitochondria in endothelial cells, macrophages, and vascular smooth muscle cells, revealed the underlying mechanisms of mitochondrial dysfunction in pro-atherosclerosis microenvironment, which could in future lead to the development of novel strategies to prevent atherosclerosis. Finally, Doctor Martino Alfredo Cappelluti presented the epigenome editing through a hit-and-run platform. Genome editing is a type of genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome. He introduced the CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) technology and its new application in transcriptional editing. In addition, the results of a case study of silencing Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) gene in vivo were presented.

In the session dedicated to genetic dyslipidemia, Professor Manuela Casula presented the pathology of familial hypercholesterolemia (FH) and its closely link to cardiovascular disease (CVD). She underlined the importance of early diagnosis and treatment initiation to prevent FH adverse outcomes. Then, she introduced the

Corresponding Author
Sining Xie: sining.xie@unimi.it

virtuous example of the Italian register LIPIGEN. The LIPIGEN (LIpid transPort disorder Italian GEnetic Network) was created in 2009 by the Italian Atherosclerosis Society (Società Italiana per lo Studio dell'Aterosclerosi - SISA) through its Foundation (Fondazione SISA) to promote and facilitate the clinical and genetic diagnosis of familial dyslipidaemias. Until now, the network involves 60 Italian centres specialized in the management of patients affected by primary dyslipidemias throughout the national territory, including paediatric clinics. Data of more than 11,000 patients are collected; about 20% are under the age of 18. The analysis of these data allowed to outline the current gaps in FH diagnosis, as for example: the limited ability of clinical algorithms to identify affected individuals, or the presence of unknown genetic and/or environmental factors could result in a FH phenotype consistent with that observed in monogenic FH. The results from FH awareness survey addressed to both clinicians and FH patients were presented in the end of her lecture. Next, Professor Laura D'Erasmo explained the structure and content of consensus document on diagnosis and management of FH from SISA. She started with the definition, pathology, and classification of FH, followed with the novel technologies in FH diagnosis and current drug treatment strategies. FH includes disorders with a semi-dominant or recessive pattern of inheritance, which were formerly defined as Autosomal Dominant Hypercholesterolemia (ADH) and Autosomal Recessive Hypercholesterolemia (ARH). *LDLRAPOB*, *PCSK9*, *LDLRAP1* are major FH candidate genes, while apolipoprotein E (*APOE*), ATP-binding cassette sub-family G member 5 (*ABCG5*), *ABCG8*, and *LIPA* were involved in other genetic disorders of lipid metabolism mimicking the FH phenotype. She introduced the molecular analysis using next-generation sequencing (NGS), which improved the genetic analysis of FH patients allowing to analyse several genes at the same time; the imaging techniques, which could help subclassify FH patients. Finally, she concluded that the updated consensus document provided a pragmatic guidance to improve early diagnosis and to plan appropriate LDL-C lowering therapies. The information about the LIPIGEN paediatric group was presented by Doctor Cristina Pederiva. The LIPIGEN paediatric group is a subgroup of LIPIGEN network involving 39 centres, both specially dedicated to paediatric patients or adult clinics dealing with paediatric patients. The main objective is to improve the detection, diagnosis, and management of paediatric FH patients. Currently, more than 2,000 children and adolescents have been enrolled in the study. She introduced the results at the current stage and future perspective of LIPIGEN paediatric group, the investigation is still ongoing. The rational use of drugs controlling hypercholesterolemia has been in the forefront of our thoughts. Professor Alberico Corsini provided us with the novel therapeutical strategies of traditional lipid-lowering treatments (LLT). He emphasized that the addition of ezetimibe to statins or bempedoic acid reduced LDL-C levels to a greater extent than monotherapy, which was also associated with a reduced risk of CVD. Furthermore, PCSK9 monoclonal antibodies (PCSK9mAbs) – alirocumab and evolocumab, as well as small interfering RNA - inclisiran can also be considered as part of the combination. In the end, he introduced the data from ongoing clinical trials for newly developed treatments including oral PCSK9 inhibitor – MK-0616 and CETP inhibitor – obicetrapib. Based on this summary of the current therapeutical strategies, Doctor Gabriella Iannuzzo and Doctor Laura D'Erasmo focused on those drugs mainly used for homozygous FH (HoFH) patients. HoFH is a rare and life-threatening disease originally characterized by bi-allelic pathogenic variants of the genes involved in FH aetiology. In most cases, the gene involved is *LDLR*, and variants result in a defective LDLR function. Thus, HoFH patients had poor response to those therapies targeting LDLR, such as statins, ezetimibe, and PCSK9 inhibitors. Evinacumab is an inhibitor of angiopoietin-related protein 3 (ANGPTL3). Clinical trials indicated that evinacumab consistently and substantially reduced LDL-C levels regardless of LDLR function and was generally well tolerated. The efficacy and safety of evinacumab in HoFH population were also confirmed by the LIPIGEN group. Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP), can decrease very low-density lipoprotein (VLDL) assembly and secretion in the liver, consequently, reduce LDL-C levels through a LDLR independent pathway. They finally concluded that although these two drugs were both approved for the treatment of HoFH, further investigations are required to understand their long-term efficacy and safety in the real world.

An increased focus on novel treatments targeting PCSK9 dedicated to the second day. Starting from monoclonal antibodies (mAbs), Prof Alberto Zambon overviewed the European and Italian data on lipid-lowering efficacy and therapeutical adherence of PCSK9mAbs in real-life and clinical trials. The real-life data showed that PCSK9mAbs were safe and effective in clinical practice, leading to very high adherence and persistence to therapy and achievement of recommended LDL-C target, especially when used as combination therapy. Data from clinical trials confirmed the previous findings and highlighted the safety of alirocumab in vulnerable population identified before randomization. Additionally, intensive and early lipid-lowering therapy using PCSK9mAbs in patients with acute coronary syndrome (strike early–strike strong strategy) is safe and effective in clinical practice and associated with a reduction of residual CV risk, due to its contribution to coronary plaque stability. Finally, he outlined that the combination of statins and ezetimibe, or even the addition of PCSK9 inhibitors or bempedoic acid, should be considered a first-line treatment option for patients at high risk of CVD. Next, Professor Maurizio Averna shared with us the origins, development and future of oral PCSK9 inhibitors research. MK-0616 is an orally bioavailable macrocyclic peptide that inhibits binding of PCSK9 to the LDLR. In phase 1 trials, once-daily dose of 20 mg MK-0616 provided a >93% geometric mean reduction of free plasma PCSK9, and maximum 61% geometric mean reduction of LDL-C on top of statin treatment. The results form its phase 2 trial confirmed that MK-0616 significantly reduced LDL-C by 60.9% from baseline and was well tolerated. Notably, it also reduced lipoprotein(a) [Lp(a)] levels by around 20%. All this information indicates that MK-0616 has the potential to be a novel and highly effective option for patients requiring intensive LDL-C reduction. The success of this drug promotes the development of oral PCSK9 inhibitors; several recently designed oral PCSK9 inhibitors are undergoing clinical studies. The gene silencing approach for PCSK9 was presented by Professor Giuseppe Danilo Norata. Small interfering RNAs (siRNA) selectively and catalytically silence the translation of their complementary target messenger RNAs (mRNAs) in a sequence-specific manner through the formation of effector RNA-induced silencing complexes. Inclisiran is a chemically synthesized siRNA molecule that has produced sustained hepatocyte-specific, PCSK9-specific RNA silencing. Comparing to PCSK9mAbs, inclisiran provides a long-lasting reduction in LDL-C with injections on day 1, day 90, and every 6 months. In addition, inclisiran was well tolerated, with only a small number of patients developing anti-drug antibodies in long-term studies (5.5% in the ORION-8 trial). He summarized that inclisiran could be a robust option to lower LDL-C up to 50% on top of other LLT. Finally, Professor Aldo Pietro Maggioni introduced the OMERO study. This is a multicentre study evaluating the long-term efficacy and tolerability of alirocumab in patients with severe hypercholesterolemia in an Italian real-life setting. The objective is to help maximise the proportion of

patients achieving the LDL-C target, and the follow-up duration will be about 3 years for all patients. Notably, this study has pioneered the implementation of digital tools such as electronic informed consent (eIC), with multimedia tools (such as audio, video, links) integrated with electronic trial master file (eTMF), electronic case report form, and the electronic patient-reported outcome (ePRO) app, thereby streamlining the data collection process.

The Congress traditionally hosts a joint symposium of the Lombardy sections of AMD (Association of Diabetes Physicians), SID (Italian Society of Diabetology), and SISA. This year, the presentations have focused on the therapeutical strategies in patients with specific disease. In this session, Doctor Stefano Ciardullo discussed the epidemiological and clinical evidence for increased CV risk in patients with metabolic dysfunction associated steatotic liver disease (MASLD). This disease is characterized by steatosis, inflammation and fibrosis of the liver, so treatment strategies focused on these three points. He presented the mechanism and clinical data of thyroid hormone receptor-beta (THR-β) agonist resmetirom, and antidiabetic medications such as incretine, semaglutide, tirzepatide, concluded that the management of MASLD should focus on both glucose-lowering/weight loss and liver-directed therapy. Doctor Silvia Cecilia Severgnini overviewed the novel technologies for patients with type 2 diabetes mellitus (T2DM). T2DM is characterized by high blood sugar, insulin resistance, and relative lack of insulin. The development of continuous glucose monitoring (CGM) had facilitated the routine care of patients with T2DM who are on basal insulin-only regimens or are managed with other medications. CGM could minimize hypoglycaemia while allowing efficient adaptation and escalation of therapies and enables target values of glycated haemoglobin A1c (HbA1c). In the Lombardy Region, guidelines for the use of glucose monitoring techniques in patients with T2DM entered into force on 1st January 2024. In the last part of this session, Professor Paolo Magni talked on the molecular mechanism between inflammation and atherosclerosis, the impact of obesity and diabetes on this progression, and possible treatment strategies. He outlined that the CV prevention should also include the assessment on inflammatory biomarkers (such as C-reactive protein) and factors released or secreted by adipose tissue (leptin, adiponectin, resistin, etc.). In terms of disease diagnosis, novel approaches such as multi-omics and nuclear magnetic resonance (NMR) should be considered.

More personalized and precise strategies of CV prevention was discussed on the final day. The different responses to LLT in women and men was presented by Professor Fabrizia Bonacina. Sex differences in human could be genetic determinate, i.e. XX or XY chromosomes, or by the gonads, which are differentiated by hormones (testosterone or estrogen). Both estrogen and X chromosome have beneficial effects on the atherosclerotic plaque and hepatic lipid metabolism. However, according to epidemiological data, mortality from CVD appears to be higher in women than in men. The evidence from randomized controlled trials indicated that statins with or without ezetimibe, bempedoic acid and PCSK9 inhibitors had similar lowering effect on lipid concentrations and major CV events in both men and women. She concluded that the higher incidence of mortality in women could be attributed to their lower adherence to treatments, a female-specific strategy is required in CV prevention. Next, Doctor Federica Galimberti explained the comparison between LDL-C, apolipoprotein B (apoB) and triglyceride (TG) levels in CV risk assessment. ApoB is the structural framework of all lipoprotein particles. Evidence from population studies showed high variability of apoB at specific levels of LDL-C and TG coupled with meaningful differences in 10-year atherosclerotic CVD rates, suggesting that the clinical benefit of lowering LDL-C and TG levels may be proportional to the absolute change in ApoB. She summarized that apoB should be routinely measured in clinical practice and considered in risk prediction, as it best recapitulates the individual CV risk. The story of bempedoic acid was recounted by Professor Alberto Corsini. Bempedoic acid is a recent, once-daily oral lipid-lowering agent that activated in the liver to bempedoyl-CoA, which subsequently inhibits ATP-citrate lyase, an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Notably, it is not activated in the skeletal muscle, thus does not result in muscular adverse effects. No dose adjustments are necessary for patients with mild or moderate renal impairment. Clinical trials had identified its efficacy regarding the LDL-C reduction and CV events, as well as its safety. An addition of bempedoic acid on top of existing LLT is recommended for intensive LDL-C lowering. In the last session, Professor Stefano Carugo explained the single-pill combination for patients with hypertension. Hypertension has persisted to be the leading cause of CV mortality. He described the types of antihypertensive drugs and the current strategy of using combination therapy with more than one drug for high-risk patients. In addition, single-pill combination therapy appeared to provide better control of blood pressure than free combination. Finally, he outlined that it is important to improve patient compliance with multiple therapies, so the next step is to develop new technologies such as antisense oligonucleotides (ASO), siRNA or mAbs for antihypertensive treatment. Next, Professor Andrea Baragetti provided the new insights into cholesterylester transfer protein (CETP) inhibitors. CETP inhibitors are known to raise high-density lipoprotein (HDL) cholesterol and reduce the CV risk. However, previous genetic studies and clinical trial evidence have not shown a causal relationship between HDL or conventional CETP inhibitors and reduced risk of CVD. He presented the data on the possible apoB-lowering effects of CETP inhibitors, as well as published and ongoing clinical trials of the novel drug obicetrapib. The pathology and treatment strategies of lysosomal acid lipase (LAL) deficiency was presented by Professor Laura Calabresi. The primary function of this lysosomal enzyme is to hydrolyse lipids such as TG and cholesterol esters and release free fatty acids and free cholesterol in the cytosol. Patients affected by LAL deficiency, an autosomic recessive disease, are characterized by lipid accumulation predominantly in liver, intestine, spleen, adrenal glands, bone marrow, and macrophages. The disease is caused by variants in the *LIPA* gene and, when early identified, can be controlled by enzyme replacement therapy, LLTs or liver transplantation. In the last session, Professor Massimiliano Ruscica summarised the evidence on Lp(a). Large epidemiological studies, Mendelian randomized studies, and genome-wide association studies confirmed that elevated Lp(a) concentration is an independent risk factor for CVD. He outlined the importance of Lp(a) measurement in CV risk assessment and introduced the ongoing clinical trials of novel Lp(a)-lowering treatments.

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XVIII SITeCS Congress 2024 - Selected Abstracts

Investigating plasma and brain cholesterol esterification in patients with amyotrophic lateral sclerosis

Chiara Comi[1], Chiara Pavanello[1], MatteoFarè[2,3], Francesca Gerardi[3], Federica Cerri[3], Lucio Tremolizzo[2], Laura Calabresi[1]

[1]Centro Grossi Paoletti, Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano
[2]Clinica Neurologica, IRCCS San Gerardo Dei Tintori, Monza
[3]Centro Clinico Nemo, Milano
https://doi.org/10.56095/eaj.v3i3.80
Chiara Comi: chiara.comi@studenti.unimi.it

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, with metabolic alterations, abnormal cholesterol and lipid levels in the bloodstream and central nervous system (CNS). Similar to plasma, cholesterol in the cerebrospinal fluid (CSF) is carried by lipoproteins known as "HDL-like particles," due to their close similarity in density and composition to plasma HDL. Lecithin cholesterol acyltransferase (LCAT) is a key enzyme in HDL metabolism, catalysing cholesterol esterification in both plasma and CSF, thus facilitating HDL maturation. This study aimed to investigate cholesterol esterification in plasma and CSF and to characterize HDL subclass distribution in patients with ALS. The study included 20 ALS patients and 20 controls, in whom lipoprotein profile and cholesterol esterification were evaluated in both plasma and CSF. Plasma lipid levels were similar between patients and controls; however, the amount of discoidal preβ-HDL was significantly reduced in ALS patients compared to controls (8.5±4.9% vs 13.6±4.1%, $p<0.0001$). A significant increase in CSF unesterified cholesterol levels was observed in ALS patients compared to controls (0.22±0.07 mg/dL vs 0.15±0.04 mg/dL, $p<0.01$), leading to an increased unesterified/total cholesterol ratio in ALS patients (0.52±0.12 vs 0.40±0.12, respectively). While plasma cholesterol esterification remained unchanged in ALS patients, the cholesterol esterification rate was significantly reduced in their CSF (0.12±0.08 vs 2.41±1.98, $p<0.01$), consistent with the previous data. In conclusion, these results suggest a hampered cholesterol esterification in the CSF of ALS patients. Whether this defect is related to the severity or progression of the disease remains to be defined.

Neutrophil behavior during the metabolic adaptations to short term high fat feeding

Anna Parolini, Annalisa Moregola, Lorenzo Da Dalt, Alessia Rubino, Ottavia Terenghi, Giuseppe Danilo Norata, Andrea Baragetti

Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy
https://doi.org/10.56095/eaj.v3i3.84
Anna Parolini: anna.parolini@unimi.it

Background and Aims: Neutrophils participate to the chronic metabolic consequences of High Fat Diet (HFD). Nevertheless, neutrophils are characterized by short half-life which is determined by a fine tuning in expression and function of CXCR4, which dictates the egress from the bone marrow (BM), and CXCR2, which facilitates their mobilization from BM and the patrolling activity in the periphery. In the quest to study the behavior of the neutrophil with the short-term consequences of HFD feeding, we studied whether the metabolic adaptations affect blood neutrophil count and the membrane expression of their indirect markers of function.
Methods: To assess the gluco-metabolic impact of a short-term HFD feeding, indirect calorimetry and plasma glucose dosage were performed on mice previously fed a HFD (60% Kcal from fat) for seven days, followed by immunophenotyping of blood over 24 hours. To test whether changes in circulating neutrophil count during short-term HFD feeding were related to a differential egress from the BM, we repeated the same experimental design in mice harboring a conditional deletion of CXCR4 (CXCR4fl/flMrp8Cre+).
Results: Short-term HFD feeding was sufficient to induce a profound metabolic impact (e.g. reduced respiratory exchange ratio, increased energy expenditure, and insulin levels), and to induce an increase of circulating neutrophils (p=0,052), without impacting other leukocytic fractions over 24 hours, compared to chow diet feeding mice (20% Kcal from fat). HFD feeding significantly altered the expression pattern of multiple membrane markers of neutrophil function (CD11b, CD62L, CXCR2) over 24 hours, driving neutrophils toward a phenotype featuring increased migration and activation. Finally, the CXCR4fl/flMrp-8Cre+ mice, which present significantly higher circulating neutrophilia, showed lower insulin sensitivity upon HFD compared to WT.
Conclusions: We suggest that the metabolic adaptations induced by a short-term exposure to HFD affect neutrophil behavior, surmising it as an appealing target for cardio-metabolic diseases.

Modulation of mitochondrial dynamism in Kupffer cells impacts systemic metabolism

Francesca Fantini[1], Lorenzo Da Dalt[1], Annalisa Moregola[1], Giovanni Battista Vingiani[1], Ottavia Terenghi[1], Elena Donetti[2], Silvia Roda[1], Patrizia Uboldi[1], Monika Svecla[1], Jasmine Nour[1], Rossella Bellini[1], Fabrizia Bonacina[1], Giuseppe Danilo Norata[1]

[1]*Department of Excellence of Pharmacological and Biomolecular Sciences, University of Milan, Italy*
[2]*Department of Biomedical Science for Health, University of Milan, Italy*
https://doi.org/10.56095/eaj.v3i3.81
Francesca Fantini: francesca.fantini1@unimi.it

Background: Kupffer cells (KCs) are hepatoresident macrophages that are essential for liver physiology and contribute to the development of nonalcoholic hepatic steatosis (NAFLD). The liver of patients with MAFLD shows different expressions of some key regulators of inner mitochondrial membrane fusion compared with healthy subjects, including OPA1 protein, which is a mitochondrial protein whose activity promotes mitochondrial fusion and modulation of oxidative phosphorylation.
Aims: Given the close interaction that KCs have with cells in the hepatic niches, they play both a crucial immune and metabolic role, which is why their mitochondria are critical for their function. This project aims to investigate how modulation of OPA1-driven mitochondrial fusion in KCs can affect lipid metabolism and immune response at the systemic and hepatic levels.
Methods: Mice selectively lacking OPA1 in the KCs were fed a Standard Diet or a High Fat Diet for 20 weeks. The immune phenotype was assessed by cytofluorimetry while the metabolic profile by in vivo indirect calorimetry and with plasma and tissue lipid profile analysis. Single cell RNA sequencing was also performed to profile the impact of OPA1 deficiency on KC function and possible paracrine effects on hepatocytes.
Results: Under standard dietary conditions, mice selectively lacking OPA1 in KCs show a different metabolic substrate preference compared to wild type, with an immunophenotype characterized by a higher proportion of pro-resolution KC2 than pro-inflammatory KC1. Functionally, KCs also exhibit dissimilar phagocytic and proliferative capacity. During the high-fat diet, we observed a significant reduction in liver fibrosis.
Conclusions: Taken together, these data suggest that OPA1 plays a key role in the function of Kupffer cells and that the lack of OPA1, causing metabolic reprogramming, affects their interaction with resident liver cells, influencing the development of fibrosis and the progression of MAFLD.

Efficacy of Oral Semaglutide on Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus: A Real-Life Study

Francesca Nicolì[1], Giulia Ongis[1], Provvidenza Villari[2], Giancarla Meregalli[1], Antonio Maria Labate[3]

[1]*ASST Bergamo Ovest*
[2]*ASST Garda*
[3]*ASST Mantova*
https://doi.org/10.56095/eaj.v3i3.82
Francesca Nicolì: francesca_nicoli@asst-bgovest.it

Background: The efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in glycemic control and cardiovascular risk reduction in type 2 diabetes mellitus (T2DM) is well established. Real-world, non-interventional studies are increasingly essential to gather information from routine clinical practice.
Objective of the Study: This multicenter, observational, retrospective, single-arm study aims to assess the effect of oral semaglutide on surrogate markers of cardio-metabolic risk (such as Visceral Adiposity Index, triglyceride-glucose index, Lipid Accumulation Product), as well as on glycemic control, renal function markers (creatinine, eGFR, microalbuminuria), and lipid profile, in adult patients with T2DM who are naive to GLP-1 RA therapy.
Materials and Methods: A total of 154 adult diabetic patients (106 male, 48 female; mean age 64.4±10.5 years) with an average disease duration of 10 years (10.1±8.4) were evaluated. Patients initiated oral semaglutide treatment according to AIFA note 100 guidelines and were followed at diabetes outpatient clinics in ASST Bergamo Ovest, Garda, and Mantova. Clinical, biochemical, and anthropometric data for each patient were collected at the beginning of treatment (T0) and after 12 months (T12).
Results: The main results are presented in the table below:

Variables	T0	T12	P-value
BMI, Kg/m² (mean±SD)	31.2±5.2	29.6±5.1	<0.001
Waist circumference, cm (mean±SD)	105.9±10.3	99.9±9.9	<0.001
Fasting glucose, mg/dL (mean±SD)	154.7±43.1	124.8±30.5	<0.001
HbA1c, % (mean±SD)	7.8±1.2	6.7±0.9	<0.001
Total cholesterol, mg/dL (mean±SD)	171.9±40.0	154±34.7	<0.001
HDL cholesterol, mg/dL (mean±SD)	47.7±11.9	52.0±12.2	<0.001
LDL cholesterol, mg/dL (mean±SD)	93.8±36.1	81.5±80.8	0.05
Triglycerides, mg/dL (mean±SD)	157.2±74.2	132.9±57.0	<0.001
eGFR, ml/min/1.73m² (mean±SD)	62.8±17.2	67.7±20.6	<0.001
Urinary albumin/creatinine ratio, mg/g [median (IQR)]	38.5 (14.3-81.8)	12 (5.6-34.3)	<0.001
Systolic blood pressure, mmHg (mean±SD)	134.8±14.6	131.4±15.2	0.015
Diastolic blood pressure, mmHg (mean±SD)	78.3±8.7	75.8±8.5	0.003
Visceral Adiposity Index [median (IQR)]	2.4 (1.6-3.4)	1.7 (1.0-2.6)	<0.001
Triglyceride-glucose index [median (IQR)]	5.9 (4.8-5.2)	4.8 (4.7-4.9)	<0.001
Lipid Accumulation Product [median (IQR)]	77.0 (52.8-111.6)	56.1 (35.2-80.9)	<0.001

Conclusions: Exposure to oral semaglutide for 12 months in T2DM patients resulted in significant improvements in glycemic control, renal function parameters, and surrogate markers of cardiovascular risk.

A retrospective cohort study on factors influencing the initiation of lipid-lowering therapy in hospitalized patients following a cardio-cerebrovascular event

Elena Olmastroni[1,2], Stefano Scotti[1], Federica Galimberti[1], Asiiat Alieva[3], Sining Xie[2], Alberico L. Catapano[1,2], Manuela Casula[1,2]

[1]Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy
[2]IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy
[3]Research laboratory of lipid disorders and atherosclerosis, Almazov National Medical Research Centre, Saint Petersburg, Russia
https://doi.org/10.56095/eaj.v3i3.83
Elena Olmastroni: elena.olmastroni@unimi.it

Introduction: Current European guidelines on cardiovascular prevention recommend lipid-lowering therapies for patients who have experienced an atherosclerotic cardiovascular disease (ASCVD) event.
Objectives: This study aims to provide updated data on the prescription of lipid-lowering therapies in patients discharged after an ASCVD event and to investigate the characteristics associated with a higher likelihood of receiving such therapy following the event.
Methods: Using administrative data from the Lombardy region, individuals of both sexes aged ≥40 years hospitalized for an incident ASCVD event during the first nine months of 2019 were identified. The prevalence of those receiving a prescription for lipid-lowering therapy within 90 days of the event was assessed. A multivariable logistic regression model was applied to evaluate the impact of various factors on the likelihood of initiating treatment (odds ratio [OR] and 95% confidence intervals [95%CI]).
Results: In a cohort of 18,370 individuals with an incident ASCVD event, 50.70% did not receive a prescription for any lipid-lowering therapy. The likelihood of initiating therapy was higher in individuals who experienced a cardiovascular event compared to a cerebrovascular event (OR 2.94, 95%CI 2.74-3.14), in patients aged 51-60 years (OR 1.22, 95%CI 1.10-1.36, compared to 61-70 years), and in those receiving antidiabetic (OR 1.42, 95%CI 1.25-1.61) or antihypertensive therapy (OR 1.77, 95%CI 1.64-1.92). Conversely, older age (71-80 years: OR 0.70, 95%CI 0.64-0.77; >80 years: OR 0.38, 95%CI 0.35-0.42), female sex (OR 0.81, 95%CI 0.75–0.87), prior exposure to antithrombotic medication (OR 0.67, 95%CI 0.60-0.73), and excessive polypharmacy (OR 0.57, 95%CI 0.49-0.66 for ≥10 medications) were associated with a lower likelihood of initiating treatment after the event.
Conclusions: The study highlights a suboptimal initiation of lipid-lowering therapy in patients discharged after an ASCVD event. Additionally, the results emphasize the importance of understanding influencing factors to improve patient management in secondary prevention.

Angiopoietin-like 3 (ANGPTL3) deficiency alters metabolic substrates utilization and reprograms hepatic metabolism

Ottavia Terenghi, Lorenzo Da Dalt, Francesca Fantini, Giovanni Battista Vingiani, Annalisa Moregola, Patrizia Uboldi, Fabrizia Bonacina, Giuseppe Danilo Norata

Laboratory of Pharmacology of Cardioimmunometabolic Disorders, Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy
https://doi.org/10.56095/eaj.v3i3.85
Ottavia Terenghi: ottavia.terenghi@unimi.it

Angiopoietin-like 3 (ANGPTL3) is a lipases-inhibiting hepatokine, thus prevents VLDL and LDL-derived triglycerides, regulating fluxes of triglycerides to the tissues. Aim of this study is to investigate the association between hypolipidemia-induced metabolic alteration, due to ANGPTL3 deficiency, and potential hepatic responses, depending on the source of energetic substrates available.
Full-knockout (KO) mice and littermate controls (WT) underwent a standard chow diet or High Fat Diet (HFD, 60% kcal from fat) regimen for 16 weeks. Metabolic responses have been assessed through indirect calorimetry, lipid, glucose and insulin tolerance test, and circulating lipid levels have been evaluated.
ANGPTL3 KO mice are hypolipidemic at fasting, postprandially and in fast refeeding, both at chow and HFD.
After an oil gavage, ANGPTL3 KO mice absorb less triglycerides both at fasting (area under curve: HO:3320.8mg/dL*min±1214.9vsWT:17303 mg/dL*min±11765.2, p=0.07) and postprandially (area under curve: HO:447.3mg/dL*hr±20.9vsWT: 938.2mg/dL*hr ±294.9, p=0.016), and this associates with a lesser hepatic lipoprotein production, also at HFD. Glucose metabolism is not affected, and liver histology of KO mice at chow and HFD do not show increased steatosis compared to control group. Indirect calorimetry data show an increased trend of oxidative metabolism in the postprandial phase compared to controls (Respiratory Exchange Ratio at ZeitgeberTime21: HO: 0.889±0.102vsWT: 0.969±0.089; p=0.074).
Hepatic mTOR activation has been investigated with western blotting, to understand a possible nutrient sensing alteration, by evaluating the phosphorylation of downstream effectors S6K (fold on housekeeping: HO:0.28±0.122vsWT:0.647±0.119; p=0.021) and 4E-BP1 (fold on housekeeping: HO: 0.503±0.193vsWT:1.043±0.270, p=0.048) and a dampened activation is observed. This is associated with a lower protein synthesis. RNA sequencing data confirmed that at chow diet KO mice face the activation of metabolic pathways such as urea cycle and bile acids production. Hepatic signalling pathways, like LXR, are blunted, at chow and HFD.
ANGPTL3 deficiency alters the metabolic phenotype, reducing circulating lipemia, and an adaptive metabolic response occurs depending on the metabolic substrate availability.

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Corrigendum to: LDL-cholesterol goal attainment with ezetimibe and bempedoic acid in patients at high and very-high cardiovascular risk: A simulation study in the Italian cohort of the SANTORINI study

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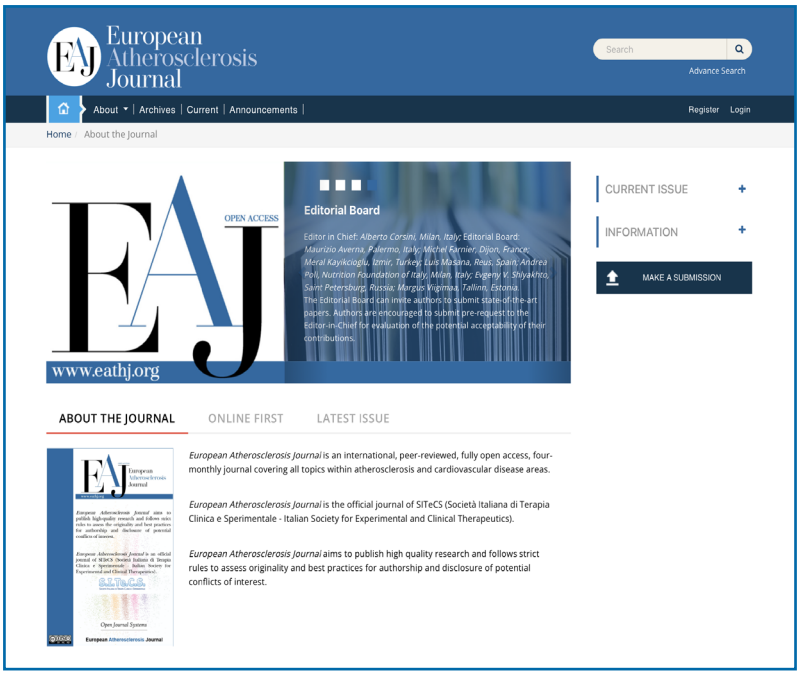
Communication from the Authors:

We found a minor issue with the calculation of confidence intervals (CIs) included in the manuscript. These CIs were used solely to illustrate the variability of simulated values and were not used for statistical testing or hypothesis evaluation.

Upon review, we found that CIs were calculated using an earlier formula, which did not fully capture the variability in the simulated mean LDL-C values. After updating the calculation in accordance with the predefined statistical analysis plan, the CIs are slightly wider, ensuring they more accurately reflect the variability. Importantly, these adjustments do not affect the conclusions or scientific interpretations of the manuscript, while increasing the accuracy of the reported data.

The following post-publication corrections have been made to this article:

Parameter	Original CI	Updated CI	Page
CI for simulated mean LDL-C level	44.0-46.2	43.7-46.4	61
CI for simulated mean LDL-C level	83.5-86.2	83.3-86.5	61
CI for simulated mean LDL-C level	89.7-91.3	89.5-91.4	61
CI for simulated mean LDL-C level	104.6-108.7	104.2-109.1	61
CI for simulated mean LDL-C level	86.8-88.4	86.6-88.6	61
CI for simulated mean LDL-C level	72.7-75.7	72.5-76.0	61
CI for simulated mean LDL-C level	76.6-85.7	75.7-86.7	61
CI for simulated mean LDL-C level	71.5-74.5	71.2-74.8	61
CI for simulated mean LDL-C level	43.9-45.5	43.8-45.7	61
CI for simulated mean LDL-C level	43.2-43.9	43.1-44.0	61
CI for simulated mean LDL-C level	70.4-72.6	70.2-72.8	62
CI for simulated mean LDL-C level	43.0-45.1	42.7-45.3	62
CI for simulated mean LDL-C level	81.6-84.4	81.3-84.6	62
CI for simulated mean LDL-C level	87.0-88.6	86.8-88.7	62
CI for simulated mean LDL-C level	70.5-73.5	70.2-73.8	62
CI for simulated mean LDL-C level	100.7-104.8	100.3-105.2	62
CI for simulated mean LDL-C level	73.5-82.8	72.7-83.6	62
CI for simulated mean LDL-C level	84.3-86.0	84.2-86.2	63
CI for simulated mean LDL-C level	69.4-72.5	69.2-72.8	63
CI for simulated mean LDL-C level	43.1-44.6	42.9-44.7	63
CI for simulated mean LDL-C level	42.3-43.0	42.2-43.0	63
CI for simulated mean LDL-C level	70.7-71.6	70.6-71.7	63
CI for simulated mean LDL-C level	62.1-63.7	62.0-63.8	63



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