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Evidence based policy decisions through a Bayesian approach: The case of a statin appraisal in the Netherlands

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ABSTRACT

It has often been suggested that Bayesian statistics is more congenial to the informational needs of policy makers than the standard frequentist methods. In order to illustrate this claim, we use both a Bayesian and a frequentist approach for revisiting a recommendation by the Dutch National Health Insurance Board that for all patients requiring lipid reduction, the cheapest alternative (Simvastatin) should be prescribed. We investigate whether Simvastatin and Atorvastatin, the most commonly used alternative, can be considered equivalent in terms of lipid control for patients with heterozygous familial hypercholesterolemia.

Priors were elicited from GPs, cardiologists and internists. A systematic review for studies comparing Simvastatin and Atorvastatin was performed. The data from these studies were combined with the priors in a Bayesian meta-analysis. For comparability a frequentist meta-analysis was also performed.

The two approaches lead to similar point estimates and 95% intervals. However, the Bayesian outcomes are easier to understand and interpret, and our Bayesian analysis leads to additional outcomes that would have more direct pertinence for policy makers, and which could help them to assess what the data have to say about the questions that are most relevant to the problems they face.

1. Introduction

Policy decisions regarding the reimbursement of drugs have major implications for access to medical treatments for patients. They also have important consequences for physicians, pharmacists, insurers, and manufacturers. For reasons such as these, the available evidence on clinical and cost effectiveness of drugs should be carefully assessed when reimbursement decisions are made. Clearly, identification and appraisal of the relevant evidence base, and presentation of the results in a format that is transparent and understandable for decision makers poses a considerable challenge. What would be needed, is a way of analyzing and presenting the available data in such a way, that clear answers can be given to relevant policy issues, taking into account the limitations that are inherent to the data.

It has often been suggested that a Bayesian approach to data analysis may be better suited than the standard frequentist methods for answering policy questions (e.g. [1–8]). There are three main reasons for this. Firstly, Bayesian methods offer much flexibility for integrating evidence from various sources, including evidence derived from clinicians' and or patients' experiences. The Bayesian approach incorporates a formal model for combining prior

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information with newly available information, so that previously held judgments are updated. Secondly, Bayesian statistics has important conceptual advantages over frequentist statistics, making the outcomes easier to correctly interpret and understand for relative lay persons (i.e. members of appraisal committees). And thirdly, a Bayesian approach allows for more flexibility in presenting outcomes that are of particular interest and relevance, such as the probability that the parameter of interest exceeds some value that is thought to be particularly relevant by the user (such as a clinically relevant difference).

In spite of these potential advantages, the Bayesian approach is relatively unfamiliar and little used in the context of supporting policy decisions. In order to illustrate the above claims about the advantages of Bayesian methods for policy making, we revisit a Dutch statin appraisal by using a Bayesian approach. For comparability we also performed a frequentist counterpart to the Bayesian analysis. In this particular study we mainly focus on the second and third of the abovementioned advantages of Bayesian methods (i.e. the conceptual advantage), although this paper also touches on the first. For a more elaborated illustration of the first advantage, see for instance Woertman and van der Wilt [9].

Here we review a specific recommendation made by the National Health Insurance Board of the Netherlands (College voor Zorgverzekeringen, CVZ), an advisory body to the Ministry of Health on coverage issues. In 2008, it recommended that for all patients requiring lipid reduction, the cheapest alternative (Simvastatin) should be prescribed by Dutch GPs and clinicians, except when for some patient it is shown to be insufficiently effective or if there is some other medical reason why treatment with Simvastatin is not possible [10]. It was estimated that this could result in annual savings of 168–226 million euros [10]. The policy was vigorously opposed by clinicians, manufacturers and patient organizations [11,12]. The principal issue was the presumed equivalence of statins, failing to take into account the differences between various patient subgroups. Statins have widely been recognized as the principal lipid lowering drugs. Extensive evidence from randomized controlled clinical trials and cohort studies prove that statins significantly reduce the risk of cardiovascular disease and mortality [13–19]. The purpose of the present paper is to explore what inferences can be made using a Bayesian approach regarding the therapeutic value in terms of lipid lowering of Simvastatin and Atorvastatin (the most commonly used alternative) in the treatment of patients with heterozygous familial hypercholesterolemia (HeFH). Patients with HeFH are at an increased risk of premature coronary artery disease, and this group of patients is frequently used as a model for lipid-lowering interventions [20]. The main point of this paper has to do with the difference in implications between a Bayesian and a frequentist approach, and to this end it suffices to only look at the surrogate endpoint of lipid control.

2. Materials and methods

In this paper we use both Bayesian and the standard frequentist methods to analyze data.

Bayesian statistics works with three main entities: the prior, the likelihood and the posterior. The prior distribution is a probability distribution that expresses the uncertainty about the parameter of interest that exists *before* the new data from an experiment or study is seen or considered. This prior information about the parameter of interest could for instance be based on previous research or on expert opinion. All the new information from the experiment or study is condensed in the likelihood function. This likelihood function expresses how likely the different values of the parameter of interest are, given the observed data. The posterior distribution combines the information contained in the prior and likelihood, and expresses the uncertainty that is present about the parameter of interest, given the observed data. In a Bayesian analysis all conclusions are based on the posterior distribution.

2.1. Prior probability elicitation

In the current study the prior distribution is based on expert opinion. 109 physicians with relevant experience in treating HeFH patients were invited to provide prior probability estimates. 40 internists and 34 cardiologists were recruited from the Radboud University Nijmegen Medical Centre in the Netherlands. 35 general practitioners, associated with 9 different practices, were recruited from the Nijmegen regional Academic Network for General Practitioners.

Respondents were asked to provide probability estimates through a pre-tested, web-based valuation form. The form provided a short patient description of an adult, newly diagnosed patient with HeFH, without co-morbidity or medication history, and a baseline plasma LDL-C level of 7.0 mmol/L. One of the two treatments was assumed to be started and a follow-up period of six months was presumed. For each treatment, clinicians were asked to provide probabilities that after six months of this treatment, the reduction in LDL-C would be between 0 and 10 percent, between 10 and 20 percent, etc. up to between 90 and 100%. The web-based valuation form was designed to ensure that the probabilities in the ten categories would always sum to one. The programme was set up to allow for an iterative process of providing probabilities, seeing the summed probabilities, and adjusting the probabilities if the sum of probabilities did not equal one. Respondents' answers were saved only if the probabilities indeed summed to one and the respondents confirmed that these probabilities represented their beliefs correctly.

For Atorvastatin and Simvastatin separately, the individual prior probability estimates for any 10 percent category were averaged over the clinicians to produce composite priors (arithmetic pooling [1]). These two composite priors were converted from relative terms (a percent reduction) to absolute terms, after which we determined the means and standard deviations and expressed them in terms of normal distributions.

For both statins, we determined composite priors for all responding physicians combined, as well as (composite) priors for internists, cardiologists and GPs separately.