A FLEXIBLE APPROACH BASED ON MULTI-STATE MODELS AND MICROSIMULATION TO PERFORM A REAL-WORLD COST-EFFECTIVENESS ANALYSIS FOR THE USE PCSK9-i IN HYPERLIPIDEMIA

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Introduction

Antibodies that inhibit proprotein convertase subtilisin–kexin type 9 (PCSK9-i) have emerged as a new class of drugs that effectively lower low-density lipoprotein levels, thus preventing cardiovascular events. Majority of the evidence in terms of the risk-benefit profile and economic-health assessments on the use of PCSK9-i is based on randomized clinical trials [1,2]. However, real-world data could add evidence to this topic. Indeed, using the healthcare utilization databases integrated with electronic health records, it is possible to (i) identify the eligible population for the treatment PCSK9-i, and (ii) assess the effectiveness and cost-effectiveness profile of PCSK9-i. However, statistical challenges in performing such analyses are the identification of appropriate methods to 1) take into account of observational nature of data, 2) model health outcomes and cost in complex time-to-event framework, 3) integrate methods for health-economic evaluations. Decision-analytic models are common choices in economic evaluations to perform a comparison between competing decisions under uncertainty. Albeit these models are usually adopted to perform cost-effectiveness analyses based on data derived from randomized controlled trials, they are less applied in studies based on real-world data [3].

Objective

The aim of this work is to perform a cost-effectiveness analysis for the use of PCSK9-i using real-world data coming from an Italian electronic health database through target trial emulation techniques [4], and flexible parametric multi-state models within a microsimulation framework.

Methods

A cohort of Trieste and Gorizia residents eligible for PCSK9-i was identified from July 2017 to December 2020. Among these, those who started the PCSK9-i therapy were identified and the date of first drug prescription was defined *index date*. For patients that do not initiate PCSK9-i the index date was the eligibility date. Members of the cohort were classified by the treatment strategy, i.e., Lipid-Lowering Treatment (LLT) *vs* LLT + PCSK9-i.

To investigate the cost-effectiveness profile of PCSK9-i, the incremental cost-effectiveness ratio (ICER), defined as the difference in costs between the two competing strategies divided by the difference in clinical outcomes over a time horizon of interest, was calculated. The ICER can be compared with a threshold value to determine whether PCSK9-i are cost-effective. Both model and non-model based methods were applied in this work.

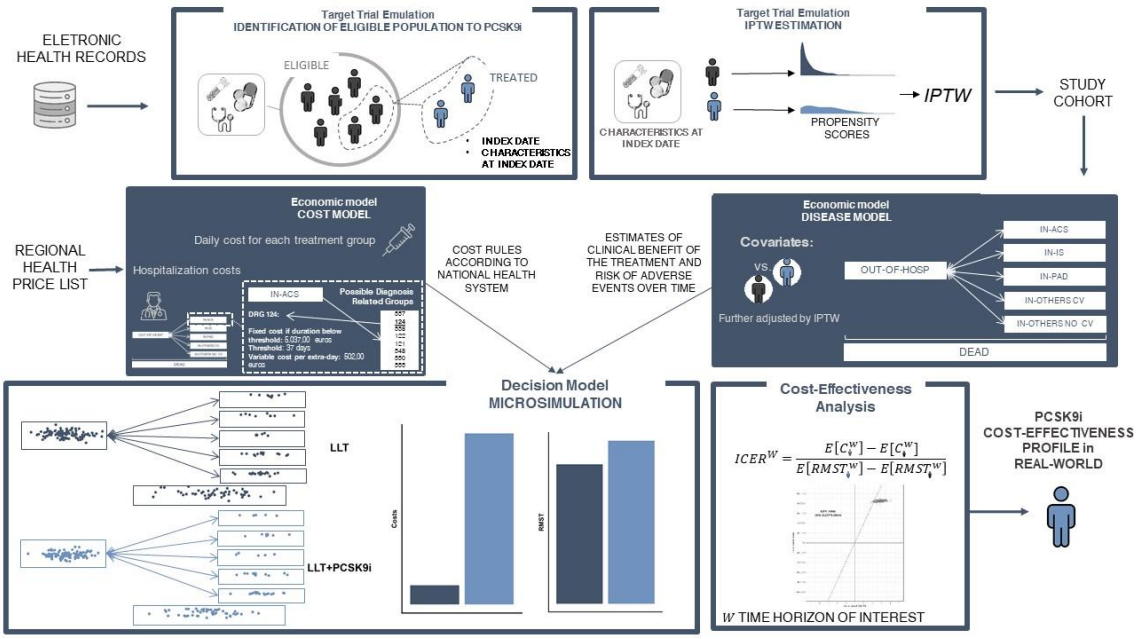
In non-model based methods, healthcare costs accumulated during follow-up were calculated by means of the Bang & Tsiatis estimator [5], a method that takes into account censored cost data. As far as health-related outcome is a concern, Kaplan Meier curves depicting time-free-of-death were calculated. The restricted mean survival time (RMST), calculated through the area under the Kaplan-Meier curve, represented the survival time on average experienced by each cohort member.

Individual decision time models [6] were chosen for their flexibility among model-based methods. The disease plays a crucial role in describing the healthcare paths of individuals over time, including clinical outcomes and cost-related events. A multi-state model with states: “OUT-OF-HOSPITAL”, “IN-HOSPITAL FOR ACUTE CORONARY SYNDROME”, “IN-HOSPITAL FOR ISCHEMIC STROKE”, “IN-HOSPITAL FOR PERIPHERY ARTERY DISEASE” “IN-HOSPITAL FOR OTHER CARDIOVASCULAR CAUSES”, “IN-HOSPITAL FOR NON-CV CAUSES”, “DEAD” was employed. Transition hazards were estimated conditionally on the treatment strategy using a Royston-Parmar spline-based parametric model [7], providing parametric yet flexible hazard estimates. To account for the process history, a time-dependent covariate counting past hospitalizations and a frailty term were considered. The cost model utilized Diagnosis Related Group codes and regional health price lists. Microsimulations were employed to estimate the Restricted Mean Survival Time (RMST) and average healthcare costs for the two treatment groups in the economic model.

Both approaches utilized inverse probability of treatment weights to adjust for varying propensities to receive PCSK9-i in the treatment groups. These weights were estimated using demographic and clinical covariates.

Results

The pipeline of the analysis is summarized in **Figure**. For the disease-model, the “time-reset” time scale was found to be the most appropriate in terms of goodness of fit. Two time-horizon were employed in the analysis: the median observation period in the data (34 months) and the lifetime. The short-term ICER at 34 months obtained with the model-based and non-model based approaches were not statistically different and showed a very high cost-effectiveness threshold (Euro >200 000). On the other hand, in the long-term analysis (only possible with the microsimulation), an ICER of Euro 29 540 (95%CI: 23 773-38 949) was obtained. The sensitivity analysis conducted to evaluate the impact of extrapolating beyond the observed data period in the lifetime microsimulation resulted in an ICER of Euro 28 447, which did not show a significant difference compared to the ICER obtained in the primary analysis. Furthermore, a subgroup analysis showed that patients with diabetes with organ damage and a risk factor have a lower cost-effectiveness threshold.



Conclusions

The PCSK9-i treatment resulted cost-effective in the long term considering a threshold of at least Euro 39 000. The individual-based microsimulation approach demonstrated its significant utility in several ways. Unlike non-model based or alternative model-based methods, it enabled to 1) investigate long-term cost-effectiveness comprehensively, 2) employ an appropriate disease model that aligns with the specific problem under study, and 3) conduct subgroup-specific cost-effectiveness analyses to gain more targeted insights.

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