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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

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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-

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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.

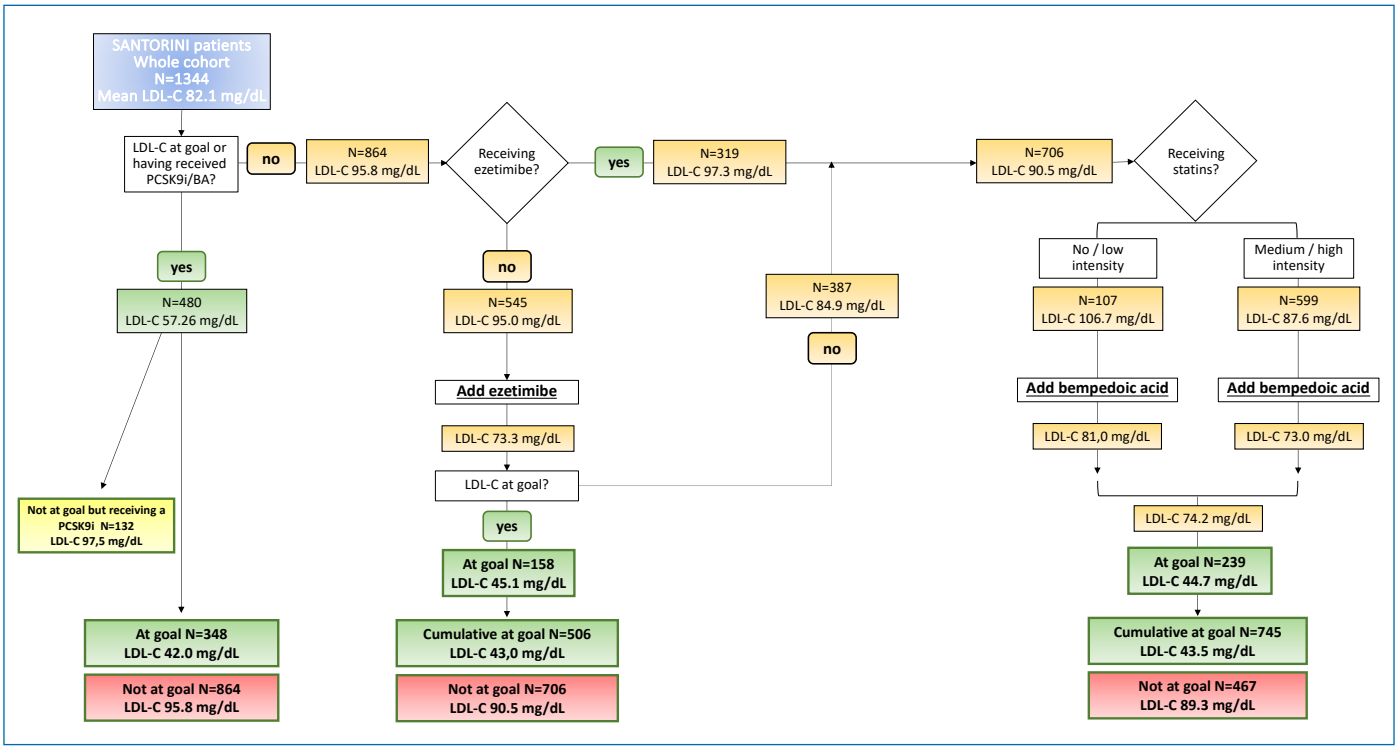

Figure 1 | Application of the simulation algorithm in eligible patients (N=1344) of the Italian cohort of the SANTORINI study; results were obtained based on the LDL-C goals recommended by the 2019 ESC/EAS guidelines.

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

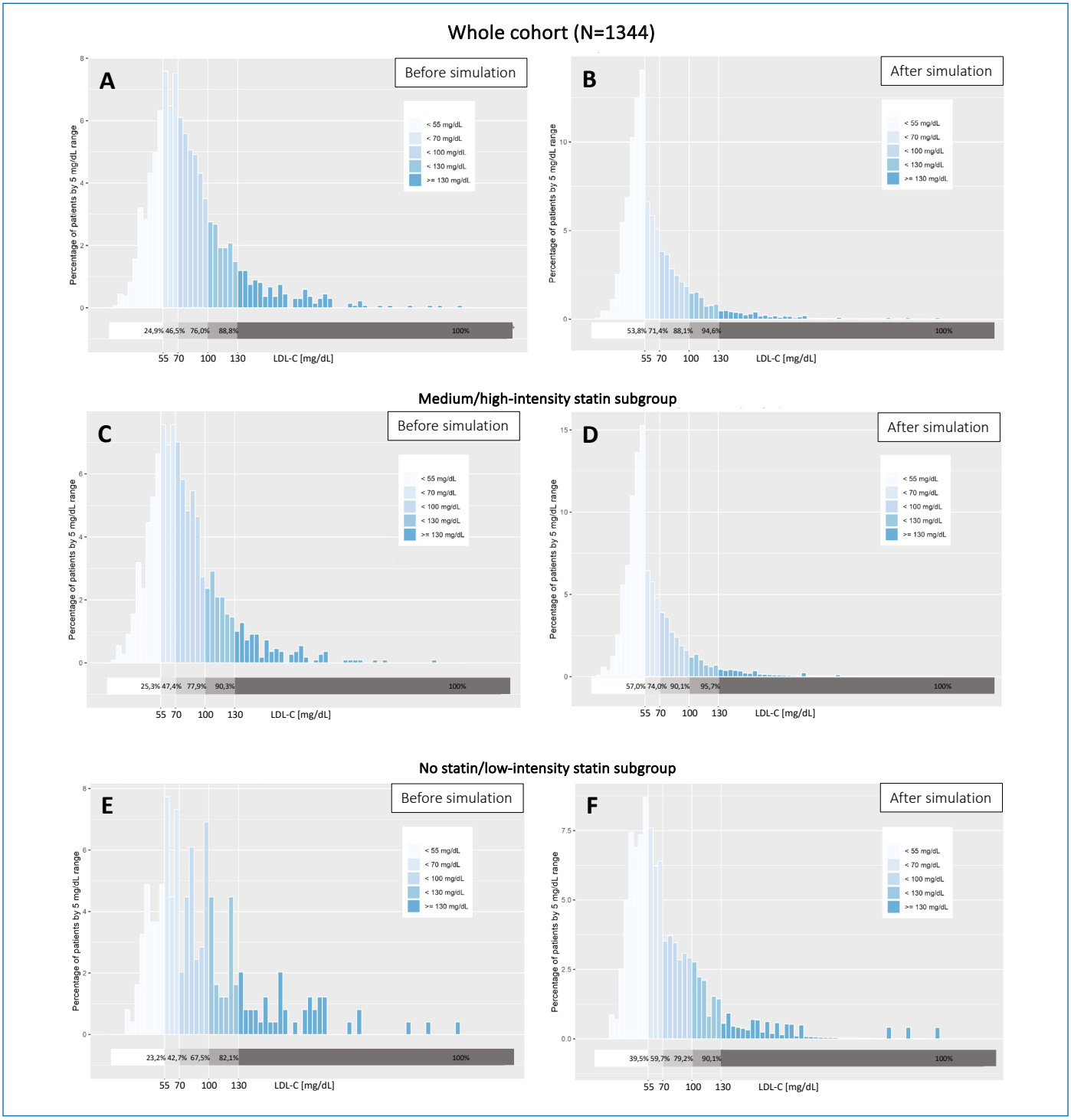

Figure 3 | LDL-C distribution before and after the simulation in the whole cohort (A, B), in the subgroup with no/low-dose statin (C, D) and in the subgroup with medium/high-dose statin (E, F).

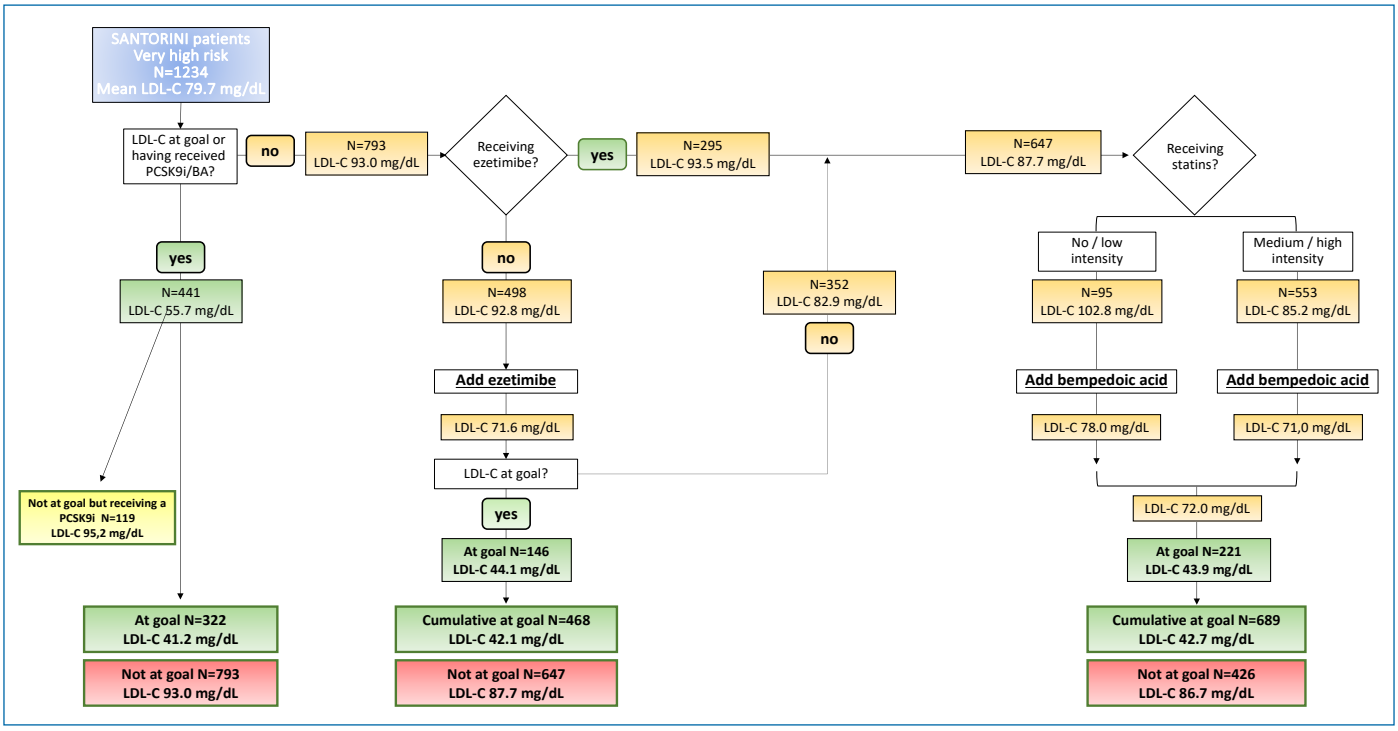

Figure 4 | Application of the simulation algorithm in the very-high-risk subgroup (N=1234) of the Italian cohort of the SANTORINI study; results were obtained based on the LDL-C goals recommended by the 2019 ESC/EAS guidelines.

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-

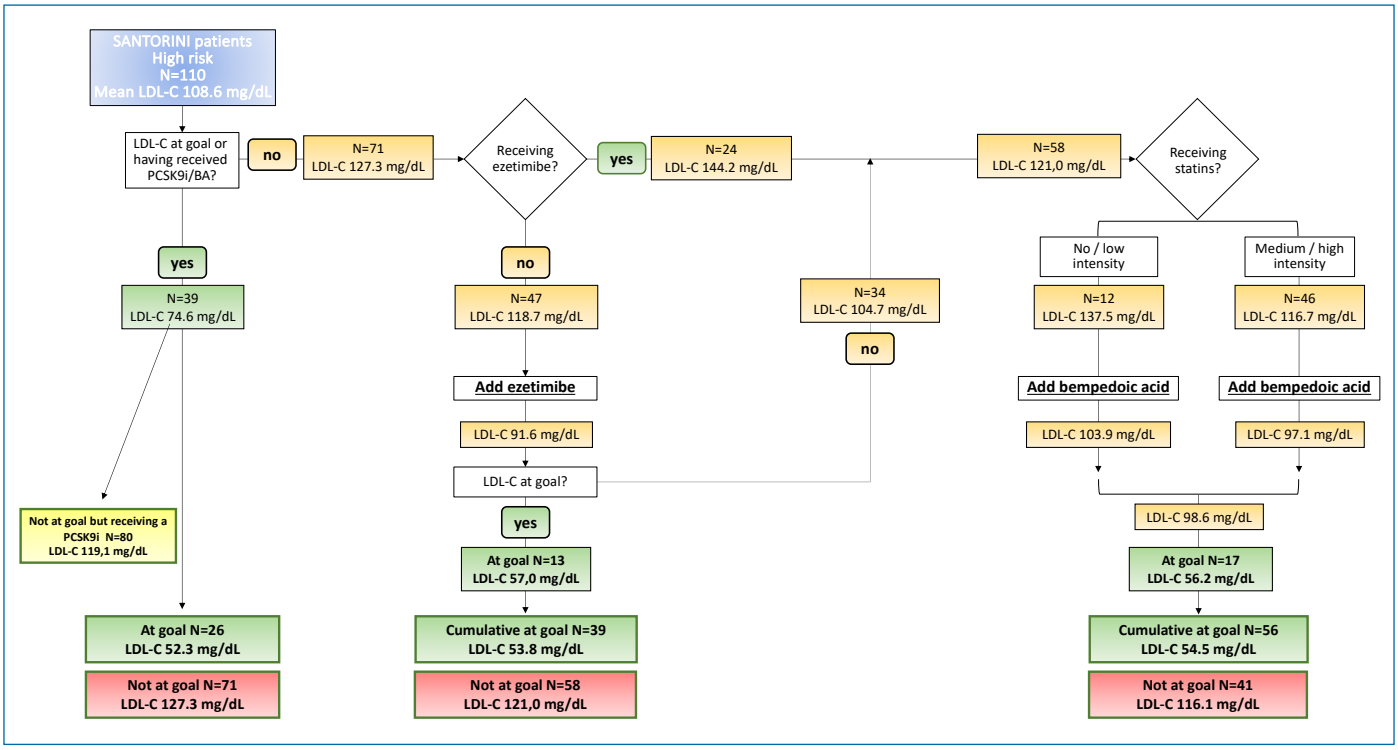

Figure 5 | Application of the simulation algorithm in the high-risk subgroup (N=110) of the Italian cohort of the SANTORINI study; results were obtained based on the LDL-C goals recommended by the 2019 ESC/EAS guidelines.

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.

References

[1] Pirillo A, Norata GD. The burden of hypercholesterolemia and ischemic heart disease in an ageing world. Pharmacol Res 2023; 193:106814.

[2] Mensah GA, Fuster V, Murray CJL, et al. Global Burden of Cardiovascular Diseases and Risks, 1990-2022. J Am Coll Cardiol 2023; 82:2350-473.

[3] Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017; 38:2459-72.

[4] Boren J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020; 41:2313-30.

[5] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41:111-88.

[6] Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37:2999-3058.

[7] De Backer G, Jankowski P, Kotseva K, et al. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. Atherosclerosis 2019; 285:135-46.

[8] Ray KK, Molemans B, Schoonen WM, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. Eur J Prev Cardiol 2021; 28:1279-89.

[9] Landmesser U, Pirillo A, Farnier M, et al. Lipid-lowering therapy and low-density lipoprotein cholesterol goal achievement in patients with acute coronary syndromes: The ACS patient pathway project. Atheroscler Suppl 2020; 42:e49-e58.

[10] Ray KK, Haq I, Bilitou A, et al. Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study. Lancet Reg Health Eur 2023; 29:100624.

[11] Arca M, Calabrò P, Solini A, et al. Lipid-lowering treatment and LDL-C goal attainment in high and very high cardiovascular risk patients: Evidence from the SANTORINI study-The Italian experience. Eur Ath J 2023; 2:1-13.

[12] Ballantyne CM, Bays H, Catapano AL, et al. Role of Bempedoic Acid in Clinical Practice. Cardiovasc Drugs Ther 2021; 35:853-64.

[13] Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med 2023; 388:1353-64.

[14] Cannon CP, Khan I, Klimchak AC, et al. Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease. JAMA Cardiol 2017; 2:959-66.

[15] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372:2387-97.

[16] Descamps O, Tomassini JE, Lin J, et al. Variability of the LDL-C lowering response to ezetimibe and ezetimibe + statin therapy in hypercholesterolemic patients. Atherosclerosis 2015; 240:482-9.

[17] Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. JAMA 2019; 322:1780-8.

[18] Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019; 380:1022-32.

[19] Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019; 8:e011662.

[20] Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis 2018; 277:195-203.

[21] Agenzia Italiana del Farmaco. DETERMINA n. 435/2022. GU n.138 del 15-6-2022.

[22] Agenzia Italiana del Farmaco. DETERMINA n. 434/2022. GU n.138 del 15-6-2022.

[23] Yu M, Liang C, Kong Q, et al. Efficacy of combination therapy with ezetimibe and statins versus a double dose of statin monotherapy in participants with hypercholesterolemia: a meta-analysis of literature. Lipids Health Dis 2020; 19:1.

[24] Bays HE. Cholesterol-lowering drugs: Focus on Ezetimibe. Eur Ath J 2022; 1:14-24.

[25] Brennan S, Mc Evoy JW. Bempedoic acid and PCSK9 inhibitor eligibility in a contemporary population with atherosclerotic cardiovascular disease. Eur J Prev Cardiol 2022; 29:zwac056.165.

[26] Katzmann JL, Becker C, Bilitou A, Laufs U. Simulation study on LDL cholesterol target attainment, treatment costs, and ASCVD events with bempedoic acid in patients at high and very-high cardiovascular risk. PLoS One 2022; 17:e0276898.

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