ORIGINAL ARTICLE
ARTIGO ORIGINAL

Application of the MCDA method for assessing new technologies for familial hypercholesterolaemia treatment

Aplicação do método MCDA para avaliar novas tecnologias para o tratamento da hipercolesterolemia familiar

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DOI: 10.21115/JBES.v13.n1.p14-20

Keywords
MCDA, decision-making, familial hypercholesterolaemia, health technology assessment

ABSTRACT

Objective: Familial hypercholesterolaemia is a hereditary disease characterized by very high levels of low-density lipoprotein cholesterol and an elevated risk of early-onset cardiovascular disorders. New drugs provide alternatives for the treatment of patients with homozygous familial hypercholesterolaemia. The study aims to explore a practical application of multiple-criteria decision analysis on prioritization of new and emerging technologies for familial hypercholesterolaemia. **Methods:** The decision model was constructed using the MACBETH method. There were three stages: structuring the problem, measuring the performance of alternatives, and building the model. The weights for alternatives and levels were obtained by indirect comparisons, which evaluated the attractiveness of the performance levels of the criteria using the swing weights technique. **Results:** The drugs lomitapide, ezetimibe, evolocumab, and mipomersen were selected as alternatives for decision-making. "Cardiovascular Death", "Stroke" and "Acute Myocardial Infarction" had the three most significant weights. The criteria with the lowest weights were "Comfort" and "LDL-C Reduction". The top-ranked technology was evolocumab, with an overall score of 59.87, followed by ezetimibe, with a score of 37.21. **Conclusion:** How to apply the result of a higher score in the actual decision-making process still requires further studies. The case in question showed that evolocumab has more performance benefits than other drugs but with a cost approximately 50 times higher.

Palavras-chave:
MCDA, tomada de decisão, hipercolesterolemia familiar, avaliação de tecnologias em saúde

RESUMO

Objetivo: A hipercolesterolemia familiar é uma doença hereditária caracterizada por níveis muito elevados de lipoproteína de baixa densidade (LDL-colesterol) e um risco elevado de doenças cardiovasculares de início precoce. Novos medicamentos oferecem alternativas para o tratamento de pacientes com hipercolesterolemia familiar homozigótica. Esse estudo tem como objetivo explorar uma aplicação prática da análise de decisão multicritério na priorização de tecnologias novas e emergentes para hipercolesterolemia familiar. **Métodos:** O modelo de decisão foi construído usando o método MACBETH. Três etapas foram criadas: estruturação do problema, mensuração do desempenho das alternativas e construção do modelo. Os pesos para alternativas e níveis foram obtidos por comparações indiretas, que avaliaram a atratividade dos níveis de desempenho dos critérios usando a técnica de pesos de balanço. **Resultados:** Os medicamentos lomitapida, ezetimiba, evolocumabe e mipomersen foram selecionados como alternativas para a tomada de decisão. "Morte Cardiovascular", "Acidente vascular cerebral" e "Infarto Agudo do Miocárdio" tiveram os três pesos mais significativos. Os critérios com os menores pesos foram "Conforto" e "Redução do LDL-C". A tecnologia mais bem avaliada foi o evolocumabe, com pontuação geral de 59,87, seguido da ezetimiba, com pontuação de 37,21. **Conclusão:** Ainda são necessários estudos para determinar como aplicar o resultado de uma pontuação mais alta no processo de tomada de decisão. O caso em questão demonstrou que o evolocumabe tem benefícios mais significativos em relação aos outros medicamentos, mas com um custo cerca de 50 vezes maior.

Received on: 03/03/2021. **Approved for publication on:** 04/16/2021.
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Financial disclosure: None reported.
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Introduction

Familial hypercholesterolaemia (FH) is a hereditary autosomal dominant syndrome characterized by very high levels of low-density lipoprotein cholesterol (LDL-C), cholesterol deposits (xanthomas) in tendons and skin, and an elevated risk of early-onset cardiovascular diseases (Rosenson & Durrington, 2019). FH can be classified as homozygous or heterozygous. The homozygous form is rarer and associated with more severe cases.

The prevalence of FH is often based only on clinical criteria and LDL-C levels without genetic testing, leading to varied estimates. A study conducted in 2012 in the general population in Denmark estimated the prevalence of FH as 1 per 137 individuals, and only 48% of individuals classified as having FH used lipid-lowering agents (Benn *et al.*, 2012). Homozygous familial hypercholesterolaemia (HoFH) is classified as ultra-rare, with an estimated prevalence in the Netherlands of 1:300,000 individuals. This syndrome is associated with mutations in genes that regulate lipid metabolism: the LDL receptor (LDLR) gene, the apolipoprotein B-100 (APOB) gene or the proprotein convertase subtilisin-like/kexin type 9 (PCSK9) gene (Rosenson & Durrington, 2019; Khera *et al.*, 2016; Drummond *et al.*, 2007). Technologies are currently being tested for each of these targets. In the absence of genetic tests to determine which mutation is present, the diagnosis of FH is based on the evaluation of clinical criteria such as total cholesterol and LDL-C levels, physical examination, and family history (Rosenson & Durrington, 2019).

Coronary artery disease (CAD) and stroke have a higher incidence in patients with FH. LDL-C higher than 190 mg/dL (FH phenotype) is associated with a five times higher risk of CAD and four times higher risk of stroke (Khera *et al.*, 2016). For patients with LDL-C above 190 mg/dL and mutations in either the LDLR, APOB or PCSK9 gene, the risk of CAD could be 22 times higher (Khera *et al.*, 2016).

Treatment of FH with statins is ineffective in decreasing LDL-C levels (Rosenson R, Durrington, 2019). New drugs provide alternatives for the treatment of patients with FH, especially for homozygous individuals. Evaluation for decision-making on which drug to choose is complex given the high direct costs of drugs for rare diseases (Drummond *et al.*, 2007). Cost-effectiveness analysis is usually considered inadequate for rare diseases because their low prevalence in the population results in a small drug production volume. The monopoly of innovations generates incremental cost-effectiveness ratios (ICER) well above the traditional thresholds, making alternative assessment methods necessary (Drummond *et al.*, 2007).

Healthcare decisions are usually characterized by a low degree of transparency due to lacking a systematic decision analysis structure (Muhlbacher & Kaczynski, 2016). In some health technology assessment agencies, such as the National Institute for Health and Care Excellence (NICE) in England, the main driver of decisions is the estimated ICER. In this context, multiple-criteria decision analysis (MCDA) methods have been suggested as great value alternatives in decision-making. They allow structuring the problem, assessing options with pre-established criteria, aggregating values, and calculating the final score of other options transparently and systematically.

Objectives

The study aim was to test the application of the MACBETH method for decision-making on the prioritization of new and emerging technologies for FH. It includes: identify criteria that have a more significant influence on the final decision; obtain a ranking of the technologies for FH according to their performance in each evaluation criterion; and define the efficiency of each technology using the cost-per-unit metric of MCDA.

Methods

Construction of the decision structure

The decision model was constructed in three stages: structuring the problem, measuring alternatives performance, building the model.

Cardiologists and experts in hypercholesterolaemia from the Brazilian National Institute of Cardiology (*Instituto Nacional de Cardiologia* – INC) constructed the definition of the decision problem. Personal interviews and a literature review were conducted to obtain information on FH management. Participants validated an initial set of criteria before the first decision conference.

Once the drugs to be evaluated (alternatives) and the initial criteria were defined, the next step was to find the evidence available for each option. For that purpose, a structured search was designed for the MEDLINE database and adapted to other sources: ClinicalTrials.gov, European Medicines Agency (EMA), Food and Drug Administration (FDA), Integrity®, Cortellis®, and UptoDate®. To define drug prices, the median value of purchases listed on the Price Panel of the Ministry of Planning, Development, and Management of Brazil, was used (Ministério do Planejamento, Desenvolvimento e Gestão. Painel de Preços MPOG).

The model was constructed as a value tree using M-MACBETH© software, including sensitivity and robustness analysis.

Measuring attractiveness by a categorical-based evaluation technique, known by the acronym MACBETH, is an MCDA value measurement model that estimates an overall value for each assessed alternative and ranks them in descending order (Belton & Stewart, 2002).

The MACBETH method has been used in different fields of knowledge, including health care, to support

decision-making, allowing the assessment of several options based on multiple criteria. It has a constructivist approach in which a consultant or decision analyst assists those involved in solving the decision problem that best fits the context and needs of the decision-makers while recognizing the subjectivity of the process (Bana e Costa *et al*., 2012).

The MACBETH method involves binary comparisons between the alternatives for each criterion using qualitative judgments about differences in attractiveness. Thus, given two options or performance levels, with the first being better than the second, the difference in attractiveness between them may be null, very weak, weak, moderate, strong, very strong, or extreme, corresponding to categories on the MACBETH scale (Belton & Stewart, 2002). Lastly, an additive model is created by aggregating scores (performance of technologies) and their weights to produce a ranking of the alternatives. The MACBETH method has some similarities with the analytic hierarchy process (AHP), such as pairwise comparison using a specific scale and differences regarding the calculation of weights and the lower probability of inconsistent judgments (Bana e Costa *et al*., 2008).

The decision conference was held with two face-to-face meetings. This process of obtaining preference included eight participants. According to the literature, this is a good number of participants because it enhances discussions (Moore *et al*., 2017). Participants were explained the method and dynamics of the selection process on the first day. Firstly, the criteria that should remain in the model were evaluated, and then participants made judgments among the performance levels for each criterion. On the second day, the weights of the criteria were determined. The comparison basis used to obtain the weights (for each alternative and each level within the options) was an indirect comparison, which evaluated the attractiveness of the performance levels of the criteria using the swing weights technique (Bana e Costa *et al*.). All choices were made by consensus among all participants.

The technology ranking results were presented at the end of the second meeting. At that time, the participants were able to modify intervals of the performance levels generated by the value function for each criterion.

Results

Based on the literature review and experts' opinion, the drugs lomitapide (LOMI), ezetimibe (EZE), evolocumab (EVO), and mipomersen (MIPO) were selected as alternatives for decision-making.

The value tree was divided into two major dimensions: outcomes and costs (Figure 1).

Participants in the decision-making conference opted for reducing the number of criteria, eliminating three of the ten initially proposed items. The eliminated criteria were

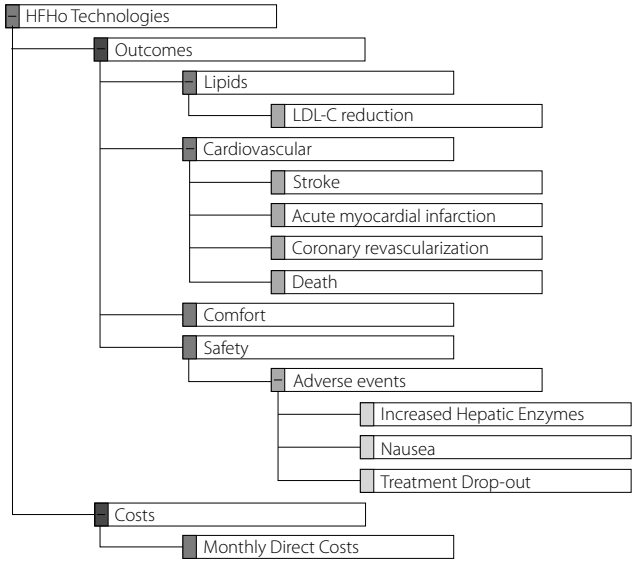

Figure 1. Decision Tree – Familial Hypercholesterolemia Treatment

myocardial revascularization (for being partially redundant with myocardial infarction and cardiovascular death) and the adverse events: increased transaminases and nausea (for being somewhat redundant with Treatment drop-out). Thus, the seven criteria shown in Figure 1 remained in the final model.

The first group of judgments (scoring) evaluated the intra-criterion weights (weights for each level of each criterion). Pairwise qualitative judgments of the difference in attractiveness were obtained for seven evaluated criteria, obtaining a matrix of judgments and respective scores. The decision-makers discussed and validated the constructed value function for each criterion. It is important to note, according to participants, that in the criterion "Treatment drop-out", there was a jump in the value function after the 10% level for "Treatment drop-out".

The second group of pairwise judgments evaluated attractiveness between the different criteria. Notably, the group chose to work with relative risk reduction values and, at times, resorted to absolute risk reduction data available in the report to better understand the problem.

The Cost criterion was used in two ways: as part of the full judgment and then removed from the judgment to be used only as a direct parameter in the cost-benefit analysis (efficiency frontier).

The performance of the technologies within the criteria was estimated from literature data, as shown in Table 1. No evidence was found on cardiovascular effects for mipomersen and lomitapide; therefore, an assumed relative risk value equal to 1 was imputed (without impacting the reduction in stroke, acute myocardial infarction (AMI), and cardiovascular death).

Table 1. Technologies performance

Criteria	Evolocumab	Ezetimib	Lomitapid	Mipomersen
% LDL-C reduction	18.3[a]	20.7[b]	41.1[c]	21.3[d]
RR Stroke	0.79[e]	0.83[f]	-	-
RR Acute myocardial infarction	0.73e	0.88[f]	-	-
RR Cardiovascular Death	0.2[g]	0.93[f]	-	-
Comfort	SC low rate of local reaction	PO	VO	SC high rate of local reaction
% Treatment Drop-out	3.7[g]	6.0[b]	11.8[h]	43.0[i]
Direct costs/month (US$)	US$ 638,7 (R$ 2567.46)[j]	US$12,8 (R$ 51.60)[j]	US$ 38,2 (R$ 153.59)[j]	US$ 20,861.07 (R$ 83,861.52)[j]

[a] Stein *et al.* (2013) and Raal (2010); [b] Gagne *et al.* (2002); [c] Chucel (2013); Chucel (2013); Blom *et al.* (2017) and Harada-Shiba *et al.* (2017); [d] Raal (2010); [e] Sabatine (2017); [f] Cannon (2015); [g] Koren (2014); [h] Cuchel, Blom *et al.* (2017) and Harada-Shiba *et al.* (2017); [i] Santos (2015); [j] PAINEL DE PREÇOS – MPOG (n.d.).

Table 2. Scores, costs and cost per unit for the selected technologie

	Evolocumab	Ezetimib	Lomitapid	Mipomersen
MCDA Global Options Score	59.87	37.21	18.93	9.23
Monthly Cost (R$)	2,567.46	51.60	153,591.60	83,861.52
MCDA Cost Per Unit	42.88	1.38	8,113.66	9,085.76

For the Comfort criterion, EZE and LOMI occupied the same top position in the ranking due to the same oral pharmaceutical form. On the other hand, MIPO was ranked last due to its subcutaneous pharmaceutical form and because it causes frequent local reactions. Despite being a subcutaneous form, EVO did not cause frequent local reactions. It was ranked at an intermediate position between the two extremes.

When evaluating the criteria, "Cardiovascular Death", "Stroke" and "Acute Myocardial Infarction" were the most important ones in the technology ranking with the three highest weights, i.e., 24%, 22%, and 20%, respectively. The criteria with the lowest weights were "Comfort" and "LDL-C Reduction" with weights equal to 2.8% and 4.9%, respectively.

The top-ranked technology was EVO, with an overall score of 59.87, followed by EZE, with 37.21. The third-ranked technology was LOMI, with a score of 18.93, followed by MIPO, the lowest-ranked technology, with a score equal to 9.23.

Analysis of the efficiency frontier indicated that MIPO and LOMI were the dominant options (more expensive and less effective) considering costs and the overall score evaluated under the six criteria.

The cost per MCDA score was calculated based on the treatment cost and the overall score, as shown in Table 2, indicating that EZE had the lowest cost per MCDA score (approximately 1.38). Despite having obtained a lower overall score than EVO (37.21 *versus* 59.87, respectively), EZE had the lowest monthly treatment cost, about 50 times lower than that of EVO.

The robustness analysis showed that the model and the technology rankings were robust, with no inconsistencies between the pairwise comparisons.

In the sensitivity analysis, the final technology rankings were not modified weight variations for the Stroke, AMI, Death, and Treatment drop-out criteria. The technology rankings have been changed only for the weight variation in the LDL-C Reduction and Comfort criteria.

For the LDL-C Reduction criterion, a weight increase to 40.9% would result in EVO switching positions with LOMI, maintaining the latter as the most attractive among all alternatives in all subsequent simulations.

In the Comfort criterion, only after weight of 41.0%, first-ranked EVO would be replaced by EZE, and its result is maintained to the upper weights.

The decision conference participants considered the method to be valid and applicable for decision-making in a scenario of multiple conflicting dimensions. Their comments emphasize the need for a considerable time investment for the Decision Conference, which should be reserved for complex decisions.

Discussion

The study in question showed the results of a different method for health decision making, including a decision conference and a multi-criteria decision analysis (MACBETH Method) for FH with four drugs.

With a group of experts and managers, the decision conference defined essential criteria for incorporating technologies, accompanied by their respective weights.

The drugs EVO and EZE had the highest scores, thus dominating the alternatives MIPO and LOMI.

One of this research strengths is to offer an option for difficult decisions in health, especially for rare diseases. Health

technologies assessment in highly specialized technology is a challenge. Prices reach high levels, explained by monopolies and by the value attributed to the supply of treatment for unmet needs. Such drugs are often the only therapeutic option available and are usually not cost-effective.

Hence, incorporation decisions need to consider different perspectives, incorporating elements of value that go beyond the clinical benefits and cost dimensions. In turn, trust in evidence is limited. There are failures in sample size, generating accuracy, and heterogeneity issues. Typically, the natural history is unknown, patient follow-up times are short, and study designs have a high risk of bias and intermediate outcomes. On the other hand, the budgetary impact on the health care system is more negligible due to the small number of disease cases. In this complex scenario, decision-making is impaired, and thus, alternative strategies have been suggested in the literature, such as multiple-criteria analysis methods. MCDA structures the problem based on relevant criteria, considering all the requirements simultaneously in a decision-making context. The transparent structure justified decision-making with pre-defined stages and was validated by the stakeholders according to their preferences (Khera *et al.*, 2016; Thokala *et al.*, 2016).

MACBETH method application was considered satisfactory and feasible by all participants, ranking drugs for FH according to their overall score. AHP method could be an alternative, but only with numeric judgment instead of MACBETH that allows numeric and categoric assessments. Other methods as outranking methods and Goal, aspiration and reference methods are not applicable for the desired context. As positive points, with MACBETH, there is a better understanding of the problem, support for more rational decisions, and greater transparency and justification for the process.

As limiting aspects of the MACBETH method stand out the face-to-face time required for decision conferences, the coordination team needs to train with the specific support software. The absence of patients in the decision conference was a negative aspect since they would broaden the perspectives included in the decision-making process.

There is no comparison in this scenario with the traditional deliberation method using cost-effectiveness data. Probably most drugs for rare diseases are not cost-effective with usual thresholds. NICE (UK agency) moves to work with different limits for rare diseases.

The selected and ranked criteria were limited in part by the restricted literature involving rare diseases. Global mortality data were not available, and cardiovascular mortality was only available for EVO and EZE, requiring a no-effect assumption for others. The present study involved heterozygous and homozygous populations with different risk profiles, representing significant limitations in the interpretation. We chose to define the problem as FH, although the population of interest is HoFH patients.

The technology rankings favored EVO. It was expected because the drug is injectable and has a higher LDL-C reduction power.

Regarding the weight attributed to the criteria (value of each criterion for the decision-makers), the low weight for LDL-C Reduction (4.8%) and Comfort (2.8%) stands out. LDL-C represents a surrogate outcome that has no direct impact on the patient-related outcomes. A recent review (Ravnskov *et al.*, 2018) questions the LDL-C role in cardiovascular disease. The presence of three physicians with evidence-based medical training may have influenced the lower weight attributed to LDL-C Reduction.

The group considered the percentage of Treatment drop-out due to adverse events as the best safety proxy because it was assumed that, given the risk of severe consequences such as stroke, the patient would discontinue treatment only if experiencing severe adverse events. Nausea and increased liver enzymes were considered minor, and when severe, they would be captured by drop-out. It is essential to avoid double counting in the construction of the MCDA model.

The metric cost/MCDA value still lacks further evidence to be used as a guide for decision-making. It is not possible to incorporate a technology only because it generates a higher number of aggregated points. The large discrepancy in the cost per MCDA score's values (R$ 42.88/MCDA score for EVO and R$ 1.38/MCDA score for EZE) raises doubts if expenses are justified. Indeed, the cost/MCDA metric, in parallel to the cost/QALY, reflects the efficiency of technologies but lacks further theoretical support and considerations as to their adoption. Angelis (2018) analyzed prostate cancer technologies using the MACBETH method and found a cost/MCDA value of £ 419.00; £ 3,173.00; and £ 17,509.00 for enzalutamide, abiraterone, and cabazitaxel, respectively.

The information obtained from the Evidence Summary construction should be interpreted with caution since it has significant methodological limitations, especially the external validity of the evidence. Studies by Stein *et al.* (2013), Raal *et al.* (2015), Raal *et al.* (2010), Gagne *et al.* (2002), Cuchel *et al.* (2007), Cuchel *et al.* (2013), Blom *et al.* (2017), and Harada-Shiba *et al.* (2017) analyzed only homozygous patients. As many included mixed populations (homozygous and heterozygous), we chose to analyze the homozygous population. Notably, the prices charged for LOMI and MIPO are not regulated in Brazil, reflecting only the market by court orders.

The decision conference occurred so that participants interacted with each other (Phillips & Costa, 2007) to construct the model, defining differences in attractiveness for each comparison between pairs of criteria, always anchored on the scales (swing weights). The lack of scale anchoring can generate the so-called "most common critical error" (Keeney, 2002).

The efficiency frontier considers the overall score of each alternative and its costs for one month of treatment. Results indicated that the two predominant technologies were EVO and EZE because both had the lowest prices and highest scores among the four.

MIPO is a subcutaneous drug and, in addition to having a high cost, has a high rate of Treatment drop-out due to adverse events, solid local reactions, and a reduction in LDL-C on average close to other alternatives. Comparing different technologies, LOMI has the highest reported cholesterol reduction; however, it has the second-highest frequency of Treatment drop-out. Its low MCDA score may have been influenced by its high cost, which was the highest among the four alternatives. Notably, different studies were used without adjustments by indirect comparisons, which may only reflect differences between the baseline risk of the populations.

Some of the benefits of MCDA methods are the construction and understanding of the problem. Those involved in the decision-making process are encouraged to think about the situation, its dimensions, and the possible solutions (Keeney). The stage of problem construction and assessment of possible solutions was initially developed by the researchers at the Centre for Health Technology Assessment (Núcleo de Avaliação de Tecnologia em Saúde) through a search for alternatives for the said disease treatment, the collection of evidence, and the preparation of reports.

This strategy of involving participants from the beginning of the process was advantageous, as they understood the decision process, presenting a robust result for the revealed preferences. A similar approach can be performed for other decision-making problems within the hospital setting in which several dimensions may influence the outcome.

Questions arising in the process still lack research. How does one interpret whether a score gain justifies paying R$ 2,500.00 more per MCDA score (difference in monthly cost between EVO and EZE)? Is it possible to create a cost per MCDA score threshold to facilitate interpretation? Is it possible to transfer the gain in the score to a price analysis based on value? These are questions that still need to be answered before a more expanded use of MCDA in decision-making on incorporating health technologies. How to apply the result of a higher score in the actual decision-making process still requires further studies. The case in question showed that EVO has more performance benefits than comparative drugs but with a cost approximately 50 times higher.

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