Impact of sequential oral lipid-lowering therapy optimisation on LDL-C goal attainment and inclisiran eligibility in UK patients with ASCVD: A Monte Carlo simulation based on SANTORINI

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BACKGROUND

- Elevated low-density lipoprotein cholesterol (LDL-C) levels are a proven, direct cause of atherosclerotic cardiovascular disease (ASCVD)[1,2]
- The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) and the National Institute for Health and Care Excellence (NICE) guidelines recommend lowering LDL-C levels to reduce cardiovascular (CV) risk[1–3]
- Both sets of guidelines establish risk-based LDL-C goals (ESC/EAS: <1.8 mmol/L [<70 mg/dL] and <1.4 mmol/L [<55 mg/dL] for high- and very high-CV risk patients, respectively; NICE: ≤2.0 mmol/L [≤77 mg/dL] for patients in secondary prevention), and recommend stepwise escalation with ezetimibe and bempedoic acid alone or in combination with other lipid-lowering therapies (LLTs) if patients are unable to reach their goal with the maximum tolerated dose of statins, or if patients have statin intolerance (SI)[1–3]
- However, achieving LDL-C goals in clinical practice remains challenging, with most patients not achieving the recommended LDL-C levels[4]

OBJECTIVES

To evaluate the potential impact of sequential oral LLT optimisation with ezetimibe and bempedoic acid on LDL-C goal attainment, predicted 10-year CV risk, and inclisiran eligibility in the UK SANTORINI-like cohort of patients with ASCVD and SI

Table 1. Clinical characteristics of patients with SI and ASCVD at the 1-year follow-up visit, based on the synthetic cohort data (N=100,000)

Clinical characteristics, n/mean	Patients who met the narrow definition of SI†	Patients who met the broad definition of SI‡
Number of patients, n	2561	17,658
Age, years (SD)	61.80 (8.5)	67.85 (8.3)
Female (%)	848 (33.1)	4686 (26.5)
BMI (SD)	26.68 (3.4)	29.28 (5.2)
Very high risk (per ESC/EAS) (%)	2561 (100.0)	17,658 (100.0)
Coronary artery disease (%)	1641 (64.1)	12,620 (71.5)
Cerebrovascular disease (%)	920 (35.9)	5858 (33.2)
Patients in secondary prevention* (%)	2561 (100.0)	17,658 (100.0)
Receiving statin at follow-up (%)	0 (0.0)	15,097 (85.5)
Medium intensity	0 (0.0)	14,822 (83.9)
Low intensity	0 (0.0)	275 (1.6)
No statin (narrow definition) (%)	2561 (100.0)	2561 (14.5)
Ezetimibe (%)	883 (34.5)	1688 (9.6)

*History of clinically manifested ASCVD. †The narrow definition of SI included patients who received no statin therapy. ‡The broad definition of SI included patients with no, low- or medium-intensity statin therapy.
ASCVD, atherosclerotic cardiovascular disease; **BMI**, body mass index; **EAS**, European Atherosclerosis Society; **ESC**, European Society of Cardiology; **SD**, standard deviation; **SI**, statin intolerance.

METHODS

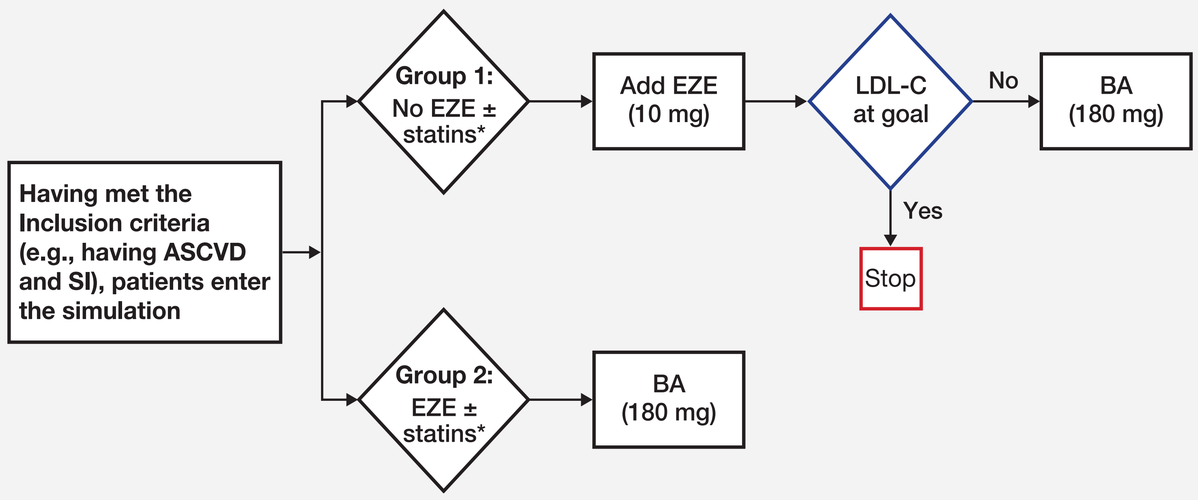
A Monte Carlo simulation was used to model sequential LLT optimisation based on the 2025 Focused Update of the 2019 ESC/EAS guidelines:

1. In total, 366 patients were selected from the SANTORINI UK cohort with known ASCVD status, non-missing CV risk (per the ESC/EAS guidelines), LDL-C levels and statin intensity at 1-year follow-up, and who were not receiving treatment with bempedoic acid or proprotein convertase subtilisin/kexin type 9 inhibitors
2. A synthetic cohort was created based on resampling the selected SANTORINI UK cohort with replacement (100,000 patients overall)
3. The Monte Carlo simulation was conducted in the subset of patients with ASCVD and SI at 1-year of follow-up by random sampling from the specified distributions for treatment efficacy based on published data from clinical trials[4]. Patients with SI who were not already treated with ezetimibe, were simulated to receive ezetimibe treatment, followed by bempedoic acid if they remained above their LDL-C goals (**Figure 1**)

Two operational definitions of SI were applied based on statin therapy observed at 1-year follow-up:
- No statin therapy (narrow definition)
- No, low-, or medium-intensity statin therapy (broad definition)

Outcomes included LDL-C levels before simulation, simulated LDL-C goal attainment according to ESC/EAS recommendations, predicted 10-year CV risk (REACH), and simulated inclisiran eligibility (LDL-C >2.6 mmol/L). Achievement of the NICE lipid target for secondary prevention was assessed in a sensitivity analysis

Figure 1. Treatment strategies evaluated for LLT optimisation in patients with SI



*For broad SI definition.
ASCVD, atherosclerotic cardiovascular disease; **BA**, bempedoic acid; **EZE**, ezetimibe; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy; **SI**, statin intolerance.

RESULTS

Patient characteristics

- Among the synthetic cohort of 100,000 UK SANTORINI-like patients, 44,414 had ASCVD, 2561 met the narrow definition of SI and 17,658 aligned with the broader definition of SI. Clinical characteristics are shown in **Table 1**

LDL-C goal attainment and predicted 10-year CV risk (per the ESC/EAS guidelines)

- In the base-case analysis, simulated LDL-C goal attainment increased with LLT use (**Figure 2A**) while predicted 10-year CV risk decreased (**Figure 2B**)

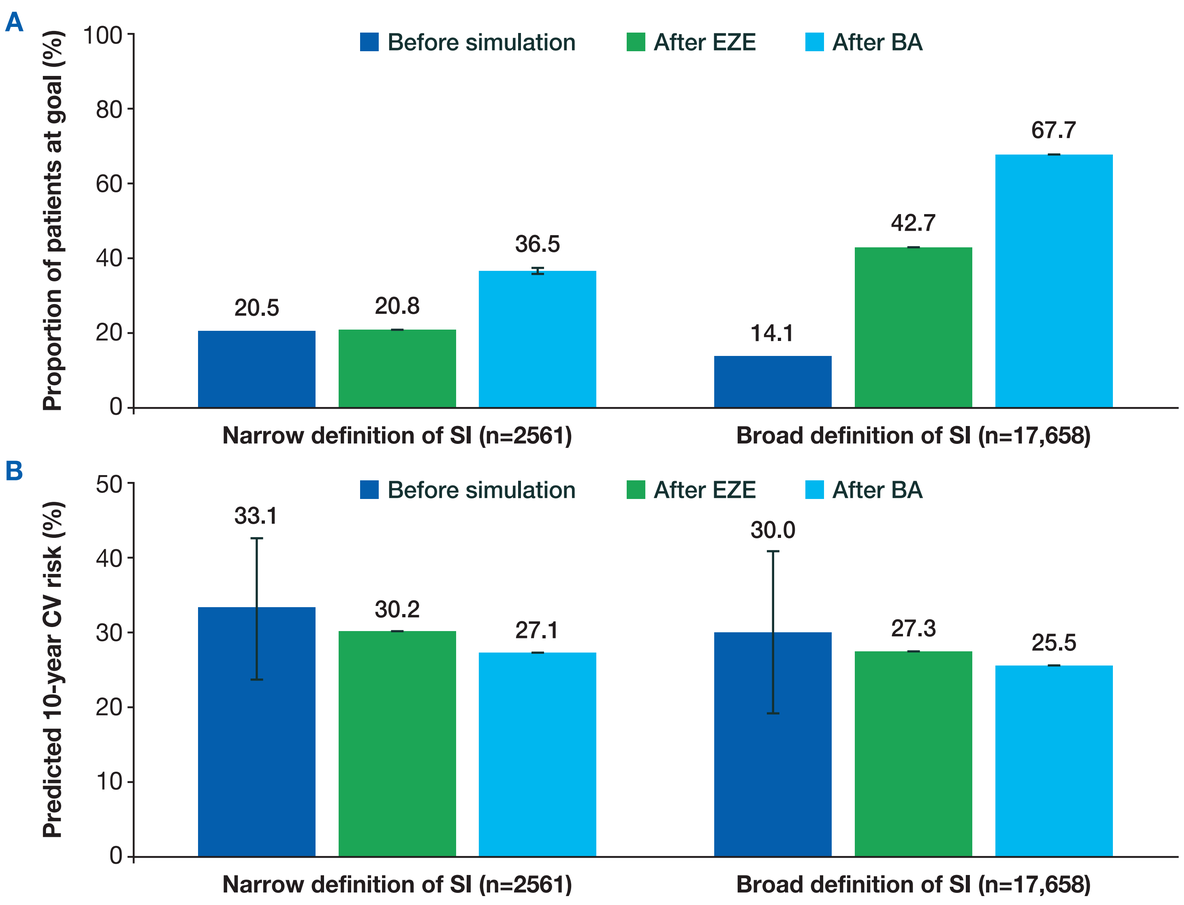
Inclisiran eligibility

- Under the narrow definition of SI, the proportion of patients eligible for inclisiran treatment decreased from 56.8% (n/N=1454/2561) of patients before simulation to 43.0% (n/N=1102/2561) after the simulated addition of ezetimibe, and to 23.6% (n/N=605/2561) after the subsequent simulated addition of bempedoic acid
- Under the broad definition of SI, inclisiran eligibility decreased from 23.5% (n/N=4152/17,658) of patients before simulation to 12.9% (n/N=2279/17,658) after the simulated addition of ezetimibe, and to 7.4% (n/N=1302/17,658) after the subsequent simulated addition of bempedoic acid

Scenario analysis: LDL-C goal attainment based on the NICE NG238/NHS England secondary prevention lipid target[3]

- Under the narrow definition of SI, LDL-C goal attainment increased from 44.6% before simulation to 49.6% after the simulated addition of ezetimibe and to 70.2% after the subsequent simulated addition of bempedoic acid. Predicted 10-year CV risk decreased from 33.1% to 30.2% and 28.1%, respectively, and the number of patients eligible for inclisiran decreased from 56.8% (n/N=1454/2561) to 43.0% (n/N=1102/2561) and 27.9% (n/N=715/2561) of patients, respectively
- Under the broad definition of SI, LDL-C goal attainment increased from 57.9% before simulation to 76.0% after the simulated addition of ezetimibe and to 88.4% after the subsequent simulated addition of bempedoic acid. Predicted 10-year CV risk decreased from 30.0% to 28.4% and 27.5%, respectively, and the number of patients eligible for inclisiran decreased from 23.5% (n/N=4152/17,658) to 12.8% (n/N=2264/17,658) and 7.8% (n/N=1370/17,658) of patients, respectively

Figure 2. LDL-C goal attainment (A) and predicted 10-year CV risk (B), per the ESC/EAS guidelines, after the sequential addition of ezetimibe and bempedoic acid in the resampled SANTORINI UK cohort with replacement focusing on patients with ASCVD and SI



Data are presented as mean (SD).
BA, bempedoic acid; **CV**, cardiovascular; **EAS**, European Atherosclerosis Society; **ESC**, European Society of Cardiology; **EZE**, ezetimibe; **LDL-C**, low-density lipoprotein cholesterol; **SD**, standard deviation; **SI**, statin intolerance.

CONCLUSIONS

Simulated sequential optimisation of oral LLT with ezetimibe and bempedoic acid substantially increased LDL-C goal attainment and reduced predicted CV risk among UK patients with SI and ASCVD

Across all scenarios, the number of patients remaining eligible for inclisiran was reduced by more than half, suggesting that optimisation of oral LLT may decrease the need for escalation to injectable therapies

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