



## ORIGINAL ARTICLE

# An alternative approach identified optimal risk thresholds for treatment indication: an illustration in coronary heart disease

Anoukh van Giessen<sup>a,\*</sup>, G. Ardine de Wit<sup>a,b</sup>, Karel G.M. Moons<sup>a</sup>, Jannick A.N. Dorresteijn<sup>c</sup>, Hendrik Koffijberg<sup>a,d</sup>

<sup>a</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O. Box 85500, STRAT 6.131, 3508 GA, Utrecht, The Netherlands

<sup>b</sup>National Institute for Public Health and the Environment, P.O. Box 1, 3720 BA, Bilthoven, The Netherlands

<sup>c</sup>Department of Vascular Medicine, University Medical Center Utrecht, PO Box 85500, F02.126, 3508 GA Utrecht, The Netherlands

<sup>d</sup>Department of Health Technology and Services Research, MIRA Institute, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

Accepted 22 September 2017; Published online xxxx

---

**Abstract**

**Objectives:** Treatment thresholds based on risk predictions can be optimized by considering various health (economic) outcomes and performing marginal analyses, but this is rarely performed. We demonstrate a general approach to identify treatment thresholds optimizing individual health (economic) outcomes, illustrated for statin treatment based on 10-year coronary heart disease (CHD) risk predicted by the Framingham risk score.

**Study Design and Setting:** Creating a health economic model for a risk-based prevention strategy, risk thresholds can be evaluated on several outcomes of interest. Selecting an appropriate threshold range and decrement size for the thresholds and adapting the health economic model accordingly, outcomes can be calculated for each risk threshold. A stepwise, or marginal, comparison of clinical as well as health economic outcomes, that is, comparing outcomes using a specific threshold to outcomes of the former threshold while gradually lowering the threshold, then takes into account the balance between additional numbers of individuals treated and their outcomes (additional health effects and costs). In our illustration, using a Markov model for CHD, we evaluated risk thresholds by gradually lowering thresholds from 20% to 0%.

**Results:** This approach can be applied to identify optimal risk thresholds on any outcome, such as to limit complications, maximize health outcomes, or optimize cost-effectiveness. In our illustration, keeping the population-level fraction of statin-induced complications < 10% resulted in thresholds of T = 6% (men) and T = 2% (women). Lowering the threshold and comparing quality-adjusted life-years (QALYs) after each 1% decrease, QALYs were gained down to T = 1% (men) and T = 0% (women). Also accounting for costs, net health benefits were favorable down to T = 3% (men) and T = 6% (women).

**Conclusion:** Using a stepwise risk-based approach to threshold optimization allows for preventive strategies that optimize outcomes. Presenting this comprehensive overview of outcomes will better inform decision makers when defining a treatment threshold. © 2017 Elsevier Inc. All rights reserved.

*Keywords:* Treatment threshold; Risk stratification; Coronary heart disease; Marginal analysis; Cost-effectiveness; Optimization

---

## 1. Introduction

Risk prediction models are tools that combine multiple predictors by assigning relative weights to each predictor

to estimate the probability of a current (diagnostic model) or future (prognostic model) outcome [1]. Based on thresholds specifying certain risks, individuals can be classified into risk categories, which allow tailoring of preventive treatment to individuals who are at high risk and therefore expected to benefit most. In this manner, risk prediction models have become an important aid in clinical decision making [2]. For instance, individuals at high risk (> 20%) for coronary heart disease (CHD), according to a Framingham risk score (FRS), are commonly recommended preventive statin treatment [3,4].

**Funding:** This work was supported by NWO, The Netherlands Organization for Scientific Research (grant number 916.11.126 to H.K.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Conflict of interest:** None.

\* Corresponding author. Tel.: +31-88-7568251; fax: +31-88-7568099.

E-mail address: [a.vangiessen@umcutrecht.nl](mailto:a.vangiessen@umcutrecht.nl) (A. van Giessen).

**What is new?**

- Identifying the optimal threshold based on risk-based (marginal) outcomes provides a treatment threshold above which the preventive treatment will not only be cost-effective on average across the risk levels of all treated individuals, but it will be cost-effective for *all* risk levels of treated individuals. Evaluating risk-based (marginal) outcomes is essential in gaining a comprehensive evidence base to inform society, as well as decision makers and developers of treatment guidelines, on the consequences of defining a particular treatment threshold and inform them in defining the most suitable and adequate threshold. Using health economic modeling and a stepwise (or marginal) risk-based approach to treatment threshold optimization treatment, such as proposed in this paper, risk-based (marginal) outcomes can be evaluated and treatment thresholds can be identified that optimize such outcomes, providing the required comprehensive evidence base.

Risk-based treatment thresholds, such as for CHD prevention, are commonly specified in clinical guidelines. They implicitly aim to trade-off effectiveness and possible harms, as well as costs, of preventive treatment [5–7]. Whereas such evidence-based thresholds are ideally derived from randomized (prediction-treatment) trials studying benefits, harms, and costs of introduction of risk-based prevention strategies, these are often infeasible and rarely performed [8,9]. Instead, health economic models may be constructed to assess the cost-effectiveness of a risk prediction–based preventive treatment strategy, including the application of a specific risk threshold. In such evaluations, commonly, only one or a few risk thresholds are evaluated. Hence, the evaluated threshold with best performance may not actually be optimal when a much larger range of thresholds would have been considered [10–12]. As many existing treatment thresholds are derived from evaluations with the aforementioned limited scope, current preventive strategies may therefore not be optimal.

The identification of an optimal treatment threshold may be improved in two ways. First, for example, Pandya et al. have evaluated the cost-effectiveness of a number of 10-year atherosclerotic cardiovascular disease (ASCVD) risk thresholds, using the new ASCVD risk score, to find its optimal value based on the incremental cost-effectiveness ratio (ICER) [6,13]. Sporadically, similar studies have evaluated the impact of a (limited) number of thresholds to select the one optimizing a specified outcome [13–19]. Instead of only evaluating thresholds on a single specific

outcome, such as the ICER, insight into intermediate, clinical outcomes (e.g., numbers of treated individuals or complications) as well as long-term outcomes (e.g., life-years or costs) may be very informative for decision makers and clinicians who will ultimately define and apply the optimal threshold. Second, recent threshold studies have focused on absolute, or average, outcomes, that is, outcomes when using one specific threshold, or incremental outcomes, that is, the difference between outcomes when using a specific threshold and outcomes when using the current threshold as specified in guidelines [13,17,20,21]. Based on these average or incremental outcomes, one may conclude that applying a prediction model using a (new) threshold may be cost-effective, but as outcomes are averaged over groups of individuals with different risks, this threshold may not be optimal on the level of individual patients. For example, if a new 5% threshold has shown to be cost-effective compared to an original 20% threshold, this implies that the treatment is on average cost-effective across all individuals with predicted risks between 5% and 20%. However, it may be the case that the treatment is cost-effective among the individuals that have a risk between 8% and 20% but not among the individuals in the 5–8% risk category. In that case, the 8% threshold would thus be optimal, for all targeted individuals, which will not be identified if only a one new threshold (5%) or a few (e.g., 5%, 10%, 15%) are evaluated. Assessing marginal outcomes, that is, the difference in outcomes when using risk thresholds that are varied gradually in small steps may thus provide key additional information [20,21].

Considering various (intermediate) outcomes and performing marginal analyses for the identification of a treatment threshold are rarely performed, and a general structured approach to identify optimal treatment thresholds is currently lacking. In this paper, we demonstrate such an approach to identify optimal treatment thresholds and illustrate this approach in a simplified case study for identifying the threshold for risk-based preventive statin treatment for CHD.

**2. Methods**

We propose a general approach of six steps to identify the optimal risk-based treatment threshold based on marginal comparison and resulting in multiple (intermediate) outcomes for decision makers, which is depicted in Fig. 1. These steps will be explained below and are illustrated by the following simplified example.

*In this illustration, we aim to identify the risk-based treatment threshold for CHD prevention by statin treatment and evaluate the use of the adult treatment panel (ATP) III guideline, which recommends statin treatment for CHD prevention in individuals classified into the high-risk category (FRS > 20%) [3,4]. Recently, it has been demonstrated that statins also reduce cardiovascular events in people with (much) lower risk [22]. Lowering the current threshold might further improve health outcomes [6,23,24], but this may also lead to*

Download English Version:

<https://daneshyari.com/en/article/7519064>

Download Persian Version:

<https://daneshyari.com/article/7519064>

[Daneshyari.com](https://daneshyari.com)