CO152

# Simulation of Long-Term Impact of Bempedoic Acid and Ezetimibe on Atherosclerotic Cardiovascular Disease Outcomes in Europe

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## Background

- Elevated low-density lipoprotein cholesterol (LDL-C) is a causal and modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD) events.
- The 2019 European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) guidelines endorse the use of lipid-lowering combination therapy to achieve recommended LDL-C levels.
- Bempedoic acid (BA; 180 mg) and its fixed-dose combination (FDC) with ezetimibe (EZE; 10 mg) are available in several European countries for patients with inadequate cholesterol control for their level of ASCVD risk based on the LDL-C–lowering efficacy in phase 3 trials.[1-4]

## Objective

- To estimate the long-term (over 10 years) reduction in ASCVD events, which is potentially achievable with the additional use of BA-EZE FDC (versus no additional treatment on top of background therapy with/without EZE and/or maximum-tolerated or low-dose statin) in clinical practice in Europe, using Markov model simulation.

## Methods

- Baseline LDL-C and other ASCVD risk factors were sourced from observed treatment data with 1-year follow-up in the real-world, observational SANTORINI study (NCT04271280, sponsored by Daiichi Sankyo Europe GmbH)[5] in patients with hypercholesterolaemia with high/very high ASCVD risk in 14 European countries (Table 1).
- The analysis used a Markov cohort model[6] (Figure 1) that has been accepted by multiple health technology assessment agencies (e.g., TA694[3]). The model simulated the natural history of ASCVD events in 4 patient cohorts:
  1. Patients with statin intolerance not taking background EZE
  2. Patients with statin intolerance taking background EZE
  3. Patients on maximum-tolerated statin not taking background EZE
  4. Patients on maximum-tolerated statin taking background EZE
- In the model, evidence of LDL-C reduction was drawn from a network meta-analysis that included 5 pivotal BA trials. The LDL-C reduction then was mapped to ASCVD risk reduction using the relationship demonstrated by the widely accepted Cholesterol Treatment Trialists' Collaboration meta-analysis.[7-9] LDL-C reduction with BA-EZE FDC versus EZE plus background therapy was 27.3% in statin-intolerant (SI) patients and 12.4% in patients on maximum-tolerated statin (MTS); versus background therapy without EZE, reduction was 54.1% (SI) and 29.9% (MTS).[10]
- The model calculated the expected ASCVD event reduction with BA-EZE FDC for Western Europe overall based on patient characteristics for each treatment cohort from all 14 SANTORINI countries and ESC Atlas prevalence estimates.[11]

**Table 1. Patient Baseline Characteristics for the Pooled 14 SANTORINI Countries Used for the Modelled Population**

| | Statin intolerant[a] | | Maximum-tolerated statin | |
|---|---|---|---|---|
| | No EZE | With EZE | No EZE | With EZE |
| Age, mean, years | 66.3 | 66.7 | 66.5 | 63.7 |
| Female (%) | 37.2 | 41.3 | 26.2 | 25.3 |
| Diabetes (%) | 39.3 | 43.3 | 41.1 | 33.5 |
| Heterozygous familial hypercholesterolemia (%) | 7.4 | 8.0 | 4.4 | 11.4 |
| Secondary prevention[b] (%) | 55.4 | 72.0 | 73.9 | 85.3 |
| Prior unstable angina (%) | 7.0 | 8.0 | 11.0 | 13.5 |
| Prior myocardial infarction (%) | 21.8 | 30.7 | 39.9 | 53.0 |
| Prior transient ischaemic attack (%) | 3.7 | 7.3 | 4.6 | 3.2 |
| Prior ischaemic stroke (%) | 4.0 | 8.0 | 7.2 | 5.5 |
| Baseline LDL-C, mean (SD)[c] | | | | |
| mmol/L | 3.23 (0.65) | 2.55 (0.51) | 2.01 (0.40) | 1.77 (0.35) |
| mg/dL | 124.87 (24.97) | 98.76 (19.75) | 77.59 (15.52) | 68.53 (13.71) |

SD = standard deviation.
[a] Patients on EZE only; patients on low-intensity statin and EZE; patients on no lipid-modifying therapies; patients on low-intensity statin only.
[b] Patients with clinically manifest ASCVD, where clinically manifest ASCVD includes: angina pectoris, unstable angina, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, TIA, stroke, carotid artery disease, lower extremity artery disease, retinal vascular disease, abdominal aortic aneurysm, renovascular disease.
[c] SD was not used as an input parameter in the model.

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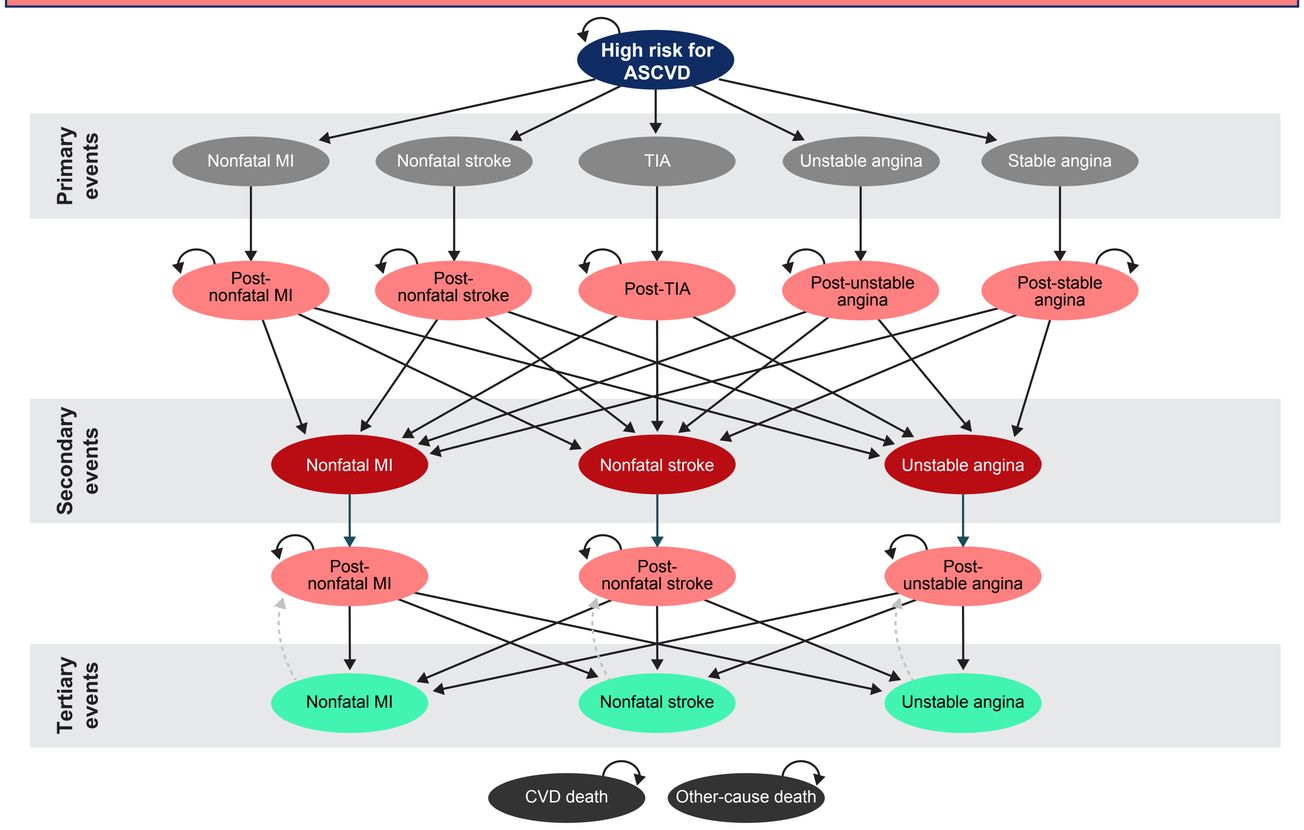
**Figure 1. Model Diagram**




MI = myocardial infarction; TIA = transient ischaemic attack.
Note: Revascularisations were modelled as an event that can occur within any health state.

## Results

- The number of people with high/very high ASCVD risk in Western Europe was estimated to be 39,623,567.
- Over 10 years, and when aggregating the results of our 4 analysed patient cohorts, treatment with BA-EZE FDC would potentially avoid an estimated 1,557,087 ASCVD events (39 per 1,000 patients) versus no additional treatment (Table 2 and Table 3), representing a 7.3% reduction in events.
- The simulated reductions were predominantly in myocardial infarction and ASCVD death, with smaller reductions in ischaemic stroke, unstable angina, and revascularisation.

**Table 2. 10-year Incidence and Number of Cardiovascular Events With and Without FDC in Western Europe (All 4 Patient Cohorts Combined)**

| | 10-year incidence of CV events (per 1,000 patients) | | | Number of CV events over 10 years in Western Europe | | |
|---|---|---|---|---|---|---|
| | With FDC | Without FDC | Rate ratio | With FDC | Without FDC | Events avoided |
| Myocardial infarction | 94.3 | 105.6 | 0.89 | 3,738,468 | 4,183,267 | 444,798 |
| Unstable angina | 47.2 | 52.9 | 0.89 | 1,871,762 | 2,097,782 | 226,019 |
| Ischaemic stroke | 75.9 | 82.9 | 0.92 | 3,005,844 | 3,284,446 | 278,602 |
| Transient ischaemic attack | 34.0 | 34.0 | 1.00 | 1,348,248 | 1,346,187 | –2,061 |
| Revascularisations | 39.8 | 44.8 | 0.89 | 1,578,901 | 1,775,476 | 196,575 |
| Cardiovascular death | 204.4 | 214.9 | 0.95 | 8,100,403 | 8,513,557 | 413,154 |
| **Total** | **495.8** | **535.1** | **0.93** | **19,643,626** | **21,200,714** | **1,557,087** |

**Table 3. Number of Events Avoided in Western Europe by Cohort and Overall**

| | Statin intolerant | | Maximum-tolerated statin | | All 4 cohorts combined |
|---|---|---|---|---|---|
| | No EZE | With EZE | No EZE | With EZE | |
| Myocardial infarction | 79,405 | 15,569 | 288,595 | 61,229 | 444,798 |
| Unstable angina | 38,940 | 7,842 | 147,579 | 31,658 | 226,019 |
| Ischaemic stroke | 49,782 | 11,398 | 184,024 | 33,398 | 278,602 |
| Transient ischaemic attack | –642 | 48 | –1,241 | –226 | –2,061 |
| Revascularisations | 38,339 | 6,891 | 126,479 | 24,866 | 196,575 |
| Cardiovascular death | 69,184 | 14,715 | 276,453 | 52,802 | 413,154 |
| **Total** | **275,009** | **56,464** | **1,021,888** | **203,726** | **1,557,087** |

## Conclusion

Use of BA-EZE FDC with or without statins in the oral lipid-lowering treatment pathway in Western Europe could lead to a substantial 7.3% reduction in the number of ASCVD events over 10 years in patients at high or very high ASCVD risk.

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