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The Importance of Model Structure in the Cost-Effectiveness Analysis of Primary Care Interventions for the Management of Hypertension

Maria Cristina Peñaloza-Ramos, MA[1,*], *Sue Jowett, PhD*[1], *Andrew John Sutton, PhD*[2], *Richard J. McManus, MA, PhD, MBBS, FRCGP, FRCP*[3], *Pelham Barton, PhD*[1]

[1]Health Economics Unit, University of Birmingham, Birmingham, UK; [2]Health Economics Unit, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK; [3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

A B S T R A C T

Background: Management of hypertension can lead to significant reductions in blood pressure, thereby reducing the risk of cardiovascular disease. Modeling the course of cardiovascular disease is not without complications, and uncertainty surrounding the structure of a model will almost always arise once a choice of a model structure is defined. **Objectives:** To provide a practical illustration of the impact on the results of cost-effectiveness of changing or adapting model structures in a previously published cost-utility analysis of a primary care intervention for the management of hypertension Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups (TASMIN-SR). **Methods:** The case study assessed the structural uncertainty arising from model structure and from the exclusion of secondary events. Four alternative model structures were implemented. Long-term cost-effectiveness was estimated and the results compared with those from the TASMIN-SR model. **Results:** The main cost-effectiveness results obtained in the TASMIN-SR study did not change with the implementation of alternative model structures. Choice of model type was limited to a cohort Markov model, and because of the lack of epidemiological data, only model 4 captured structural uncertainty arising from the exclusion of secondary events in the case study model. **Conclusions:** The results of this study indicate that the main conclusions drawn from the TASMIN-SR model of cost-effectiveness were robust to changes in model structure and the inclusion of secondary events. Even though one of the models produced results that were different to those of TASMIN-SR, the fact that the main conclusions were identical suggests that a more parsimonious model may have sufficed.

Keywords: cardiovascular disease, decision-analytic modeling, hypertension, modeling, structural uncertainty.

Introduction

High blood pressure (BP) (or *hypertension*, defined as BP that is persistently high [140/90 mm Hg or higher]) is one of the most important but preventable causes of premature morbidity and mortality in the United Kingdom and worldwide [1–3]. Hypertension is a major risk factor for ischemic and hemorrhagic stroke, myocardial infarction (MI), heart failure (HF), chronic kidney disease (CKD), cognitive decline, and premature death. It has been estimated that in England, a 2 mm Hg reduction in average systolic BP for 40- to 69-year-olds could save 1500 to 2000 lives per year [4]. One of the most common interventions in primary care is the management of hypertension. Self-management of hypertension, in which individuals monitor their own BP and adjust their own medication, has been shown to lead to significantly lower BP in those with hypertension, including individuals with higher cardiovascular risk [5–7].

Economic evaluations can be undertaken alongside randomized controlled trials (RCTs) in which costs and health outcomes are measured. The primary outcome of RCTs in hypertension is often a change in BP. A change in BP, however, corresponds to an intermediate outcome, wherein the final outcome of interest in this case is the risk of cardiovascular disease (CVD). Because RCTs rarely follow patients over the long-term, decision-analytic modeling (DAM) provides a vehicle to extrapolate the impact of a change in BP on the risk of CVD events in the long-term. Modeling the course of CVD can be challenging, requiring CVD risk factors (smoking, cholesterol, and diabetes), interactions among the risk factors, adverse events, and the resulting health states (e.g., stroke sequelae and angina) to be considered.

The targets and self-management for the control of blood pressure in stroke and at risk groups (TASMIN-SR) [6] trial aimed to determine the effect of self-monitoring with self-titration (self-management) of antihypertensive medication on systolic BP

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* *Address correspondence to:* Maria Cristina Peñaloza-Ramos, Health Economics Unit, Institute of Applied Health Research, University of Birmingham, Public Health Building, Edgbaston, Birmingham B15 2TT, UK.

E-mail: m.c.penaloza@bham.ac.uk.

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among hypertensive patients with suboptimal BP control and pre-existing CVD, diabetes mellitus, and CKD compared with usual care. An economic evaluation was undertaken to assess the cost-effectiveness of the self-management intervention compared with usual care [7]. The main results indicated that self-management of BP in high-risk patients with poorly controlled hypertension not only reduced BP compared with usual care but also represented a cost-effective use of health care resources.

The aim of this study was to assess the structural uncertainty in the TASMIN-SR model–based cost-effectiveness analysis [7] and to provide a practical illustration of the impact on the results of cost-effectiveness of changing or adapting model structures in a model-based economic evaluation on the primary prevention of CVD.

Structural Uncertainty

We consider *structural uncertainty* as uncertainty associated with all aspects of model structure, that is, health states and relationships between health states. This is in contrast to parameter uncertainty, which is very much focused on the parameters used in a model and their uncertainty. Structural uncertainty reflects the extent to which a given model differs from the real system it is intended to reflect [8,9], and will almost always arise once a choice of model structure or choice of relationships between inputs and outputs is defined within the model development process [10].

Differences in model structure are dependent on the importance given to various aspects of the process being modeled, allowing in some instances for model simplifications. In some cases, these originate when data are not available, although their inclusion could potentially still be relevant for the analysis.

The nature of models being a simplification of reality means that many assumptions need to be adopted during the model-building process [10–12]. This can potentially lead to a wide variation in model predictions with potential impact on funding decisions [13].

Various alternative statistical methods have been proposed to address the impact of structural uncertainty on the results of cost-effectiveness [8,10,13–23], whereas some other authors have provided examples on how to implement some of these methods in different clinical areas [24–26]. Nevertheless, it has been recognized that methods for quantifying structural uncertainty are less well described if compared with methods for characterizing parametric or methodological uncertainty [8,10,13,16]. A main challenge in addressing structural uncertainty is posed by the many issues that have been identified as “structural uncertainty,” making it a complex task (which may not even be cost-effective) to address properly [27].

Previous studies [16,28–30] indicate that even though elements pertaining to structural uncertainty are occasionally considered, the assessment of structural uncertainty is not common practice and most modeling tends to omit testing for structural uncertainty. It is, however, essential to assess the extent to which model predictions are influenced by such choices made within the model development process [28].

Challenges posed by the assessment of structural uncertainty might be overcome if additional research is undertaken on an experimental basis. Case studies aimed at measuring the impact of changing or adapting chosen model structures on previous results of cost-effectiveness could provide insightful evidence of how much results would be altered when alternative model structures are implemented. This would also provide evidence of what other elements, besides model structure, may be critical in affecting results of cost-effectiveness.

Methods

Taking the TASMIN-SR model as the case study, the research methods of this study are outlined as follows: 1) description of the TASMIN-SR model; 2) alternative model structures to the TASMIN-SR model; 3) definition and implementation of changes to the structure of the TASMIN-SR model; 4) inclusion of secondary events in the TASMIN-SR model; and 5) identification of alternative model input parameters and analysis.

Description of the TASMIN-SR Model

A detailed description of the original Markov model can be found elsewhere [7]. Briefly, the economic evaluation consisted of a model-based cost-utility analysis to assess the long-term cost-effectiveness of the self-management intervention in a high-risk patient population compared with usual care, using a Markov model to extrapolate the results of the TASMIN-SR trial [6] given in terms of BP to the long-term risk of cardiovascular end points. The study considered a cohort of 70-year-old patients (39% women) with suboptimal hypertension (BP ≥ 130/80 mm Hg at baseline), combined with a history of stroke, diabetes, coronary heart disease (CHD), and CKD. The model was run over a lifetime time horizon using a 6-month time cycle, with results presented from a UK National Health Service and Personal Social Services perspective.

The structure of the TASMIN-SR model is shown in Figure 1. Patients start in an initial “HR” or high-risk health state representing individuals with hypertension and a history of stroke, CHD, diabetes, and CKD. The model simulates the lifetime of these patients until any of three possible events occur (stroke, MI, and unstable angina [UA]) or the patient dies from other causes. Individuals who survive an acute phase in any of the health states progress into a postevent or chronic phase for that condition until death, with no recurrences of cardiovascular events being possible. A lower quality of life was permanently applied until death in all chronic health states.

The CVD history of patients entering the model was informed by the TASMIN-SR [6] trial data. Transition probabilities of suffering a stroke, MI, or UA were obtained from the literature for each of the high-risk conditions. Age-related risk reductions from treatment for MI, UA, and stroke were estimated using trial-based systolic BP reductions at 6 and 12 months (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.003). Resource use and costs were obtained from trial data and published studies (see Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.03.003).

Alternative Model Structures to the TASMIN-SR Model

Structural uncertainty was addressed here by assessing issues such as the adequacy of the type of model used (Markov), the structure of the model (health states and transition probabilities) that translates into plausible alternative model structures, and data availability to inform input parameters, for example, the risk of secondary events.

A systematic review was used to inform plausible alternative model structures [30]. The review identified model-based studies of interventions aimed at lowering the BP of patients with hypertension and at risk of CVD, in which the management of hypertension was part of a primary prevention strategy [30]. The aim of the review was to assess compliance of model-based economic evaluations to DAM guidelines [30]. The review identified 13 model-based economic evaluations from the literature that were used to inform the changes implemented to the TASMIN-SR model [30]. Information on the inclusion or exclusion of potentially relevant comparators, type of model used, health states included, recurrence of events, choice of covariate effects used in the transition probabilities, and the inclusion or exclusion of any other assumption(s) pertaining to structural