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Cost-effectiveness of evolocumab in treatment of HeFH in Bulgaria: Measuring health benefit by effectively-treated patient-years (ETPY)

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BACKGROUND

An elevated level of low-density lipoprotein cholesterol (LDL-C) constitutes an important modifiable risk factor for cardiovascular disease (CVD)[1,2], a medical condition that is the leading reason for hospitalization and accounts for nearly two-thirds of all-cause mortality in Bulgaria[3]. Individuals with heterozygous familial hypercholesterolemia (HeFH) are particularly vulnerable to CVD events and often do not achieve adequate reduction of LDL-C with standard of care (SoC).

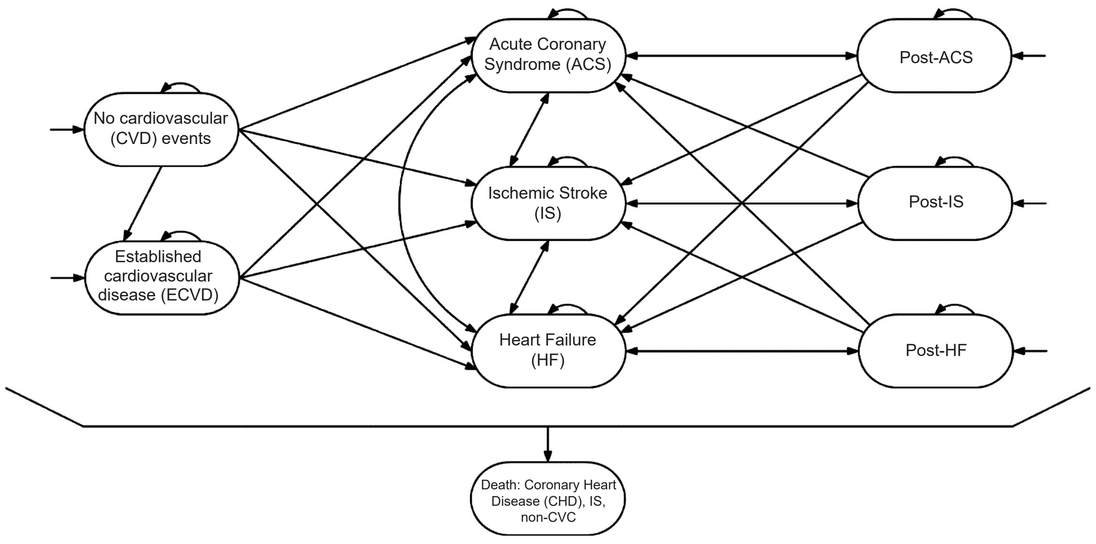
OBJECTIVES

The objective of this analysis was to compare the addition of evolocumab to SoC (high-intensity statin) versus SoC alone in patients with HeFH from the Bulgarian public health care perspective.

METHODS

- A previously published Markov cohort state transition model[4,21,22] was adapted, considering a Bulgarian payer perspective and a life-long treatment duration. The model employs annual cycles; the Markov trace was half-cycle corrected[5].
- The model comprises 11 main health states **(Figure 1)**, and 13 composite health states created to retain memory of previous CV events. The states for ACS, IS and HF cover the first year period after the event; states with the prefix 'post-' cover subsequent years.
- A disease-specific measure of health outcome, effectively treated patient-years (ETPYs), was devised. It is the product of the proportion of patients that attain a recommended[6-8] reduction in LDL-C of ≥50% and the predicted survival in each cycle. Consequently, the incremental cost-effectiveness ratio (ICER) was estimated as the incremental cost per incremental ETPY.

Figure 1. Simplified model structure



ACS, acute coronary syndrome (defined as unstable angina [UA] or myocardial infarction [MI]; ECVD, established cardiovascular disease; HF, heart failure; IS, ischemic stroke.

- Demographics, baseline characteristics and efficacy data were taken from evolocumab's phase 3 trial in HeFH patients, RUTHERFORD-2[9].
- Published risk-equations[10,11] used patient characteristics to estimate the baseline CV event risk, which was then adjusted for the increased risk in this population compared with the general hyperlipidemic population[12].
- The proportion of patients that attain a LDL-C reduction of ≥50% after adding evolocumab to SoC versus SoC alone was 79.25% (95% CI: 70.28%-86.51%) and 1.96% (95%CI: 0.05%-10.45%), respectively.
- The LDL-C reductions were translated into reduced CV event rates based on the event-specific relationship observed in the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analyses[13,14]. **Table 1** shows the CV event rate ratio per 1 mmol/L (38.67 mg/dL) of LDL-C reduction.

Table 1. Model inputs

Event	Rate Ratio (99% CI)	Direct Cost (BGN)
ECVD	0.71[a] (0.58-0.87)	582.05[b]
ACS	0.71 (0.58-0.87)	7,384.10
IS	0.69 (0.50-0.95)	4,154.84
HF	0.71[a] (0.58-0.87)	2,569.28
Post-ACS	–	582.05
Post-IS	–	223.03
Post-HF	–	2,564.61
CHD death	0.80 (0.76-0.85)	5,171.50
IS death	1.00[c]	8,095.00
RV[d]	0.66 (0.60-0.73)[e]	5,498.92

[a]Assumed to be equivalent to ACS
[b]Assumed to be equivalent to the costs attributed to subsequent years of ACS
[c]Assumed equal to 1 because of statistical non-significance (RR 1.04; 95% CI: 0.77-1.41)
[c]Revascularization: percutaneous coronary intervention or coronary artery bypass graft
[e]Denoting a 95% CI

- Annual direct costs associated with CV events **(Table 1)** were obtained from the National Health Insurance Fund (NZOK)[15,16], and expert opinion.
- The annual cost of evolocumab corresponds to the basic price in Bulgaria after applying a mandatory payback to NZOK according to local legislation[15]. Annual costs for currently reimbursed high-intensity statins in Bulgaria[17] are calculated using a weighted average based on their market share[18].
- All outcomes and costs were discounted at a rate of 5%, according to Bulgarian guidelines[19].

RESULTS

- Predicted lifetime CV event rates, ETPYs and costs are presented in **Table 2**.
- Evolocumab treatment leads to a cost increase of BGN120,111 but also a gain of 9.35 effectively treated patient-years over lifetime, implying an incremental cost per ETPY (ICER) of BGN12,846 (US$6,99020; €6,559)[20].
- It's use is associated with a relative reduction in the CV event rate by 46% (22% per 1 mmol/L), consistent with CTTC.
- Both univariate deterministic and multivariate probabilistic sensitivity analyses indicate that the ICER is robust to changes in efficacy and cost parameters.

Table 2. Cost-effectiveness results

	Evolocumab + SoC	SoC alone	Increment (Δ)
Total life years	12.07	11.15	0.93
Total ETPYs	9.57	0.22	9.35
CV event rates	1.57	2.92	-1.34
ACS	0.71	1.63-	0.93
IS	0.11	0.26	-0.15
HF	0.23	0.36	-0.13
Fatal events	0.53	0.65-	0.13
RV	0.64	1.65-	1.00
Costs (BGN)			
Total cost	139,522	19,412	120,111
Medication	129,260	1,432	127,828
Non-fatal events	2,982	7,088	-4,106
Fatal events	1,175	1,545	-370
RV	1,849	4,862-	3,012
Post-event	2,843	3,381	-537
ICER (BGN/ETPY gained)			**12,846**

CONCLUSIONS

- Adding evolocumab to SoC may be considered cost-effective in light of an additional expense per patient-year gained in which individuals with HeFH receive effective treatment under the terms of international prevention guidelines.
- Acknowledging quality of treatment, ETPYs are an intuitive and clinically meaningful measure of patient benefit that can support healthcare decision-making not subject to the cost-per-QALY paradigm.

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Disclosures

Borissov B has served as a freelance consultant to Amgen. Tsenov S and Villa G are employees and stockholders in Amgen. Urbich M and Georgieva B are employees of Amgen. This work was funded by Amgen (Europe) GmbH.