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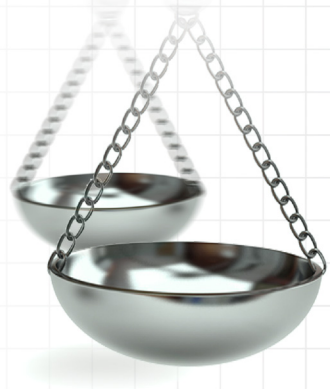

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# Health technology assessment process of a cardiovascular medical device in four different settings

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**Aim:** Health technology assessment (HTA) is a tool to help the decision-making process. The aim is to describe methods and processes used in the reimbursement decision making for drug-eluting stents (DES) in four different settings. **Methods:** DES as a technology under study was selected according to different criteria, all of them agreed by a working group. A survey of key informants was designed. **Results:** DES was evaluated following well-structured HTA processes. Nonetheless, scope for improvement was observed in relation to the data considered for the final decision, the transparency and inclusiveness of the process as well as in the methods employed. **Conclusion:** An attempt to describe the HTA processes of a well-known medical device.

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**Keywords:** cardiology/cardiovascular • comparative effectiveness research • health technology assessment

The need for a balance between patients' benefit and safety as well as cost containment has led many countries to introduce regulatory instruments to identify technologies that minimize risk and offer value for money. As a result, health technology assessment (HTA) is attracting considerable interest as a suitable tool for this purpose at global level [1].

According to WHO, *"a medical device (MD) is an article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose. Typically, the purpose of a medical device is not achieved by pharmacological, immunological or metabolic means"* [2].

The current EU regulatory framework for MDs is based mainly in the recent Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on MDs (amending Directive 2001/83/EC, Regulation (EC) Number 178/2002 and Regulation (EC) Number 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC). If a MD is approved with *Conformité Européenne* (CE) mark (safety criteria, quality in terms of reliability and performance), it allows the manufacturer to commercialize it in all EU member states [3,4]. In case of complex MDs, evaluation is conducted by notified bodies, which are independent companies that specialize in evaluating many products. By contrast, the authorization to marketing is given by the US FDA in the USA. In the latter case, authorization depends on regulatory class, which is based on risk level and the evaluation necessary to demonstrate safety and effectiveness [5].

It is noteworthy that the MDs early assessment shows as a promising tool for evidence-based decision making, yet there is still no evidence of its potential. The problem is that manufacturers are not motivated to perform early assessment, because its implementation depends on demonstrating value in practice [6].

In comparison with medicines, MDs require minimal clinical data to obtain regulatory approval. Other challenges include the learning curves of operators and generalizing MD evidence across settings. Finally, questions were recently published whether different assessment methods for MDs as compared with drugs are needed, given the

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lack of evidence from current HTA practices [7]. In this sense, two articles have recently been published that show the differences between countries in the process, structure and outcome for medicines coverage and reimbursement in a sample of countries similar to those studied here [8,9].

This paper is part of the ADVANCE–HTA project. The main objective of this project is to contribute to advancements in the methods for HTA in different settings by involving the wider stakeholder community in areas actively and heavily debated given their implications for decision making and resource allocation.

Accordingly, the aim of this paper is to describe methods and processes used in the reimbursement decision making for drug-eluting stents (DES) in a sample of countries from the Americas and Central, Eastern and Southeastern Europe (CESEE). In order to clarify the current state of MD implementation focus on pricing and reimbursement/coverage decisions in those countries and to provide recommendations to those countries.

## Methodology

A cross-sectional study was carried out on a sample of HTA institutions from the CESEE and Americas' countries. An e-mail was sent to potential key informants with an invitation to participate in the study, and they were asked if they had evaluated the DES technology. The criteria considered for the selection of the MD were agreed by a working group composed of the HTA Network of the Americas (RedETSA), the NICE International, the London School of Economics and the EASP research team as follows: high public interest, epidemiological relevance, from the point of view of public health (high prevalence/incidence or burden of disease) and relevance to the health system or health policy.

### Instrument

The questionnaire was based on key papers on surveys for HTA [10–12]. The instrument has 38 questions grouped into three dimensions: (1) HTA process: introduction, institutions, unbiased and transparent, stakeholders; (2) methods and criteria for conducting HTA: structure and methods, evidence, methods for assessing cost and benefits, social perspective, uncertainty; and (3), link between HTA and decision making: implementation, decision making, timely and communicated. The questionnaire was revised and pilot tested with HTA experts from different countries and organizations (e.g., for format, structure, formulation of questions and answer options). It included both dichotomous and multiple-choice questions, as well as a number of open-ended questions to allow for clarification and explanation of responses (full questionnaire available upon request) [8,9].

### Procedure

Before starting the survey, the authors performed a literature review to agree on concepts to be used and identify questionnaires used in similar studies. Once the questionnaire was devised, it was presented to a group of experts in HTA from different countries to test its validity and proper operation, emphasizing the format, structure, formulation of questions and answers, introduction and closing. The ADVANCE–HTA project had the necessary authorizations, furthermore, at local level, the project was authorized by the research committee of the Andalusian School of Public Health.

Key informants from institutions that had evaluated DES were identified through personal contacts and internet searches. Potential respondents were contacted and, after the objectives of the study were explained and confidentiality assured, they were invited to complete the questionnaire. Experts from the National Committee for Technology Incorporation (CONITEC, Brazil), the National Institute for Excellence in Health and Social Services (INESSS, Quebec), the Institute for Health Technology Assessment (IETS, Colombia) and the Estonian Health Insurance Fund (EHIF, Estonia) agreed to participate. An invitation was then sent by e-mail to the head of each organization, along with the questionnaire. All completed questionnaires were received and a qualitative summary of the responses was made. Once the survey responses were compiled and analyzed, results were contrasted with available assessment/appraisal reports on the different websites, a previous output of the ADVANCE–HTA project, as well as clarifications provided by the country experts involved in the respective HTA processes [13–19]. The results were analyzed according to the typical steps of an HTA process (topic selection, scoping, assessment, appraisal, decision making, dissemination, implementation and monitoring of impact) with the key principles for HTA (e.g., transparency, inclusiveness and relevance) [10,20,21].

## Results

Table 1 shows the main bodies conforming the HTA system and decisions made by setting. It is worthy to highlight

Table 1. Main bodies conforming the health technology assessment system and decision by setting and final decision on drug-eluting stents.

| Setting | Assessment body | Appraisal body | Decision-making body | Decision |
|---|---|---|---|---|
| Brazil | SBHCI + BRATS + CCATES + CONITEC | CONITEC | SCTIE/MoH | Recommended only in cases of diabetic patients and patients with lesions in small-caliber vessels |
| Colombia | IETS plus University of Antioquia | IETS | MoH | Recommended only to reduce the rate of repeated revascularization, particularly in patients with small-caliber arteries (<3 mm) and long lesions (>15 mm) |
| Estonia | Medical specialist: medical evidence-based assessment health economist: economic analysis Ministry of Social Affairs: assessment about community needs | EHIF | EHIF | Positive without restrictions |
| Quebec (Canada) | INESSS | INESSS† (made conclusions, not recommendations) | Provincial MoH | Positive with comments: – Similar selection criteria to assure equal accessibility according to clinical need and not geographic location – An evaluation is necessary to aid future decision making – Details regarding the implantation of all coated stents should be recorded in a registry to facilitate this evaluation |

†INESSS does not make decisions, only conclusion.
BRATS: Brazilian Bulletin of Health Technology Assessment; CCATES: SUS Collaborating Centre Technology Assessment and Health Excellence; CONITEC: National Committee for Health Technology Incorporation; EHIF: Estonian Health Insurance Fund; IETS: Institute for Health Technology Assessment; INESSS: National Institute for Excellence in Health and Social Service; MoH: Ministry of Health; REBRATS; Brazilian Network for Health Technology Assessment; SBHCI: Brazilian Society for Hemodynamics and Interventional Cardiology; SCTIE: Secretariat of Science, Technology and Strategic Input.

that the HTA of DES was conducted at the national level in Colombia (IETS), Brazil (CONITEC) and Estonia (EHIF), all of them supported by different bodies, by contrast the process occurred at the regional level in Quebec (Canada, INESSS).

## Topic selection

The reasons taken into account for the selection of DES as an MD to be assessed by each HTA organization are shown in Table 2. Identification by medical specialists is the most commonly cited reason by CONITEC and EHIF, whereas perceived impact on patient outcomes, potential cost of the technology/cost of illness, frequency of the clinical condition and medical practice variations are the reasons cited by INESSS and IETS. Ethical, legal or social implications were only reported to be used by INESSS. Assessment feasibility was not used by anyone. Comparing with the rest of setting, the Colombian system involved the widest range of stakeholders in priority settings and scoping (Table 3).

## Scoping

The four settings included performed a scoping exercise for considering the variables to include into the DES assessment. All of them reported include a high number of variables and aspects to consider (Table 2).

## Assessment

In relation with the principle of relevance, Table 2 also summarizes the type of clinical evidence used for that, IETS did not consider other types of available technologies and variables related to cost. Overall, clinical trials were the most common source of clinical evidence used for assessment. It is also worth noting that indirect comparison was only used by EHIF.

In relation to the methods used, economic models and budget impact analysis were performed by all agencies, except for IETS, which did not performed any economic analysis. In terms of clinical end points included in the

Table 2. Criteria considered in topic selection/scoping, sources of clinical evidence and types of end points included in each assessment.

| Topic selection criteria | INESSS | EHIF | CONITEC | IETS |
|---|---|---|---|---|
| **Criteria taken into account by countries for the selection of DES** | | | | |
| Perceived impact on patient outcomes (burden of disease): mortality, morbidity and quality of life related to a clinical condition | √ | | | √ |
| Potential cost of the technology/cost of illness | √ | | | √ |
| Frequency of a medical/clinical condition | √ | | | √ |
| Medical practice variations | √ | | | √ |
| **Assessment feasibility (e.g., available data, funding, staff)** | | | | |
| Technology identified by external stakeholders: medical specialist | | √ | √ | √ |
| Political concern (information needs of the policy maker) | √ | | | |
| Public and media concern (social interest in the management of a specific clinical condition) | | | | |
| Ethical, legal or social implications (equity criteria included) | √ | | | |
| Unknown/not sure | | | | – |
| **Type of information included in the scoping document** | | | | |
| Number of clinical events | √ | √ | √ | √ |
| Clinical needs and practice | √ | √ | √ | √ |
| Relevant patient populations to be considered | √ | √ | √ | √ |
| Other types of available technologies (range of technologies) | √ | √ | √ | |
| Alternatives or comparator medical devices/treatment | √ | √ | √ | √ |
| Evidence-based information | √ | √ | √ | √ |
| Treatment cost/illness cost | √ | √ | √ | |
| Expected outcomes with the new treatment to be assessed | √ | √ | √ | √ |
| Others | | | † | |
| **Type of clinical evidence used for the HTA report** | | | | |
| Pivotal trials | | | √ | √ |
| No pivotal trials | | | | |
| Phase I–II trials | | | | |
| Phase III trials (RCTs) | √ | √ | √ | |
| Indirect comparison | | √ | | |
| Postmarketing registry | √ | | | |
| Observational studies | √ | | | |
| Other | | | | √‡ |

†Decisions in other countries.
‡They included a Cochrane systematic review.
CONITEC: National Committee for Technology Incorporation; DES: Drug-eluting stent; EHIF: Estonian Health Insurance Fund; HTA: Health technology assessment; IETS: Institute for Health Technology Assessment; INESSS: National Institute for Excellence in Health and Social Service; MACE: Major adverse coronary event; MI: Myocardial infarction; RCT: Randomized controlled trial; TLR: Target lesion revascularization; TVF: Target vessel failure; TVR: Target vessel revascularization.

Table 2. Criteria considered in topic selection/scoping, sources of clinical evidence and types of end points included in each assessment (cont.).

| Topic selection criteria | INESSS | EHIF | CONITEC | IETS |
|---|---|---|---|---|
| **Clinical end points included** | | | | |
| Incidence of subsequent attacks of angina | | | √ | |
| Incidence of MACE | | | √ | |
| TVF | | | √ | |
| Composite event (MACE and/or TVF) | | | | |
| Risk of stent thrombosis | | | √ | |
| Risk of restenosis | √ | | √ | |
| Death/mortality | | | √ | √ |
| Acute MI | | | √ | √ |
| Revascularization rates: lesion (TLR) or vessel (TVR) | √ | | √ | |
| Angiographic binary restenosis | | | | |
| Late luminal loss | | | √ | |
| Further revascularization procedures† | | | √ | √ |
| Quality of life | √ | | | |
| Not reported | | √ | | |

†Decisions in other countries.
‡They included a Cochrane systematic review.
CONITEC: National Committee for Technology Incorporation; DES: Drug-eluting stent; EHIF: Estonian Health Insurance Fund; HTA: Health technology assessment; IETS: Institute for Health Technology Assessment; INESSS: National Institute for Excellence in Health and Social Service; MACE: Major adverse coronary event; MI: Myocardial infarction; RCT: Randomized controlled trial; TLR: Target lesion revascularization; TVF: Target vessel failure; TVR: Target vessel revascularization.

assessment, CONITEC reported that ten variables were used, while EHIF did not report any. Finally, only INESSS and CONITEC explored the uncertainties associated with the decision problem (Table 4).

## Appraisal

The HTA results were contextualized by appraisal organization or similar bodies in all cases (Table 1). In relations with transparency [22], CONITEC, IETS and INESSS published HTA reports, appraisal recommendations and supporting information relating to DES on the internet (agency websites). By contrast, although some meetings between the medical society and EHIF were celebrated, there was no publicity of the process or recommendations in Estonia. CONITEC, IETS and INESSS distinguished between the scientific assessment of the evidence and the appraisal, while this was not the case in Estonia.

## Decision making

In relation to the type of information taken into consideration for the final decision, both EHIF and CONITEC indicated that reports from other countries were adapted to their settings. In addition, CONITEC used a wide range of sources when compared with EHIF. Table 1 shows the final decision made in each country; all of them were favorable with some differences. Only Colombia showed the participation of different agents in decision making. In relation with contestability principle, only INESSS reported that the manufacturer or sponsor of the MD had the possibility of appeal against a decision. The final reports developed by INESSS and IETS did not use a transparent approach for weighing various considerations (e.g. equity, feasibility), while the Estonian respondent indicated that a transparent approach for weighing various considerations was employed. Brazil did not report this information.

## Dissemination, implementation & monitoring

These dimensions are related with timeless Drummond's principle. Thus, EHIF reported having a communication plan for the coronary stent recommendations, although no different versions of the HTA report were made available for different audiences. INESSS and CONITEC had a communication plan for all DES recommendations and decisions, while IETS had not. In Brazil, only one version of the report was produced for all sorts of audiences,

Table 3. Types of economic models and model uncertainties reported by the countries in drug-eluting stent assessment.

| Economic methods | INESSS | EHIF | CONITEC | IETS |
|---|---|---|---|---|
| **Type of economic model used** | | | | |
| Incremental cost analysis | | ✓ | | |
| Cost–effectiveness analysis | ✓ | | ✓ | |
| Cost-utility analysis | ✓ | | | |
| Cost-consequence analysis | ✓ | | | |
| Cost-minimization analysis | | | | |
| Budget-impact analysis | ✓ | ✓ | ✓ | |
| No economic model | | | | ✓ |
| **Model uncertainties** | | | | |
| Around the clinical parameters | | | | |
| Around the cost–effectiveness evidence | ✓ | | ✓‡ | |
| Clinical benefit following more time in treatment | | | ✓ | |
| Safety | | | | |
| Study design (sample size, time horizon, etc.) | ✓ | | ✓ | |
| Comparator | | | | |
| Population and generalizability | | | | |
| The nature of the quality of life estimate | | | | |
| Disease characteristics | | | | |
| Treatment characteristics† | | | | |
| No cost–effectiveness model | | ✓ | | |
| Stents cost information | ✓ | | ✓ | |
| Number of stents per procedure | ✓ | | | |
| Baseline revascularization rate with bare metal stents | ✓ | | | |
| No economic model | | | | ✓ |

CABG or repeat PCI.
†Duration of clopidogrel therapy, average number of stents used and rates of revascularization.
‡Finally, in the HTA report the cost included only the stent cost.
CABG: Coronary artery bypass grafting; CONITEC: National Committee for Technology Incorporation; EHIF: Estonian Health Insurance Fund; HTA: Health technology assessment; IETS: Institute for Health Technology Assessment; INESSS: National Institute for Excellence in Health and Social Service; PCI: Percutaneous coronary intervention.

which differs from the methodology adopted in Colombia and Quebec. INESSS established that the literature should be re-examined no later than in 6–12 months, while IETS indicated 4 years after the initial assessment. On the other hand, even though CONITEC indicated that it was not planned to repeat or update the technology assessment, this can be done when needed.

## Discussion

This work is part of the Work Package 6 of the ADVANCE–HTA project, *"Strengthening and Implementing HTA in Emerging Settings"*, aiming to bridge knowledge and implementation gaps and provide best practice recommendations for emerging settings. ADVANCE–HTA is a broader, multipartner and multidisciplinary research project [23], funded by the European Commission's Research Framework Program (FP7).

This paper attempts to characterize current HTA activities for MDs, offering an illustration of decision-making processes relative to a widespread MD. HTA processes for MDs are less described in the literature, and this study also provides examples from a selection of countries with different levels of HTA experience.

Barriers faced by the research team included data-poor survey responses, along with a lack of publicity of reports and processes, which could have been useful to complement or contrast the survey responses provided (most HTA reports were not available in a public website or written in English). Although many contacts and reminders were made to obtain further information, a more complete dataset could not be achieved.

Table 4. Stages of the health technology assessment process and level of participation of stakeholders in the drug-eluting stent assessment.

| Participation of stakeholders | Priority setting | Scoping | Submission or review of evidence | Appraisal | Draft stage | Final decision |
|---|---|---|---|---|---|---|
| INESS[†]: | | | | | | |
| – Patients groups | | | | | | |
| – Clinical specialists | | √ | √ | | | |
| – Manufacturers | | | | | | |
| – Civil society | | | | | | |
| EHIF: | | | | | | |
| – Patients groups | | | | | | |
| – Clinical specialists | √ | √ | √ | √ | | |
| – Manufacturers | | | | | | |
| – Civil society | | | | | | |
| CONITEC: | | | | | | |
| – Patients groups | | | | | | √[‡] |
| – Clinical specialists | | | √ | | | √ |
| – Manufacturers | | | | | | √ |
| – Civil society | | √ | √ | | | √ |
| IETS: | | | | | | |
| – Patients groups | √ | √ | | √ | | |
| – Clinical specialists | √ | √ | √ | √ | √ | |
| – Manufacturers | √ | | √ | √ | | |
| – Civil society | | | | | | |

[†]INESSS process is currently different (the process reported is from 2004). Patients, clinical specialists and civil society are now taking part in all of the mentioned stages.
[‡]The final decision is made after a public consultation where all stakeholders could give contributions.
CONITEC: National Committee for Technology Incorporation; EHIF: Estonian Health Insurance Fund; IETS: Institute for Health Technology Assessment; INESSS: National Institute for Excellence in Health and Social Service.

The most remarkable result to emerge from the data is that EHIF in Estonia approved DES without restrictions. This finding is in contradiction with previous results reported in the literature, indicating that DES are only cost-effective in a small proportion of the patients at very high risk of requiring re-intervention [13]. This fact could be related to a limitation of this study. The authors could not confirm if a medical specialist or hospital manager had the authority to impose other type of restrictions at a lower decision level, such as by the Health Board or State Agency for Medicines (responsible for healthcare issues). Of note, the Canadian Agency for Drugs and Technologies in Health (CCOHTA) performed two economic evaluations of DES and concluded that the technology is more expensive than the comparator but associated to a significantly lower restenosis rate 1 year after implantation, thus saving treatment costs [14,17]. Similarly, NICE issued a positive recommendation with restrictions (caliber of the lesion and price of the stent) [18].

In relation to the relevance of methods, none of the respondents reported having performed a cost utility analysis or taking into account quality of life as an end point. The use of quality-adjusted life-years allows collecting benefits and harms of an intervention more comprehensively, while enabling decision makers to compare with willingness to pay thresholds and across a wide range of interventions. Thus, the use of quality of life as an end point is widely recommended [19,21].

Although clinical trials provide the best level of evidence, this design is not suitable for collecting information on adverse events, efficacy in real-word settings (effectiveness) and other potentially important end points. Thus, it is surprising that, although all the countries performed the HTA report later than other more mature agencies such as NICE and CCOHTA, none of the respondents used those HTA reports, observational studies or postmarketing data. In this sense, taking into account the sixth Drummond's principle that recommends that *"HTAs should consider a wide range of evidence and outcomes"* , the authors recommended using all the available information to perform the assessment of MDs [10,24].

It is worth noting the departure from the tenth Drummond's principle recommending that *"those conducting HTAs should actively engage all key stakeholder groups"*. In this regard, there were HTA processes in which neither

civil society nor patient groups were included [10]. Furthermore, a review of CONITEC's documents revealed that the participation of different stakeholders did not occur at the final decision making but the appraisal stage [16].

We recommend to have an early assessment in order to improve the evidence when the HTA should be made. In the same sense, we recommend that HTA agencies provide advice to manufacturer in order to match the interest from both parties and gathering the end points and outcomes that are requested. Under this premise, the HTA work can be quicker. Finally, as it happened with medicines, transparency is a key factor in order to make more efficiency the healthcare system, especially in countries with lack of resources as these ones.

Decision makers in Americas and CESEE countries face several challenges, mainly due to differences in current standard of care, practice patterns, or gross domestic product between the developed countries where the majority of the studies are conducted and their own jurisdiction [25]. Furthermore, few advances have been made in the methods of evaluation of health technologies of MDs. In conclusion, the evidence from this study points toward the idea that more rigorous results and balanced decisions can be achieved with a greater transparency, the use of more relevant data and the involvement of a wider range of stakeholders. The multicriteria decision analysis (MCDA) is a set of methods that systematically and explicitly addresses all these criteria (sometimes maybe even conflicting) [26], which make explicit the impact on the decision of all the criteria applied and the relative importance attached to them. This could enable value assessment to be conducted from a more encompassing perspective therefore addressing a key limitation of economic evaluation. MCDA is not a tool to substitute decision making, but to contribute to the transparency and understanding of decision-making rationales. For all this, the methodology of MCDA seems to be presented as an interesting alternative, since it takes into account aspects difficult to assess such as the need, ethical aspects, among others. [27,28].

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### Authors' contributions

J Espín Balbino and A Lemgruber conceived the study. J Espín Balbino, A Lemgruber, A Olry de Labry Lima and A Caro-Martínez designed the study. A Caro-Martínez and F Lessa collected data. A Olry de Labry Lima drafted the first version of the manuscript. All authors contributed with ideas for discussion, reviewed the manuscript and approved the final version.

### Financial & competing interests disclosure

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## Summary points

- This article describes methods and processes used in the reimbursement decision making for drug-eluting stents (DES) in a sample of countries from the Americas and Central, Eastern and Southeastern Europe (CESEE).
- Medical Devices require minimal clinical data to obtain regulatory approval comparing with medicines requirement.
- According to the literature, DES are only cost-effective in a small proportion of the patients at very high risk of requiring re-intervention.
- The Canadian Agency for Drugs and Technologies in Health (CCOHTA) performed two economic evaluations of DES and concluded that the technology is more expensive than the comparator but associated to a significantly lower restenosis rate 1 year after implantation, thus saving treatment costs. NICE issued a positive recommendation with restrictions (caliber of the lesion and price of the stent)
- We recommend: (1) to have an early assessment in order to improve the evidence when the HTA should be made; (2) that HTA agencies provide advice to manufacturers in order to match the interest from both parties and gathering the end points and outcomes that are requested.

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