



EUnetHTA

**CORE HTA ON DRUG
ELUTING STENTS**

PILOT ASSESSMENT - NOT FOR DECISION-MAKING

WORK PACKAGE 4

DECEMBER 2008



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eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Core HTA on Drug Eluting Stents

was developed by

Work Package 4

The HTA Core Model

Work Package 4 Lead Partner: FinOHTA, Finnish Office for HTA, Finland



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General information on the European network for Health Technology Assessment, EUnetHTA

Background

Health Technology Assessment (HTA) is increasingly used in European countries to inform decision- and policy-making in the health care sector. Several countries have integrated HTA into policy, governance, reimbursement or regulatory processes. Therefore, the EU and Member States in 2004 expressed the need for a sustainable European network for HTA.

EUnetHTA was established to respond to this need. The European Commission and Member States co-funded the three year project (2006–2008) with the aim to develop a sustainable network and information resources to inform health policy making (1, 2, 3). The project, which was based on three prior projects, connected national HTA agencies, research institutions and health ministries and enabled an effective exchange of information and support to policy decisions (4).

What is health technology assessment?

EUnetHTA used the definition of *health technology* offered by the *International Network of Agencies for Health Technology Assessment (INAHTA)*: “Any intervention that may be used to promote health, prevent, diagnose or treat disease, or for rehabilitation or long-term care. This includes pharmaceuticals, devices, procedures and organisational systems used in health care” (5).

EUnetHTA defined *health technology assessment* (HTA) as “a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe effective, health policies that are patient focused and seek to achieve best value”.

EUnetHTA aims and strategic objectives

The EUnetHTA project was established to create an effective and sustainable network for HTA across Europe that could develop and implement practical tools to provide reliable, timely, transparent and transferable information to contribute to HTAs in Member States.

The strategic objectives of the EUnetHTA project were to:

- reduce duplication of effort in order to promote more effective use of resources
- increase HTA input to decision making in Member States and the EU in order to increase the impact of HTA
- strengthen the link between HTA and health care policy making in the EU and its member states
- support countries with limited experience of HTA.

Structure of EUnetHTA

The EUnetHTA Partnership involved 64 organisations: 1 Main Partner, 33 Associated Partners, and 30 Collaborating Partners. In total, 33 countries (Europe: 25 EU and 2 EEA countries (Norway, Iceland), Switzerland and Serbia; outside Europe: Australia, Canada, Israel, USA) participated in the project. The list of partners is accessible at: www.eunethta.net

Management and leadership

EUnetHTA governance structure consisted of

- the Steering Committee which comprised the heads of each of the Associated Partners or representatives appointed by the head. The head of the Main Partner chaired the Steering Committee. The Steering committee mandated the the management of the network to:
- the Executive Committee representing the Main Partner and Work Package Lead Partners,
- the Secretariat under the leadership of the Main Partner which provided managerial support to the overall project and ensured ongoing contact to the DG SANCO.

Collaborating Partners participated in the work packages and received internal communication on a regular basis.

The modes of operation of the network were described in a standard operating procedures (SOP) manual, a communication strategy, and supported by virtual and face-to-face meetings, website (with the Members Only work area), regular e-newsletter and other types of communication tools. The Associated Partners agreed on 3-year work plan during the first Steering Committee meeting and project results were presented at the EUnetHTA Conference “HTA’s Future in Europe”, in journal articles and conference presentations.

Work Packages and major results

The scientific work in the EUnetHTA project took place in separately managed **Work Packages** (WPs), each led by a Lead Partner. The following major results were achieved:

- A well functioning network of partners and colleagues from HTA agencies, research institutions and health ministries (WP1 - DACEHTA/National Board of Health, Denmark)
- A well functioning Information platform and website (www.eunethta.net) (WP2 - SBU, Sweden and Co-Lead Partner – DIMDI, Germany)
- Internal evaluations that helped to adjust work plans (WP3 – NOKC, Norway)
- A comprehensive, evidence-based and validated common framework for HTA information (HTA Core Model) applied to two types of technology to produce generic Core HTAs a) on medical and surgical interventions (Drug Eluting Stents) and b) on diagnostic technology (Multislice CT coronary angiography) (WP4 - FinOHTA, Finland)
- A handbook instructing in the use of the Core HTA Model (WP4 - FinOHTA, Finland)
- An Adaptation Toolkit (and a guidance document) composed of a series of checklists and resources which address the relevance, reliability and transferability of data and information from existing reports (WP5 - NCCHTA, UK)
- A book ”Health technology assessment and health policy-making in Europe” (WP6 - DACEHTA/National Board of Health, Denmark)
- A web-based Stakeholder Open Forum, a Draft Stakeholder Policy and Discussion Topic Catalogue; (WP6 - DACEHTA/National Board of Health, Denmark)
- Web-based tools for information sharing on the monitoring of new promising technologies and information service on emerging technologies (WP7 – HAS, France, and Co-Lead Partner- LBI/HTA, Austria)
- A handbook on HTA capacity building (WP8 - CAHTA, Spain)

- A proposal for a permanent EUnetHTA Collaboration after two rounds of public consultation (WP1 - DACEHTA/National Board of Health, Denmark)

Based on best practice each Work Package developed the methods suitable for their purpose, which is described in WP-specific products. The Lead Partners were responsible for coordination within the WP, for bringing work forward, producing and reporting results, for sending management information reports to the Main Partner and for responding to internal evaluation questionnaires.

The next phase

Through a series of internal and public consultation rounds, the network developed a Proposal for the EUnetHTA Collaboration (published June 16, 2008) detailing the approaches for the future development of the network. A group of founding partners was established after this to implement the proposal for EUnetHTA Collaboration.

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Core HTA on Drug Eluting Stents

This document is the final project deliverable on the 31st of December 2008.

This is a pilot assessment to test the HTA Core Model. It is not intended for actual decision-making and should not be used for it due to partial incompleteness and partially outdated content.

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Contents

Editors' Notes	10
WP4 Teams	11
General design	13
<i>Introduction</i>	13
<i>Methodology</i>	14
<i>References</i>	17
Health problem and current use of technology	19
<i>Introduction</i>	19
<i>Methodology</i>	19
<i>Assessment elements</i>	20
<i>Discussion</i>	32
<i>References</i>	32
<i>Assessment elements table</i>	34
Description and technical characteristics of technology	36
<i>Introduction</i>	36
<i>Methodology</i>	36
<i>Assessment elements</i>	36
<i>Discussion</i>	41
<i>References</i>	42
<i>Assessment elements table</i>	44
Clinical effectiveness	46
<i>Introduction</i>	46
<i>Methodology</i>	47
<i>Assessment elements</i>	49
<i>Discussion</i>	57
<i>References</i>	60
<i>Assessment elements table</i>	62
Costs and Economic Evaluation.....	67
<i>Introduction</i>	67
<i>Methodology</i>	67
<i>Assessment elements</i>	69
<i>Discussion</i>	73
<i>References</i>	74
<i>Assessment elements table</i>	75
Ethical analysis	76
<i>Introduction</i>	76
<i>Methods</i>	76
<i>Assessment elements</i>	78
<i>Discussion</i>	89
<i>References</i>	90
<i>Assessment elements table</i>	103
Organisational Aspects	105
<i>Introduction</i>	105
<i>Methodology</i>	105
<i>Assessment elements</i>	108
<i>Discussion</i>	125
<i>References</i>	126
Social aspects	137
<i>Introduction</i>	137
<i>Methodology</i>	137
<i>Assessment elements</i>	140
<i>Discussion</i>	148
<i>References</i>	150
<i>Assessment elements table</i>	151

Legal Aspects.....	165
<i>Introduction</i>	165
<i>Methodology</i>	165
<i>Assessment elements</i>	166
<i>References</i>	184

Editors' Notes

This is the final deliverable of this document, Core HTA on drug eluting stents (DES). This Core HTA is based on the HTA Core Model for medical and surgical interventions, developed by EUnetHTA Work Package 4. Readers of this document are urged to familiarize themselves with the Core Model as well.

The aim of preparing this document was to test the HTA Core Model. We wanted to gather experiences from a novel way of preparing a health technology assessment, rather than prepare a valid assessment on DES. Instead of preparing a traditional HTA-report in a single HTA-unit, the relevant assessment elements were defined and the work distributed into several research units around Europe. Because of this piloting function, not every research question was assessed with full thoroughness. Therefore we suggest that the results described in this document should not be used as a basis of decision making as such.

The current document represents a considerable amount of work by many people across Europe. It is divided into chapters, most of which present one domain of work within HTA. In the beginning of each chapter the main authors have been listed. Several others, however, have contributed to the work. Their names can be found in the chapter "Teams" of this report.

Each chapter describing domains of the model contains the following sections:

- Introduction: why is it important to assess the technology from the viewpoint of this domain?
- Methodology: what methodology was used to answer the research questions of this HTA?
- Assessment elements: answers to the issues that are defined for this domain in the Core Model.
- References
- Assessment elements table: the relevance of each assessment element in this domain and issues translated into research questions. First column contains an identification code (ID) that refers to the element in the model.

Notice that this assessment is based on a draft version of the HTA Core Model (available at http://www.eunetha.net/Work_Packages/WP_4/Activities/). Hence it does not address all the same assessment elements as the final version 1.0 of the Model.

WP4 Teams

The work on different domains has been done as a collaborative effort of WP4 teams. Each team consists of investigators that are responsible for writing the sections of the report and reviewers whose task is to provide support and feedback to investigators in their team. Each team has also a coordinator on behalf of FinOHTA.

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Introduction

The organization of health technology assessment and the settings in which HTA agencies operate vary considerably across countries.³ There are also significant differences in the practical application of HTA.³ In some countries, HTA focuses currently on clinical effectiveness, safety and cost-effectiveness of technologies, while in others also other issues (e.g. ethics or social impact) are considered.⁴ The timelines for different assessments also have a notable effect on what an HTA report can cover; a full 200-page report prepared over a period of 2-3 years naturally contains a more detailed account on the effectiveness of an intervention than a rapid review of 4 pages written in a few weeks.

The EUnetHTA project aims at facilitating HTA information sharing within Europe. This is especially important for issues that are not dependent on a specific context (e.g. country, region or healthcare system), but also for context-dependent information that is significant from the viewpoint of HTA. All information could be presented using a similar structure. This is difficult since the information structure of current HTA reports varies so much. The need for a clear structure, transparency, and rigorous handling of information in any HTA leads to a need for standardisation. Steps towards definition of some standards at the international level have been taken by INAHTA⁵ (checklist) and the previous European Projects (EUR-ASSESS⁶ and ECHTA/ECAHI⁷).

This international work was brought forward in the EUnetHTA project 2006-2008, through the development of two applications of the HTA Core Model - one for medical and surgical interventions and the other for diagnostic technologies. The EUnetHTA Core Model enables future cross-national use of HTAs through a shared and more detailed structure, suggesting what kind of information items may belong to an HTA.

This report is an HTA on drug eluting stents. It is an application of the HTA Core Model for medical and surgical interventions and hence called a "Core HTA". The aim is to test the model and provide feedback that will be adjusted based on the experiment. Besides the more

Definitions of HTA

Technology assessment in health care is a multidisciplinary field of policy analysis. It studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.

INAHTA 2007¹

Health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.

Despite its policy goals, HTA must always be firmly rooted in research and the scientific method.

EUnetHTA 2007²

theoretical work, the Core HTA functions as an example of a future generic report that facilitates information sharing within Europe.

Methodology

The work is based on the HTA Core Model for a generic, transferable HTA report⁸ which was developed by the participants in EUnetHTA Work Package 4 (WP4). This model is limited to assessing medical and surgical interventions. It defines and standardises elements of a health technology assessment, providing tools to tackle variation in the structure and contents of HTA reports.

The model employs the following nine domains that were originally identified in the EUR-ASSESS project:

1. Current use of the technology (implementation level)
2. Description and technical characteristics of technology
3. Safety
4. Effectiveness
5. Costs, economic evaluation
6. Ethical aspects
7. Organisational aspects
8. Social aspects
9. Legal aspects

Selection of topic

The WP4 first selected the technology to be assessed according to the HTA Core Model. The participating organisations of WP4 were surveyed through email a web-based questionnaire. From among 20 proposals, a two-step voting process identified the use of drug-eluting stents (DES) in coronary heart disease as a topic of high interest among the participating institutions and countries.

Application of the HTA Core Model

Assessment elements

The model is structured into nine domains, as described above. Each domain is further divided into more specific topic areas to consider, and each topic is further divided into one or more issues, i.e. questions to be answered in an assessment.

Combinations of a domain, topic and issue define the context of assessment elements, which are the basic units of a Core HTA. Each element asks a generic question which for each HTA is then specified to reflect the health problem being assessed. For example, in the domain of Effectiveness, under the topic of Morbidity, the assessment element asks: "What is the effect of the intervention on overall mortality?" For the topic covered in this report, this translates

to a specific question: "In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce overall mortality?"

The importance and transferability of each issue have been considered when the model has been created. These define whether the issue belongs to the Core HTA (as defined by WP4).

Topic-specific adjustments

When applying the core model to a single health technology assessment, topic-specific judgements and adjustments are made on two levels: when deciding about the relevance of issues, and when converting the issues into actual research questions.

Elements relevant for the technology to be assessed should be answered within the core HTA, and answers to other issues may be omitted. Omissions (and reasons for them) are recorded in the report, as it may provide useful information.

Issues defined in relevant assessment elements are converted to research questions. One issue may sometimes produce several related research questions. The core HTA finds answers to these questions.

The model guides researchers in selecting the aspects of technology or its use to study. Research tradition, methods and guidelines within each scientific domain then inform the process. The PICO question, or a wider or narrower application of it, is used in the background (see below in "Scope of assessment").

Structure of the Core HTA report

The issues and answers to them can be presented in a traditional way as a text in chapters. For the purposes of this report we have chosen a standard structure for each domain. The following main chapters are included:

- **Introduction**
puts the assessment in context within the domain. It provides information on the reasons for assessing DES (and perhaps similar technologies) from the viewpoint of the domain.
- **Methodology**
reports what kind of research methodologies, paradigms and theories have been used in the analysis.
- **Assessment elements**
is a chapter that contains information on those assessment elements that have been regarded as relevant in the context of this particular technology. The elements are organised based on topic and the generic issues of the model are replaced by topic-specific research questions. The main findings are reported under subheading "Results". Two other (optional) subheadings exist in this section. In "Methods" researchers may provide additional information on the research methodology that was used when answering this issue. In "Comment" researchers may comment on their findings. If the two optional headings have not been used, also the heading "Results" has been left out.
- **Discussion**
contains an overview of findings in this domain as well as reflections on them.

- **References**

used within the domain are listed here.

- **Assessment element table**

is an overview of all assessment elements defined in the Core Model as well as of the topic-specific judgements that have been made in this particular HTA. The relevance of assessment elements and the translated research questions are included here.

The Core Model enables the presentation of information in various formats. It also supports the presentation of the issues arranged in the form of a deck of cards; this could be stored in an electronic database and accessed for only those elements ("cards") that are relevant for the user. In the next steps of the EUnetHTA project, we will still experiment with various modes of using the Core Model and presenting the results.

This Core HTA on drug-eluting stents covers a wide range of questions in eight domains (out of nine defined in the model). One further domain, Safety, was not completed because it was thought that the safety issues were adequately addressed in the Effectiveness domain. The work has been done in a decentralised manner between 17 organisations, and producing certain parts has often required that another part has been available.

Scope of the assessment

The scope of a core HTA can be defined in several manners. Typically assessment in the effectiveness domain is started by formulating a research question that specifies the technology being assessed and those methods it will be compared to, the disease and the patient groups that will be targeted by the technology, and the health outcomes that will be considered as indicators of improvement. These can be presented in a "PICO" question, that is, by combining the definitions of **P**atients, **I**ntervention, **C**omparator and **O**utcomes. For this report, the PICO question is: In patients with coronary heart disease, how does the insertion of drug eluting stents in coronary arteries (as compared to bare metal stents) affect a broad spectrum of health outcomes?

This PICO question may need further refinement, in case it is considered important to look specifically at various patient subgroups (based on age, gender, phase of disease or other factor), variations in the intervention (such as the type of drug in the stent) or the interventions to be compared (best conservative treatment, bare metal stent, or other intervention such as coronary artery bypass graft). The relevant details may also differ in different domains - if, for example a comparator carries a high risk of serious side effects, it is probably useful to leave this comparator outside the modelling in the Cost domain - while keeping it in the Ethical domain for discussion

In the various domains, it is not always useful to limit the study of the technology to the PICO question only. The example above describes a narrower viewpoint, but it may also be necessary to take a broader view. Does the intervention to be studied belong, for instance, to a group of technologies that share similar problems? DES, for instance, is a device that releases a drug. There may be something common about this type of technologies in, for example, domains dealing with licensing.

In this core HTA the scope has been defined in somewhat different ways in the various domains, as was expected due to different research traditions. The analysis focuses in some domains (e.g. effectiveness) on comparing drug eluting stents with bare metal stents (BMS).

In other domains the view is broader, such as in the social domain in which the social aspects of both stent types are considered. Further work is required to find most suitable scoping within various domains.

Overlapping issues

Some of the issues defined in the Core Model are relevant for two or more domains. For example, the issue of approval of the technology by national or other authorities may be relevant from the viewpoint of the following domains: Health problem and current use of technology, Organisational aspects and Legal aspects. Although the simple reply to the question - yes or no- is the same, the issue is discussed from different viewpoints under each domain.

Findings

The main purpose of this Core HTA on drug eluting stents is to provide a test example on how well the Core Model can be applied in practice. The policy question to be answered in relation to drug-eluting stents can vary markedly between countries; the Core HTA covers a wide range of questions to fulfil the different needs. The Core Model can be seen (among other things) as a checklist for producing an HTA on any single topic. The Core HTA in turn acts either as a stand-alone report that can be utilized in various settings, or as a base from which HTA producers can take building blocks for their own national or regional assessments.

National, regional or local technology assessments based on a Core HTA can look very different. Depending on the country and policy question, the range of issues contained in a new HTA may vary.

The resulting reports on DES (i.e. the Core HTA and any local HTAs that are based on it) may even give different answers to the same question; for example, the price of stents, salaries of health professionals, or reimbursement systems can vary notably from country to country. In any case, a well-done Core HTA should provide a useful starting point for preparing a context-specific report more rapidly than would be possible by starting from scratch or from a traditional full-text report from another country.

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Health problem and current use of technology

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Introduction

Drug eluting stenting (DES) is a technology indicated in certain patients with coronary artery disease suitable for percutaneous coronary intervention (PCI). Stenting is a quickly evolving field of therapy, where the most recent development has been the addition of slow-release drugs to bare metal stents (BMS). The next generation of bioabsorbable DESs is likely to appear on the market in the near future.

A large number of cardiac centers worldwide have been rapid to extend the use of DES beyond the indications proposed by regulatory authorities such as FDA and NHS, and the “off label” use has been extensive. The main reason for extending the indications has been an observed reduction in the rate of restenosis in patients treated with DES compared to those treated with BMS. After a period of widespread use recently published safety data indicating an increased risk of late stent thrombosis in patients treated with DES have led to a more restrictive use in many countries.

This domain presents background information on the conditions possibly targeted by DES. It also describes alternative interventions and current use of DES in relation to its comparators in a national and international perspective. The proportional use of DES in relation to BMS varies substantially between countries and between regions within the same country. The reasons for these variations are not fully understood, but may depend on several factors including differences in the interpretation of data, local traditions and differences in reimbursement policies.

Methodology

This domain contains information from a variety of sources including international and national guidelines, HTA reports, national registers, textbooks (1) and discussions with experts (J Jensen, Director of Percutaneous Coronary Intervention Lab Department of Cardiology Karolinska University Hospital, Sweden). It does not include a systematic review of the alternative technologies used for the same conditions as DES.

By literature and internet search for publications reporting data from interventional cardiology registers several sources were identified. The Swedish Coronary Angiography and Angioplasty Register (SCAAR) (2) covers 100% of centers and 99% of the procedures in Sweden. It gathers individual data and is linked to other registries (mortality, medicament use, hospitalization). SCAAR has been used as the main source in this HTA. Other sources were identified such as the Register of the Spanish Society on Haemodynamics and Interventional

Cardiology (3), that covers 96% of the Spanish centers and gathers aggregated data for each center (no individual data). Other usable primary sources of information may include:

- Registers based on nationally or regionally collected routine statistics, including those from regulatory institutions (e.g. death registers). The Swedish National Board of Health and Welfare (4) run a number of registers including the drug register, the cause of mortality register and the registers containing the diagnoses of all hospitalized patients in Sweden. Similar national registers exist in for example Denmark and Norway.
- Manufacturers' data
- Collection of primary data through research.

Since reliable and comparable cross-European data on this topic would have been difficult to collect, we have mainly used data from one country (Sweden) to exemplify how this chapter could be constructed. Users of this Core Topic in other countries need to identify their own sources of information when wishing to describe the epidemiology in their national context, since major differences exist between countries for several of the issues (as shown in some examples).

In a national HTA report one would probably refer to eventual national guidelines rather than international guidelines as the latter may not be entirely relevant in the national perspective.

Assessment elements

Target Condition

Which disease will be treated by DES?

Drug-eluting stents are put in coronary arteries during percutaneous coronary interventions (PCI) to treat a number of conditions resulting from coronary artery disease (CAD). For a more specific description see below. The term PCI (percutaneous coronary intervention) is an umbrella term for several minimally invasive procedures including PTCA (percutaneous transluminal coronary artery angioplasty) and stenting.

Which are the diagnoses or patient groups for which DES is or may be indicated?

For treatment decisions coronary artery disease (CAD) is often divided into three categories (the first two being known as acute coronary syndromes (ACS)):

- ST segment elevation Myocardial Infarction (STEMI),
- non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina, and
- stable angina.

In a patient with STEMI, a percutaneous coronary intervention (PCI) is usually performed immediately if possible. Other less common indications for acute PCI exist and include cardiogenic shock.

In a patient with NSTEMI or unstable angina, a coronary angiography (with an eventual PCI) is usually performed within one or two days and before the patient leaves the hospital.

In a patient with stable angina, a coronary angiography and the eventual following PCI are clearly elective in nature and the prioritization is dependent of several clinical factors such as symptoms, ECG-changes, work-load test and in some cases scintigraphic findings.

The decision concerning which intervention to use is based on a number of factors (5) including the type of coronary lesion characterised as A, B or C, extent of disease (such as single/multiple lesions/ vessel characteristics), patient related risk factors (such as diabetes, familial hypercholesterolemia (FHC), ongoing anticoagulant therapy and contraindications for antiplatelet agents) and the actual clinical situation (emergency intervention or elective). In some cases evidence based decision making will clearly indicate one intervention before others, whereas in other cases the choice of intervention may be less clear.

The potential target groups for DES are people with the conditions described above where PCI is indicated. The exact target population is not clearly definable, and the practice differs between countries and even within countries. The proportional use of DES in relation to BMS has increased steadily since their introduction and until 2006. The reactions of the interventionalist community and the regulatory authorities to the recent publications concerning late serious complications related to the use of DES (6-9) have lately, however, decreased the target population in clinical practice. These data will be further discussed in the efficacy domain.

What are the symptoms of the conditions for which DES may be indicated?

When applying the model, we found that this and the next question should be answered together.

What are the most common or serious symptoms and consequences of the conditions that may be treated with DES?

CAD is caused by a reduced blood flow to the heart muscle secondary to narrowing or occlusion of the coronary arteries. The narrowing is due to atherosclerotic plaques the development of which will begin during youth and progress during life. As the disease progresses, the blood flow in single or multiple vessels will eventually decrease to a level where it leads to symptoms that can be diagnosed. Most of the diagnosed cases will have one of the conditions stated below. The symptomatic manifestations of coronary artery disease may be acute, chronic or both. The acute coronary syndromes include myocardial infarction, unstable angina and some less common conditions including cardiogenic shock and sudden death.

The typical symptom of CAD is chest pain, usually located on the left side or retrosternal and which may irradiate to left arm, neck, or jaw. It may also present as breathlessness, discomfort or pressure.

Stable angina is a chronic condition where the patient experiences episodic chest pain, usually during physical or emotional stress. Stable angina is often graded using the scale from the Canadian Cardiovascular Society (CCS (10)).

CCS Angina Classification (10)

Class	Description
Class I	Ordinary activity such as walking or climbing does not precipitate angina
Class II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
Class III	Marked limitations in ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry out any physical activity without discomfort, anginal symptoms may be present at rest

Stable angina typically is relieved by resting and by nitrates. Progression of the disease may lead to instable angina or MI.

Acute coronary syndromes

Unstable angina- is a syndrome that is intermediate between stable angina and myocardial infarction: It is characterized by chest pain that lasts longer and/or may be more severe than in stable angina. It may occur at rest or with less exertion than in stable angina. It may also be less responsive to medication. New onset angina is also included in this syndrome. The progression of unstable angina may lead to Non ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI).

Non ST elevation myocardial infarction – has the same clinical symptoms as unstable angina and in addition evidence of myocardial necrosis reflected by elevated cardiac biomarkers. Progression may lead to STEMI.

ST elevation myocardial infarction – is a very acute condition with severe symptoms in most cases. The cause is usually an occlusion of a coronary artery that without immediate treatment will result in necrosis of a region of the myocardium. This usually results in a reduced pumping capacity of the heart muscle (heart failure) leading to disability. Other complications exist such as arrhythmia, cardiogenic shock and death.

People with CAD are at increased risk of death. Besides the increased risk of death for people with CAD, the disease has also other consequences. Depending on its degree, angina may limit daily life more or less. The limitations imposed by the disease influence mood and quality of life (16, 17). The quality of life of persons with CAD is reduced compared with the

general population (17,18). Sexual functioning is also impaired in persons suffering from CAD (19).

What are the known risk factors of coronary artery disease?

Methods

Literature search for review articles, large cohort studies.

Results

The progress of atherosclerosis depends on several factors (1). In the large INTERHEART study (11), the researchers reviewed data from 15 000 patients with myocardial infarctions and an equal number of healthy controls. Approximately 90% of the myocardial infarctions could be explained by several easily identifiable risk factors: gender, heredity, high cholesterol, smoking, hypertension, abdominal obesity, diabetes, low intake of fruits/vegetables and an insufficient amount of physical activity.

What will happen if DES is not used on the different conditions where DES may be indicated?

The use of PCI is aimed at restoring the blood flow in the affected coronary vessels by increasing the lumen of the vessel. In some situations such as STEMI or cardiogenic shock, the intervention may be directly life-saving, whereas in other situations the intention may be the reduction of symptoms without shown effects on mortality. The use of DES as opposed to BMS is mainly aimed at reducing the rate of restenosis thereby decreasing the risk of recurrency in symptoms and the need for revascularisation. The evidence for the effects of DES compared to BMS in different patient populations (i.e. label use vs off-label use) will be more extensively covered in the efficacy domain.

What is the incidence of CAD?

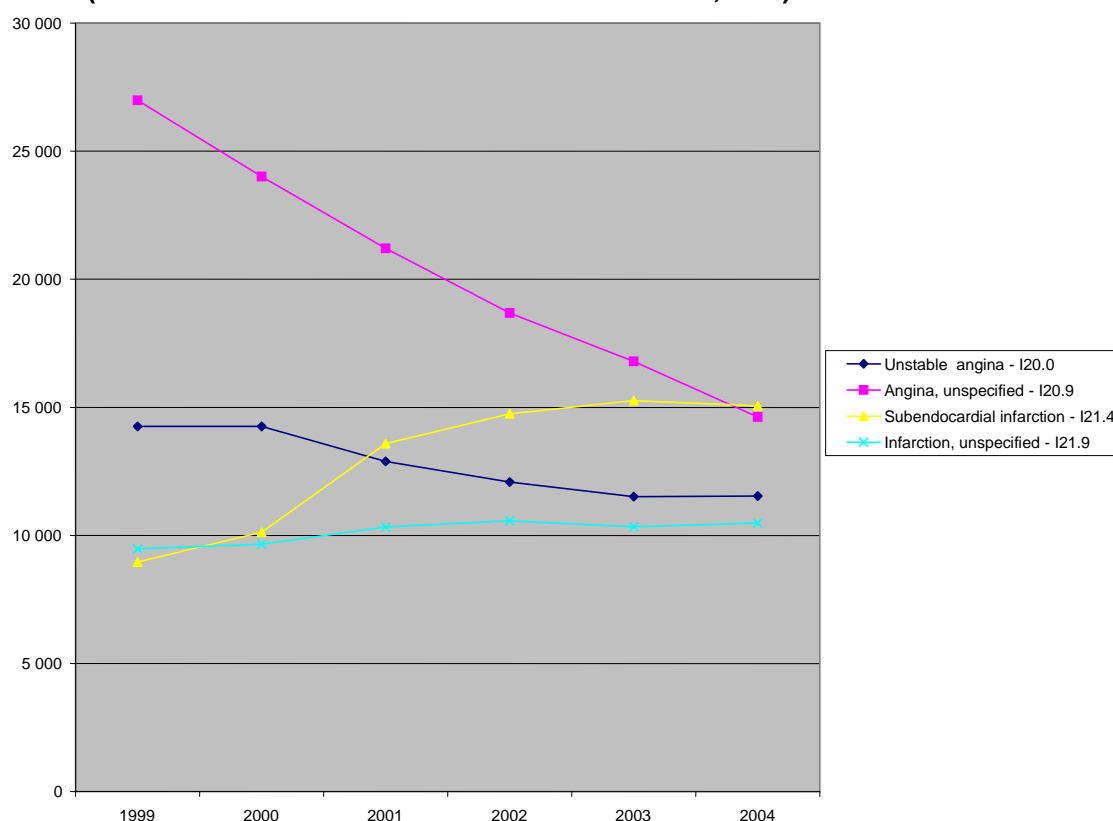
Methods

Register data from The Swedish National Board of Health and Welfare (4) and SCAAR (2) Report from the British Heart Foundation (20).

Results

The prevalence of angina pectoris among men in Sweden is about 3% in the ages between 45-50 years and 7% in the ages between 65-70 years of age. In a population of 9 million, the incidence of MI is presently 42 000 per year and about 34 000 of these are admitted to hospital. About 15 000 are admitted to hospital for unspecified angina and 12000 for instable angina yearly. About 5000 coronary artery bypass grafts (CABG) and 18 000 PCIs are performed yearly. Coronary heart disease accounts for about 18 000 deaths each year in Sweden, constituting 22% of all deaths in men and 18% in women (4).

Figure 1. Hospitalisations per year for certain types of coronary artery disease (data from the Swedish National Board of Welfare, EPC)



There are differences in the incidence of CAD across European countries and within European countries across regions. According to the latests available data from the MONICA Study, the incidence of coronary events in men varied in Europe between 835/100.000 in the Finland North Karelia population and 210/100.000 in the Spain-Catalonia population (20). Similar variations were found in women, from 777/100.000 in the UK-Glasgow population and 35/100.000 in the Spain-Catalonia population (20).

However, not all persons having CAD can be considered to be potential targets for the use DES. Under the assumption that DES substitutes BMS, the target group would be the patients currently undergoing PCI with BMS. Following this reasoning the potential target group would vary across countries according to the PCI rate and especially according to the use of stents during PCI. Stents are used in 94% of PCI (21), thus the number of PCI would provide a good estimate of the potential target group for the DES technology under the assumption of substitution of stenting. Great variations in the use of PCI have been also identified for PCI (and other procedures for treating CAD), indicating potential great variations in the target group for use of the DES technology across countries. In the year 2002 (according to available data) PCI rates per million population varied between 148 in Romania and 2439 in Germany (20).

What is the burden of coronary artery disease?

Coronary artery disease (CAD) is the leading cause of death in the developed countries and for example accounts for around 20% of all deaths in Sweden, Germany or UK. Coronary

heart disease accounts for about 18 000 deaths each year in Sweden, constituting 22% of all deaths in men and 18% in women (4).

The prevalence/incidence of early retirement due to the condition depends on the severity of the condition but also on the social security arrangements in each country. Thus, the transferability of this kind of information might be very limited.

Current management

How common is the use of DES in relation to other interventions for CAD?

Stents were in 2005 used in just over 90% of all PCIs in Sweden (2). For the use of PCI in relation to CABG from 1982 to 2005 please see fig. 2. The use of PCI for different indications as well as the proportional use of DES, please see fig. 4-7.

Figure 2. The number of all coronary artery interventions, coronary artery bypass grafts, and percutaneous coronary interventions in Sweden 1982-2005 (Data from SCAAR 2005).

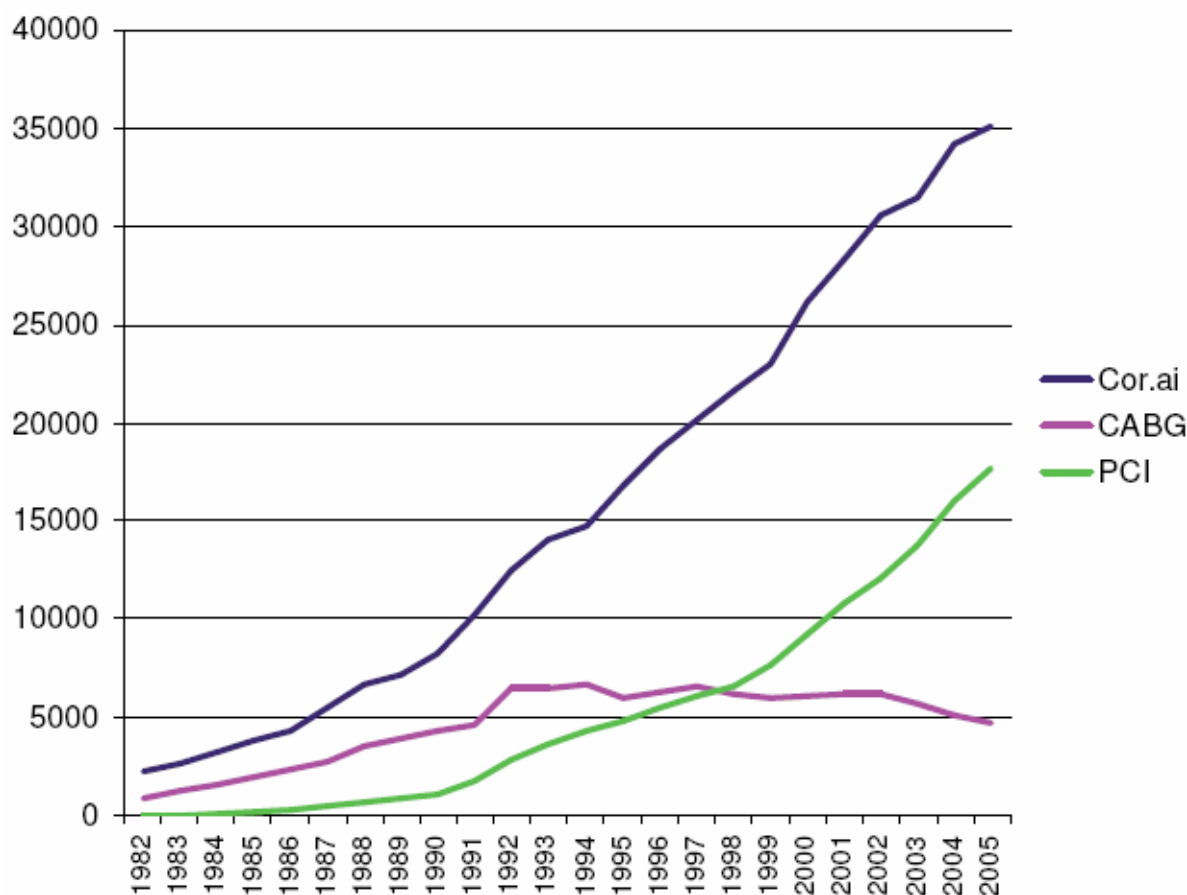


Figure 3. The proportion of patients with STEMI in Sweden that have undergone CABG 2000 to 2005 (data from SCAAR).

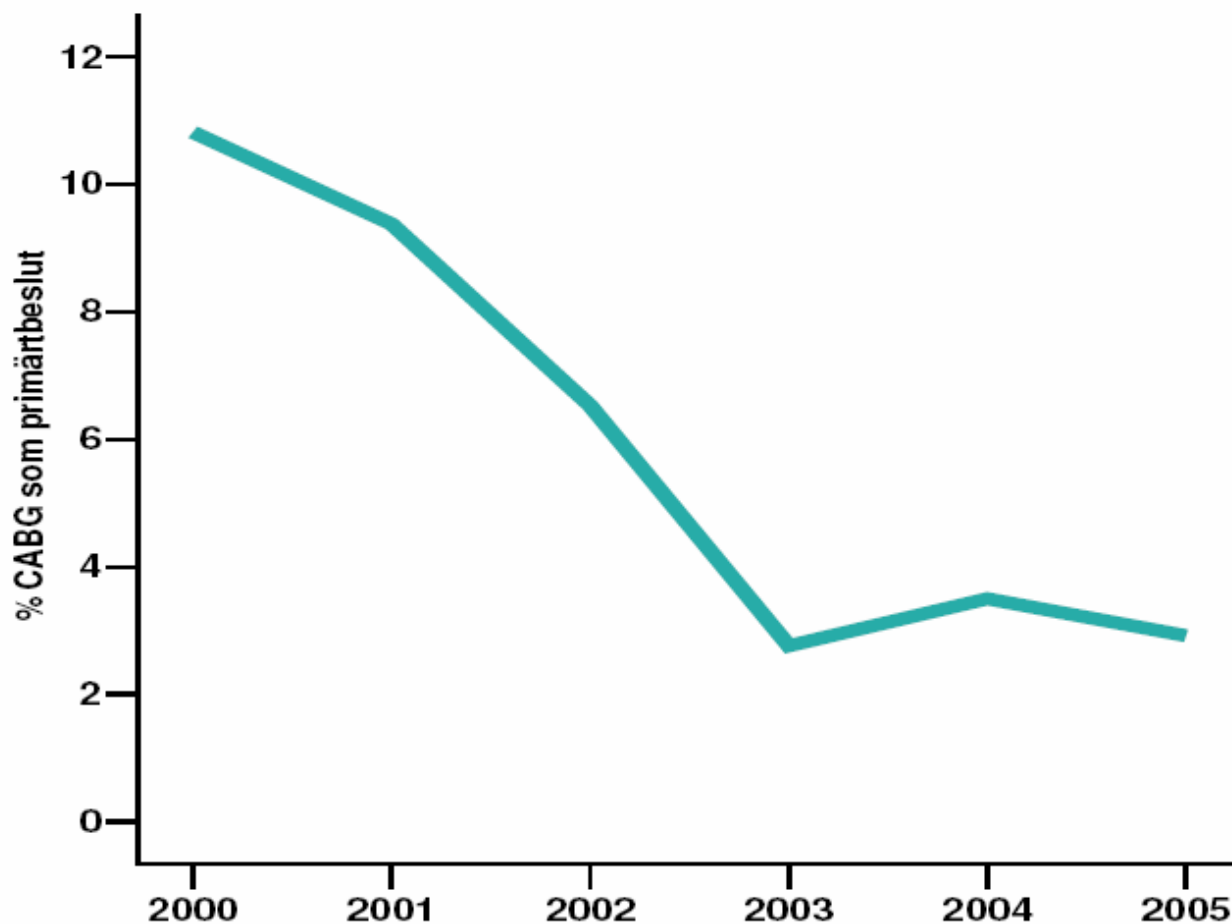


Figure 4. The number of PCIs performed in Sweden on STEMI indication 1989 to 2005 (data from SCAAR 2005).

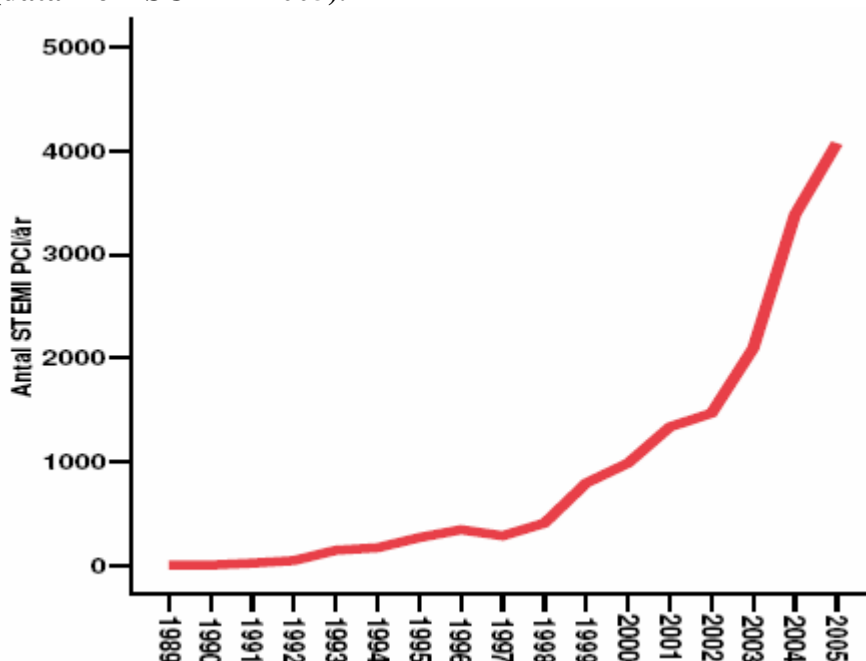


Figure 5. The proportional number of PCIs performed due to each indication. The acute coronary syndromes account for just over 70% of all performed PCIs in Sweden (Data from SCAAR 2005).

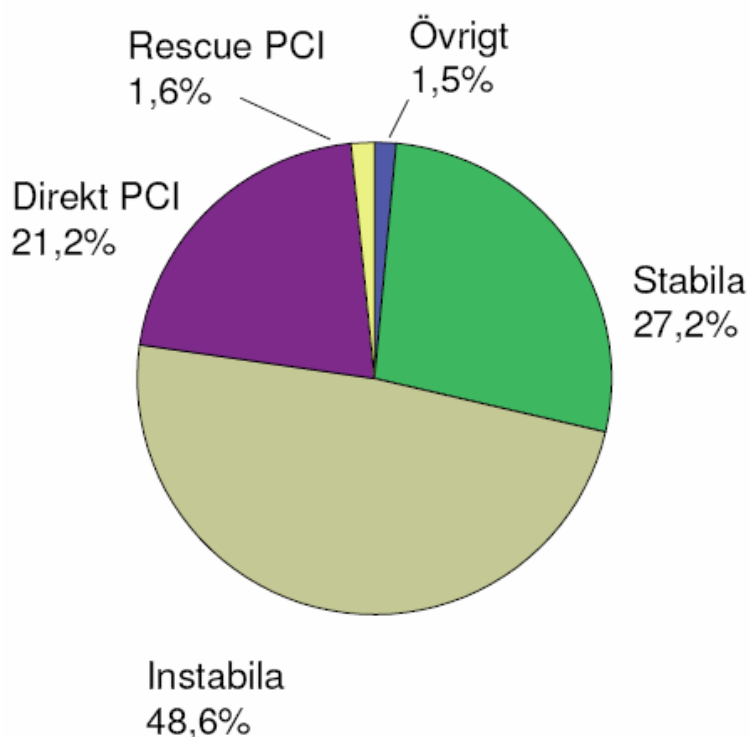


Figure 6. The proportion of patients with stable angina undergoing PCI classified using CCS guidelines (Data from SCAAR 2005).

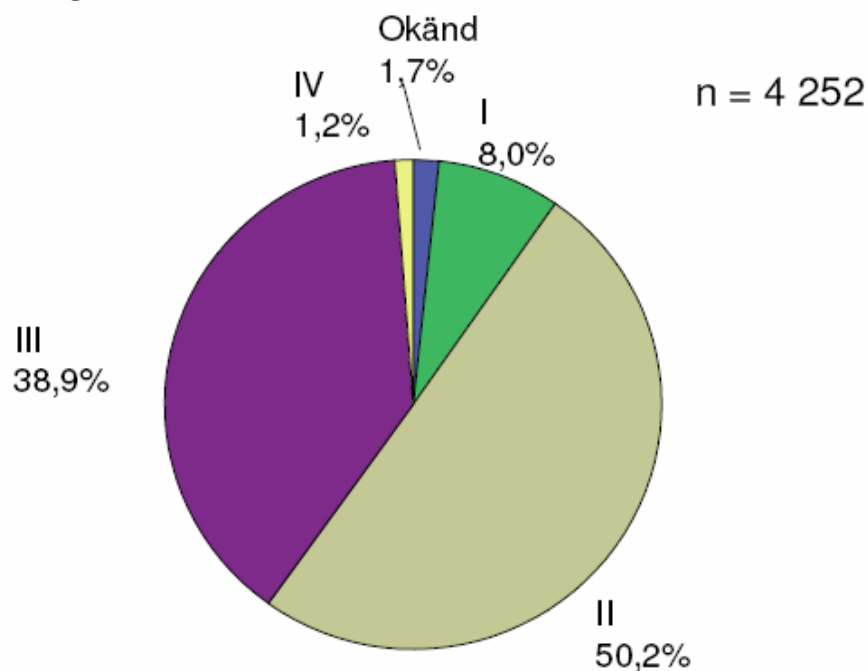


Figure 7. Illustrates the substantial local variation of the proportional use of DES between the different Swedish centers during 2005. The left figure shows the number of DES and BMS procedures performed in each Swedish center and the right figure shows the proportional use of DES (Data from SCAAR 2005).

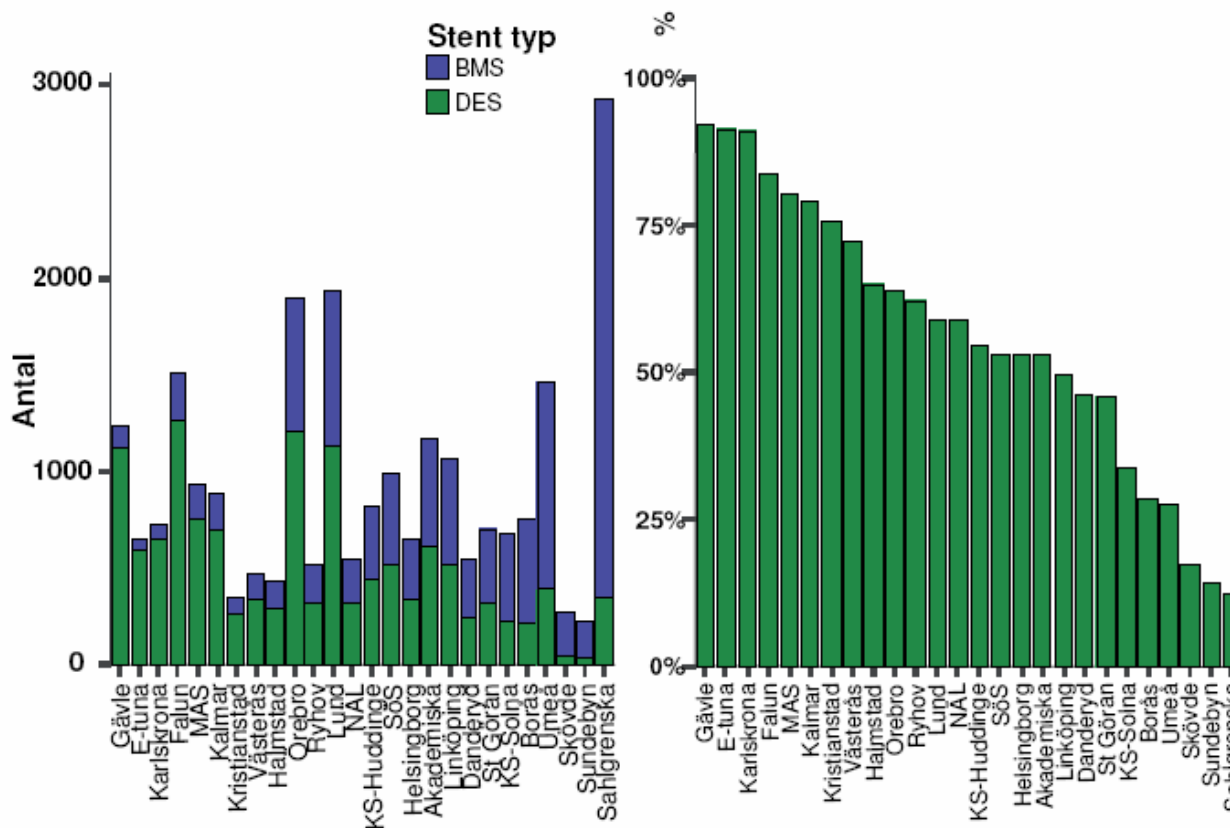
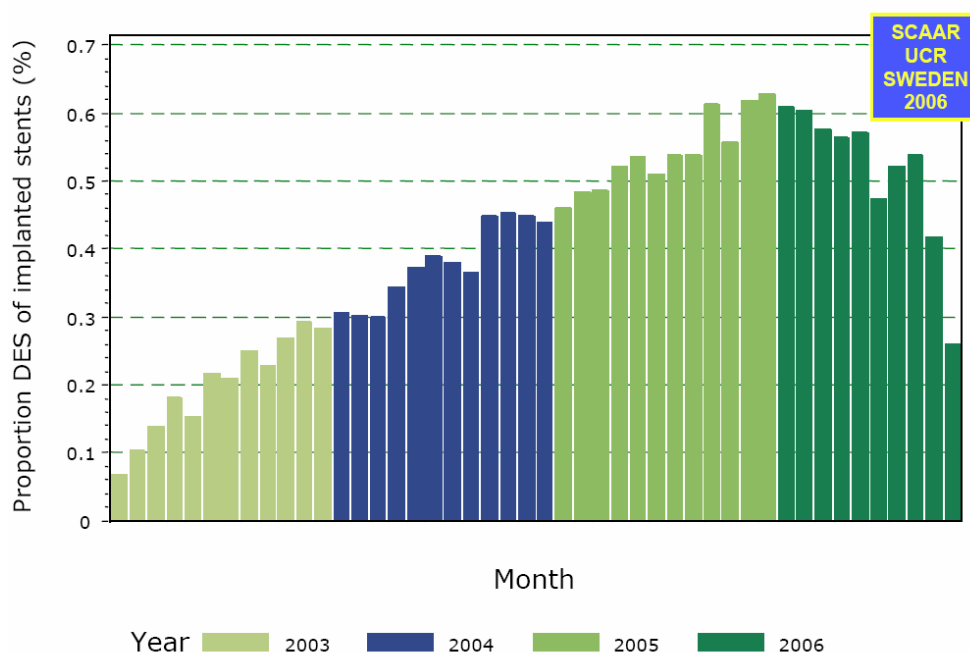


Figure 8. The proportional use of DES in Sweden increased steadily until 2006, when safety data from large observational (8) and registry studies (3, 7, 9) (SCAAR Sweden) indicated an increase in late stent thrombosis after cessation of anti-platelet therapy. After reaching a top level of over 60% (in some centers over 90%), the proportion of DES in Sweden in early 2007 is below 20%(data not shown).



Development of the use of DES in Sweden 2003 - 2006

Are there variations in the use of DES across countries in Europe? And across regions within the same country?

Both the use of PCI as such, and the proportion of DES of all stents applied, vary substantially between and within countries. These variations may reflect differences in priority setting, in funding and coverage decisions, and in other factors which influence the adoption of the technology.

The proportion of DES among the total number of implanted stents varies across European countries. The table below presents data from four countries (2, 3, 20, 25).

Year	Drug Eluting Stents % of all Stents			
	Spain	Germany	Switzerland	Sweden*
2002	4,1%	-	-	-
2003	20,2%	-	-	28%
2004	36,5%	-	66%	44%
2005	-	30%	78%	63%
2006	-	-	-	26%*

* Data from october 2006

Regional variations of the use of DES have been also described within the same country. In Spain for example the proportion of DES varied from 23 % to 56 % in 2004. Three regions

used DES in more than 50% of stent implantations, whereas four regions used DES in less than 25% of stent implantations (3). In Sweden the use of DES varied from 12% to 92% across regions (see issue above).

How is CAD currently being managed?

In different ways depending on the type of CAD, see above. Medical management is used in virtually all diagnosed cases of CAD in order to reduce symptoms, modify risk factors and to prevent disease progression and serious complications. The treatment may include the use of several drugs such as betablockers, cholesterol lowering agents, antiplatelet agents, nitrates, calcium channel blockers, potassium channel blockers and anticoagulants. Medical management of CAD is not within the scope of this report.

CABG (coronary artery bypass graft surgery) is the oldest invasive strategy presently in use. Its use has decreased on behalf of the widening indications for PCI over the last years. In certain patient categories, for example patients with main stem stenosis, CABG is still the preferred treatment alternative (1, 5). CABG is not included in the scope of this review.

Are there published algorithms or guidelines on CAD? How should the condition be managed?

Methods

We conducted a systematic search for evidence based clinical practice guidelines providing advice on percutaneous coronary intervention (PCI). We searched the GIN Database of clinical practice guidelines using combinations of the keywords „*PCI*“, „*Cardiovascular Disease*“ and „*Coronary Heart Disease*“. We identified two relevant international guidelines concerning PCI from the American Heart Association (5) and from the European Society of Cardiology (12) which had been developed following the principles of evidence based medicine and which provided recommendations graded by their level of underlying evidence. Both include details concerning the indications and procedures of PCI and DES. Many European countries have published guidelines or algorithms for the treatment of CAD. Most recommendations concerning the use of DES, however, have been issued before data from long-term follow up observational and registry studies showed a potential increase in the risk of late stent thrombosis leading to severe clinical consequences. After the presentation of these data (the SCAAR data being presented before their publication in NEJM) the US Food and Drug Administration made public its concerns regarding the adverse events related to the use of DES. The FDA acknowledged an small but significant increase in the rate of death and myocardial infarction possibly due to late stent thrombosis in patients treated with DES (13). This statement and even more recent statements from authorities and cardiologist organisations in several nations challenge aspects of the older guidelines. For example in the light of this statement the German Society of Cardiology has pleaded for thoughtful and moderated use of DES (14) and the more recently published Swedish National Guidelines on DES published by the Swedish MPA in association with the Swedish National Board of Health and Welfare and the Swedish Society of Cardiology have put restrictions on the use of DES (15).

Are there differences in the management for different stages of coronary artery disease?

Yes, depending on the severity, the type of lesion and other factors. See above.

Do other evidence-based treatment alternatives to DES exist? If so, which?

Yes, stenting with BMS, PTCA and CABG are evidence based alternatives and may be considered as alternatives depending on the clinical situation. For some situations (for example significant left main coronary disease) surgery (CABG) may be recommended over PCI (22)

Life Cycle

Is DES an experimental or emerging technology?

BMS is an established technology, while DES is currently still developing. There are new drugs being administered by drug-eluting stents, and new types of matrix materials are being developed. The new variations of DES can be considered as emerging variants of a technology that is as such established.

Regulatory status

Has DES been approved for the market by national or international authorities?

Yes, in several countries in both Europe and elsewhere. More information on this issue is found in the domain on organisational aspects as well as in the ethical domain.

Has DES been included in / excluded from the benefit basket of any country?

To our knowledge DES has not been explicitly excluded from the benefit basket of any European countries. However different reimbursement arrangements exist which may DESs are included in the benefit baskets of several care providers in several countries in and outside Europe. In Sweden the reimbursement for the care providers varies locally. In some regions all DES stents are reimbursed, whereas in some regions DES are reimbursed up to a certain percentage of all stents used. Some of these regulations are currently under revision due to new data on long-term effects of DES.

In countries with fees for case group (DRG-systems), providers might be reimbursed a fixed amount for PCI disregarding whether an stent is implanted or not, and if so disregarding which kind of stent is implanted. However, additional payments may cover the costs of DES (i.e. on top of the corresponding DRG) or even a differentiated DRG may account for the cost

differences between DES implantation and other PCI (as is the case in some regions in Italy) (23).

Discussion

DESs were introduced as a routine PCI procedure in 2002-2003. The main advantage of DES as opposed to BMS was a shown decrease in the risk of restenosis and need for revascularisation. This swiftly led to a worldwide acceptance of DES and in the beginning of 2006 DES was by far the most prevalent PCI procedure in some industrialised countries in spite of high costs and need for prolonged and costly anti-platelet therapy. The off-label use, i.e. the use in clinical situations/ in patients other than the ones for which efficacy has been proven in randomized controlled trials has been extensive (24). During 2006 and 2007 observational safety data indicated a small but statistically significant increase in the risk of late stent thrombosis and death in patients treated with DES. These late complications seem to be related to off-label use and premature discontinuation of anti-platelet therapy. These new data have resulted in a rapid decrease in the use of DES in several countries. For example the proportional use of DES in Sweden has decreased from 60% in early 2006 to below 20% in early 2007.

Some of the issues of this domain are highly context dependent and thus not easily transferable. We have shown in some examples, that the answers to the issues may vary significantly depending on the country. It was beyond the scope of this exercise to provide comprehensive comparisons including all European countries. However, such a comparison can be facilitated when agencies from single countries provide their data (i.e. their answers to the issues) following the same structure. For example if say 9 countries describe their coverage arrangements for DES, any other agency accessing this information can provide a comparative view on this issue. This kind of comparative information may be very useful for decision-makers.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of DES Yes / No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
A0001	Health Problem and Current Use of the Technology	Target Condition	Which disease/health problem/potential health problem will the intervention target?*	Yes	Which disease will be treated by DES?	3	3
A0002	Health Problem and Current Use of the Technology	Target Condition	Is there a precise definition/ characterization of the target disease?*	Yes	Which are the diagnoses or patient groups for which DES is or may be indicated?	3	3
A0003	Health Problem and Current Use of the Technology	Target Condition	What are the symptoms of the disease?*	Yes	What are the symptoms of the conditions for which DES may be indicated?	3	3
A0004	Health Problem and Current Use of the Technology	Target Condition	What are the consequences of the condition?*	Yes	What are the most common or serious symptoms and consequences of the conditions that may be treated with DES?	3	3
A0005	Health Problem and Current Use of the Technology	Target Condition	Are there known risk factors for acquiring the condition?	Yes	What are the known risk factors of coronary artery disease?	2	3
A0006	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?	Yes	What will happen if DES is not used on the different conditions where DES may be indicated?	3	3
A0007	Health Problem and Current Use of the Technology	Target Condition	How many people belong at the moment (will belong) to the specific target group?	Yes	What is the incidence of CAD?	3	2
A0008	Health Problem and Current Use of the Technology	Target Condition	What is the burden of disease (mortality, disability, life years lost)?	Yes	What is the burden of coronary artery disease?	3	2
A0009	Health Problem and Current Use of the Technology	Utilisation	How much is the technology being used?	Yes	How common is the use of DES in relation to other interventions for CAD?	2	1
A0010	Health Problem and Current Use of the Technology	Utilisation	Are there variations in use across countries/regions/settings?	Yes	Are there variations in the use of DES across countries in Europe? And across regions within the same country?	2	2
A0011	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the disease/health condition currently being managed?	Yes	How is CAD currently being managed?	3	2
A0012	Health Problem and Current Use of the Technology	Current Management of the	Are there published algorithms/guidelines? How should the condition be managed?	Yes	Are there published algorithms or guidelines on CAD? How should the condition be managed?	3	2

EUnetHTA WP4 - Core HTA on drug eluting stents (DES)
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

ID	Domain	Topic	Issue	Relevance in the context of DES Yes / No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)	Importance 3= <i>critical</i> 2= <i>important</i> 1= <i>optional</i>	Transferability 3= <i>complete</i> 2= <i>partially</i> 1= <i>not</i>
		Condition					
A0013	Health Problem and Current Use of the Technology	Current Management of the Condition	Are there differences in the management for different stages of disease?	Yes	Are there differences in the management for different stages of coronary artery disease?	2	2
A0014	Health Problem and Current Use of the Technology	Current Management of the Condition	Do other evidence-based alternatives exist? If so which?	Yes	Do other evidence-based treatment alternatives to DES exist? If so, which?	3	3
A0015	Health Problem and Current Use of the Technology	Life-Cycle	In which phase is the development of the technology (experimental, emerging, routine use, obsolete)?	Yes	Is DES an experimental or emerging technology?	2	2
A0016	Health Problem and Current Use of the Technology	Regulatory Status	Has the technology been market approved by any national/international authority?	Yes	Has DES been approved for the market by national or international authorities?	3	3
A0017	Health Problem and Current Use of the Technology	Regulatory Status	Has the technology been included in / excluded from the benefit basket of any country?	Yes	Has DES been included in / excluded from the benefit basket of any country?	2	2

Description and technical characteristics of technology

Hans van Brabant, Antti Malmivaara, Pekka Kuukasjärvi

Introduction

Percutaneous coronary intervention (PCI) is a common intervention intended to dilate narrowed coronary arteries. The technique has been introduced by Andreas Grüntzig¹ in 1977 as an extension of the work of Dotter and Judkins who introduced the procedure for transluminal recanalization of arteriosclerotic obstructions in lower limb arteries.² As such, invasive revascularisation by means of coronary artery bypass grafting (CABG) could be prevented in some patients.

An important limitation of PCI is the risk of an acute vessel closure provoked by the injury on the vessel wall resulting in intimal and medial flaps projecting into the vessel wall. Furthermore, restenosis of the dilated vessel occurs in 30 to 40% of patients.^{3,4} Several mechanisms may contribute to the process of restenosis: elastic recoil occurring immediately (i.e. between seconds and minutes after balloon deflation), platelet adherence to the injury site, inflammation of the vessel wall, neointimal hyperplasia and vascular constrictive remodelling.

Due to these limitations coronary stenting was introduced.

Methodology

The information concerning this domain has been obtained mainly from the literature, and partly from manufacturers of the technology.

Assessment elements

Features of the technology

What is BMS, what is DES?

Stenting (bare metal stent, BMS) is a technique in PCI in which a metal scaffolding is fitted into the coronary artery on the site of the dilated lesion. Drug eluting stents (DES) are coated with a drug that will inhibit cell proliferation and therefore aim to further reduce in-stent restenosis.

Why is DES used instead of BMS?

Coronary stenting (BMS) was introduced in order to try to prevent the shortcomings in PCI, particularly the restenosis of the target vessel. Although it was clear that BMS stenting reduced the occurrence of acute mechanical complications of angioplasty and diminished the rate of restenosis, both stent thrombosis and a residual late restenosis remained a major challenge to interventional cardiologists. In-stent restenosis is usually due to neointimal hyperplasia, an excessive growth of tissue in and around the stent as a reaction to injury. This process, which also occurs following standard PCI, is not prevented by the original bare metal stents; on the contrary, they actually exacerbate it. Drug eluting stents (DES) have been developed to try to antagonize this cellular reaction. The components of a DES can be divided into a platform (the stent), a carrier (usually a polymer) and an agent (the drug). The carrier coating facilitates a gradual release of the embedded drug into the local tissue. Several drugs have been studied but the current generation of DESs are coated with a polymer embedded with an antiproliferative drug. The theory base is that this drug will inhibit cell proliferation and therefore reduce in-stent restenosis.

What is the phase of technology in BMS and DES?

Stenting

Stenting was first used in 1986 by Sigwart and Puel who described the technique for treating acute vessel closure due to blood vessel wall dissection and an impairment of bloodflow by projecting intimal flaps.⁵ In 1993 two trials, BENESTENT 3 and STRESS 4, comparing combined PCI and stenting with PCI only demonstrated that intracoronary stents significantly reduced the incidence of restenosis. Gradually, coronary stents became almost routinely used in most angioplasties. Some consensus panels endorsed this clinical enthusiasm even before a large body of high-quality evidence was available.⁶ By 1999, stenting comprised more than 80% of percutaneous coronary interventions.⁷ In a meta-analysis of data from 25 trials Brophy et al. 6 calculated that stenting was associated with a 48% reduction in restenosis rate. In absolute terms, stenting reduced the angiographic restenosis rate by 14.5%. However, routine coronary stenting was not associated with important reductions in rates of mortality, acute myocardial infarction or CABG compared with standard PCI.

At the time of the STRESS and BENESTENT trials, and despite the use of an intensive coumadin anticoagulation regimen, acute vessel occlusion due to thrombus formation within the stent occurred in 3.7% of patients, a value higher than that seen with PCI alone.⁸ The subsequent use of better dilatation techniques together with dual antiplatelet therapy with aspirin and a thienopyridine (i.e. ticlopidine or clopidogrel) rather than anticoagulation resulted in a reduction of stent thrombosis in 0.5 to 1.9% of patients.⁹

Drug eluting stents

The agents that have been the subject of the most extensive research are sirolimus (rapamycin) and paclitaxel. Sirolimus is a macrolide immunosuppressant used systemically to treat renal transplant rejection. It halts proliferation of smooth muscle cells: it binds to a receptor protein and inhibits a regulatory enzyme that in turns shuts off the cell cycle. Sirolimus is incorporated in the Cypher stent, manufactured by Cordis.¹⁰ Paclitaxel is a derivative of the yew plant. It also inhibits the cell cycle and has been used as an anti-proliferative drug in the treatment of breast, lung and ovarian cancer.¹¹ This drug is used in the Taxus stent that is manufactured by Boston-Scientific.¹² Both these DES are generally referred to as “first generation stents”. Although there seems to be no

general agreement on the definition of these terms, second and third generation DES would be stents with specialized designs for complex anatomy, bioabsorbable polymers and “no polymer” systems and DES with a combination of different drugs to further reduce neointimal growth.¹³ Many of these newer DES are currently under investigation.

The first major trial that compared DES with bare metal stents (BMS) was the RAVEL study in which patients with angina were randomized to a sirolimus DES or a BMS for treatment of single, primary lesions in native coronary arteries.¹⁴ The primary endpoint was in-stent late luminal loss, i.e. the difference between the minimal diameter immediately after the procedure and the diameter at six months. Late luminal loss was significantly lower in the DES group (mean $-0.01 \pm \text{SD } 0.33$ mm) compared to the BMS group (mean $+0.80 \pm \text{SD } 0.53$ mm) resulting in a clinical significant restenosis (i.e. $> 50\%$) in not a single patient in the DES group versus 26.6% of patients in the BMS group.

In the following years, different DESs were tested in patients with more complex lesions and in the clinical context of acute coronary syndromes. From a meta-analysis, Roiron et al. concluded that major adverse cardiac events (MACEs) occurrence was highly reduced with DES from 19.9% to 10.1% compared to BMS.¹⁵ MACE was defined as a composite of death, myocardial infarction and revascularisation. However, mortality, Q-wave myocardial infarction and stent thrombosis were not significantly different between DES and the control group.

The widely held belief that the problem of restenosis has been “cured” by using DES has resulted in a new paradigm in the treatment of coronary artery disease with a dramatic shift away from CABG and an increase in the complexity of percutaneous coronary interventions resulting in, at least in some countries, a virtual replacement of BMS by DES.¹³ In 2005, in the US, 90% of stents used were DES. In 2003, in the New York State database the ratio of PCI vs. CABG had increased to 3.5/1 whereas in 2001 it was 1.9/1.¹³

Who are the users of BMS and DES?

Cardiologists in any catheterisation laboratory where percutaneous coronary interventions (PCI's) are performed for coronary artery disease.

Where are DES and BMS used?

In any organizations having a catheterisation laboratory where percutaneous coronary interventions (PCI's) are performed for coronary artery disease.

Are there any special features relevant to DES and BMS?

Favorable effects related to DES
See above.

Adverse effects related to DES

Important side-effects, some of which typically related to the action of antiproliferative agents, have drawn particular attention of clinicians when using DES. In some cases, endothelial healing was completely inhibited, preventing encapsulation of the stent and eventually leading to incomplete

apposition of it. Very late stent thrombosis (LST) has been reported and constitutes a major problem because it can lead to increased cardiac mortality.¹⁶ Hypersensitivity-reactions to the polymer, possibly leading to LST has also been reported.¹⁷ A recent meta-analysis suggests the possibility of an increase in non-cardiac late mortality.¹⁸

Unlike restenosis, thrombosis is a rare but potentially life-threatening complication of coronary stents. The clinical consequences for these patients are often catastrophic, including short-term mortality rates of up to 25% and major myocardial infarction in 60% to 70% of cases.¹⁹ Stent thrombosis usually occurs before re-endothelialization has been completed. It rarely occurs beyond 2 to 4 weeks for BMS²⁰ but is a matter of concern in DES because of the delayed endothelialization. It has been the subject of long-term follow-up reports of previous trials and in real-world registries of unselected patient groups. Randomised controlled trials suggest that thrombosis following DES placement is not more frequent than following BMS at up to one year after the procedure. In an observational study, Pfisterer et al noticed that the discontinuation of clopidogrel six months after DES implant later on was followed by a doubling of documented LST in DES (2.6%) vs. BMS (1.3%).²¹

LST is likely to be related to a delayed healing of the injury caused by the mechanical dilatation of the coronary vessel. Thus, a continued presence of a foreign body predisposes to thrombus formation. This thrombotic tendency can be more pronounced in complex coronary lesions and in patients who stopped one or both of the antiplatelet drugs that were instituted following DES implant.

Premature antiplatelet therapy discontinuation has been shown to be a risk factor for LST. In a prospective observational study, with follow-up at 9 months after DES implant, stent thrombosis occurred in 29 of 2229 patients (1.3%).²² LST occurred in 5 of 17 patients (29%) who prematurely discontinued dual antiplatelet therapy. Other independent predictors of stent thrombosis were renal failure, bifurcation lesions, diabetes and a low ejection fraction.

Nordmann et al. conducted a systematic review on mortality outcomes in randomized trials that compared DES with BMS.¹⁸ They not only included peer-reviewed publications but also incorporated results from long-term follow-up of existing studies presented at scientific meetings and follow-up information obtained directly from the principal investigators and manufacturers. They concluded that DESs do not reduce total mortality when compared with BMSs. Surprisingly, their preliminary evidence suggested that sirolimus eluting stents may lead to increased non-cardiac mortality.

Investments and tools required to use the technology

What material investments are needed when using DES instead of BMS?

The use of DES in stead of BMS does not require material for the catheterisation laboratory or organization beside the drug eluting stent itself.

What kind of special premises are needed when using DES instead of BMS?

The use of DES instead of BMS does not require any special premises for the catheterisation laboratory or organization.

What kinds of equipment and supplies are needed when using DES instead of BMS?

The use of DES instead of or along BMS does not require additional equipment or supplies to use the technology.

What kinds of records or registers are needed when using DES instead of BMS?

The use of DES instead of or along BMS does bring a further need for records and registers to monitor patients undergoing PCI. The long term follow-up becomes more important, especially for documenting the late stent thrombosis.

Training and information needed for utilizing the technology

What kind of training is needed for the personnel using DES instead of BMS?

In being essentially nothing more than an angioplasty with a specially designed stent, compared to a BMS procedure, it does not implicate specific training for the catheterisation personnel.

What kind of training is needed for the personnel treating or investigating patients with DES instead of BMS?

The training of cardiologists must be planned to cover the following topics

For the interventional cardiologist, two items deserve special attention, both related to the fear of an increased risk of LST. First, it should be taken into account that the risk of stent thrombosis is dependent on some procedure related factors: morphometric abnormalities (undersized stents, underexpansion, asymmetry), morphologic abnormalities (dissection, incomplete apposition, thrombus, tissue protrusion), and mechanical vessel injury.¹⁹ Patients treated in randomised trials mostly have simple coronary lesions which may be the reason why stent thrombosis in DES did not exceed that in BMS in these studies. The recently reported increased risk of LST can be related to the off-label use of DES in real world practice. According to some authors the majority of DESs are implanted in patients or in vessels with characteristics different than those studied to support marketing approval.²³ Following a public meeting, convened by the FDA Circulatory System Devices Advisory at the end of 2006, the panel generally agreed that off-label use of DES is associated with an increased risk of stent thrombosis, death and myocardial infarction when compared to on-label use of DES. The Panel did not find sufficient data were available to identify subsets of patients at a particularly increased risk. It is important that implanting physicians are aware of this.

Second, strong emphasis is to be put towards the patient on a correct use of antiplatelet drugs following DES implantation. Because BMS become endothelialised within a few weeks of implantation, dual antiplatelet therapy (aspirin plus thienopyridine) is only required during 3 to 4 weeks. DES on the other hand cause delayed endothelialisation and prolonged antiplatelet therapy is imperative. According to the European Society of Cardiology, it should be continued during 6 to 12 months following DES procedures.²⁴ Furthermore, physicians considering a stent implant in a patient should try to find out if that patient is likely to be compliant with prolonged antiplatelet therapy. If not, a BMS should be preferred.

What kind of training is needed for the patients receiving DES instead of BMS?

Informing the patients must be planned to cover the following topics:

Because of concerns of late stent thrombosis and the association of this potential catastrophe with the inadequate use of antiplatelet drugs, patients must be aware that dual antiplatelet therapy should not be discontinued too early, even for minor procedures such as dental care.²⁴ This means that, before introducing a DES, patient and physician should thoroughly consider whether a subsequent (non-cardiac) surgical procedure necessitating the interruption of antiplatelets is expected or is likely to be needed. If so, a DES might not be the best choice.¹⁶

The continued use of dual antiplatelet therapy also leads to an increased risk of bleeding complications. In a population-based case control study, Hallas et al found that clopidogrel by itself carries little if any risk of upper gastrointestinal bleeding, but when it is given with aspirin the risk increases beyond the effect of aspirin given alone.²⁵ In the Atrial Fibrillation Clopidogrel Trial (ACTIVE W), investigators found a comparable risk of major bleeding in patients treated with clopidogrel plus aspirin compared to patients on oral anticoagulation.²⁶

The combination of an increased risk of bleeding when using two antiplatelet agents and the increased risk of LST when discontinuing one or both of them, demands for a continuing consultation between patient and physician.

What information do patients outside the target group and the general public need on DES treatment instead of BMS treatment?

Informing patients outside the target group and the general public on the effects and adverse effects of DES vs BMS should be considered on a case by case basis.

Informing key decision makers at different levels of health care of the current evidence on DES vs BMS is important.

Discussion

Intervention contrast between DES vs BMS is limited to the carrier and the drug in DES in the metal stent, which both technologies possess. Thus the implications of using DES instead of BMS for the investments and tools to use the technology are negligible. Ensuring critically evaluated up to date knowledge on the pros and cons of using DES instead of BMS for the cardiologists and for the patients itself poses a major challenge on this rapidly evolving area.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of DES vs BMS Yes/No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
B0001	Description and technical characteristics of technology	Features of the technology	What is this technology?	Yes	What is BMS, what is DES?	3	3
B0002	Description and technical characteristics of technology	Features of the technology	Why is this technology used?	Yes	Why is DES used in stead of BMS?	3	3
B0003	Description and technical characteristics of technology	Features of the technology	Phase of the technology: When has it been developed or introduced in health care?	Yes	What is the phase of technology in BMS and DES?	3	3
B0004	Description and technical characteristics of technology	Features of the technology	Who are the users of this technology?	Yes	Who are the users of BMS and DES?	3	3
B0005	Description and technical characteristics of technology	Features of the technology	Where? Place and context for utilising the technology	Yes	Where are DES and BMS used?	3	3
B0006	Description and technical characteristics of technology	Features of the technology	Are there any special features relevant to this technology?	Yes	Are there any special features relevant to DES and BMS?	3	3
B0007	Description and technical characteristics of technology	Investments and tools required to use the technology	What material investments are needed to use the technology?	No	What material investments are needed when using DES in stead of BMS?	1	3
B0008	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of special premises are needed to use the technology?	No	What kind of special premises are needed when using DES in stead of BMS?	1	3
B0009	Description and technical characteristics of technology	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology?	No	What kind of equipment and supplies are needed when using DES in stead of BMS?	1	3
B0010	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of records are needed to monitor the use the technology?	Yes	What kinds of records are needed when using DES in stead of BMS?	3	3
B0011	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of registers are needed to monitor the use the technology?	Yes	What kinds of registers are needed when using DES in stead of BMS?	3	3
B0012	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What kind of training is needed for the personnel using or maintaining the technology	Yes	What kind of training is needed for the personnel using or maintaining DES in stead of BMS?	2	2
B0013	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What kind of training is needed for the personnel treating or investigating patients using this technology?	Yes	What kind of training is needed for the personnel treating or investigating patients with DES in stead of BMS?	3	3

ID	Domain	Topic	Issue	Relevance in the context of DES vs BMS Yes/No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
B0014	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What kind of training is needed for the patients receiving or using this technology & their families?	Yes	What kind of training is needed for the patients receiving DES in stead of BMS?	3	3
B0015	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What information do patients outside the target group and the general public need on the technology?	Yes	What information do patients outside the target group and the general public need on DES treatment in stead of BMS treatment?	2	2

Clinical effectiveness

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Introduction

This section is about the application of the core model to an HTA on "Drug Eluting Stents" (DES). The technology and its spectrum of use has been introduced in the chapters "Health problem and current use" and "Description and technical characteristics".

For health outcomes the scope of the report has been framed as a broad PICO question: "How does the insertion of DES in coronary arteries compared to bare metal stents (BMS) affect a broad spectrum of health outcomes". Our task was to assess effectiveness and we limited our considerations to that domain, but the concept can be easily applied to the domain "Safety" and the domain "Economic evaluation".

We further confined the outcome of PICO to the primary research question: In patients with coronary heart disease, how does the intervention with DES compared to BMS affect mortality, i.e. overall mortality, cardiac mortality and non-cardiac mortality (the 'issues'). The remaining topics: morbidity, function / quality of life, patient satisfaction, and societal issues were treated as secondary outcomes

Definition of outcomes

The outcomes relevant to the questions follow the four generic topics of an effectiveness question: short-term and long-term mortality, morbidity, function / quality of life (QoL) and patient satisfaction. We bore in mind that the outcome selection should not be determined by the available research evidence rather by the question what patients, clinicians, managers of the health care system would like to know about the technology. Formulating the right questions would thereby be the first step in identifying knowledge gaps.

For the effectiveness domain of the core HTA on DES, we identified a comprehensive set of outcomes ("issues") for each of the five topics, independent on our expectations of finding research results. Our group jointly judged the importance of all issues. We felt it was essential that more than one person would make the decision about the importance. We had an a priori defined way of dealing with disagreement among raters.

ⁱ R. Kunz was primary investigator for the effectiveness part of this core HTA and wrote the first draft. C de Laet, Pekka Kuukasjärvi A. Malmivaara A, M Makela and H van Brabandt contributed to the concept on how to apply the core model to the core HTA DES, helped with writing and provided input to various versions of the draft. Pekka Kuukasjärvi, and Hans van Brabandt contributed content expertise, while A. Nordmann and M Briel provided and discussed the data and ran further analyses beyond the analyses done in their original paper.

Methodology

This section follows the outline of the Methodology section in the Core Model. The work is based on the review by Nordmann et al. Mortality in randomized controlled trials comparing drug-eluting vs. BMS in coronary artery disease: a meta-analysis. *Eur Heart J* 2006; 27(23):2784-2814, including additional analyses of unpublished data.

Background work

Background work for an HTA-report requires the assessment of previous work (HTA and systematic reviews on DES). We identified 32 HTA-reports, systematic reviews and meta-analyses from the HTA-database of the Centre of Reviews and Dissemination in York (published between 2001 and 11/2006 and PubMed (published between 2003 and 11/2006) [see Appendix A]

Phrasing the problem as a focused and standardized question

The main question of this HTA report is about the effectiveness of DES compared to BMS in patients with coronary heart disease at various points in time, where "effectiveness" would be assessed across a broad range of outcomes.

This broad question needs further refinement regarding subgroups of the population (such as diabetic / non-diabetic patients; single / multiple vessel disease; first event / repeated events; acute / subacute / non-acute intervention; men / women; long vessel / short vessel lesions), and the intervention (e.g. stents using different drugs such as sirolimus or paclitaxel). The comparator – BMS - has already been defined in the scope of the review, but one might also consider other current treatment options such as bypass operations (CABG), percutaneous coronary interventions (PCI) without stent implantation, or even medical treatment which we did not do in this review. The generic issues of the core model need to be translated into context-specific issues: Researchers need to determine whether all issues of the model need to be included in the HTA-report or whether some of them are irrelevant in the context of a particular technology. In the context of the core HTA on DES, we restricted ourselves to mortality as the primary outcome and to evidence from randomized controlled trials. All other outcomes (topics: morbidity, function / quality of life, patient satisfaction) are regarded as secondary outcomes and they will be answered from the information in the reviews we identified for the primary question.

Since we wanted to demonstrate how to use the core model developed in this project, we limited ourselves to an exemplary and abbreviated approach. An exhaustive HTA, however, would require a comprehensive review of the literature for each question and each outcome specified in the main PICO-question and the related secondary questions.

Locating and selecting studies

The following data sources were searched: Medical databases: MEDLINE, EMBASE, Cochrane Library; Web of Science. (1/ 1980 to 4/2006); Additional sources: UptoDate version 2005 and Clinical Evidence Concise 2004 (issue 12). Furthermore, the "grey literature" including oral presentations was also searched since publications about long-term data on mortality were still sparse. The following three websites, all of which focus on disseminating (cardiovascular) trial

results, were accessed for additional data: www.tctmd.com , www.theheart.org, www.clinicaltrialresults.org . Additional information was requested from the original trial investigators and stent manufacturers where needed. Experts of the field were contacted and reference lists of relevant articles were searched for additional citations.

Studies were eligible when they

- included patients with coronary artery disease
- compared: drug-eluting sirolimus or paclitaxel stents with BMS
- reported data on mortality and morbidity
- followed the patients for a minimum of 1 year
- used a randomized controlled design

Studies were excluded when they:

- compared drug-eluting with BMS in non-native coronary arteries
- used other eluting drugs other than sirolimus or paclitaxel (e.g. everolimus)
- made direct comparisons of drug-eluting stents with each other

DES is a rapidly evolving technology with new evidence appearing every day. Since the purpose of this core HTA was to demonstrate how to apply the core model to a specific technology, we refrained from a more recent update once the first literature search has been done and concentrated on the application of the core model to the collected data.

Assessing study quality

The following 4 criteria were used for assessing study quality:

- concealment of treatment allocation
- blinding of patients and caregivers
- blinded outcome assessment
- loss to follow-up, full description of losses to follow-up and withdrawals.

Collecting data from individual studies – evidence summaries

A structured data extraction was performed on all included studies to generate evidence summaries with the core set of relevant data that would allow comparability of the data:

The following features were regarded as relevant:

Patient characteristics: gender; age; diabetes mellitus/non-diabetes mellitus; prior myocardial infarction; length of lesion and reference diameter;

Features of the intervention and the comparison: Sirolimus / Paclitaxel drug plus post-interventional prophylaxis as co-intervention.; only comparator: BMS

Primary outcomes: Mortality (overall mortality; cardiac mortality; non-cardiac mortality) at one, two and three years. Secondary outcomes for the remaining 4 topics morbidity, function / quality of life and patient satisfaction were included following the core model: Morbidity: impact on severity and frequency of symptoms; on severity of findings; on progression of disease (further defined as recurrence of target stenosis, clinical progression of disease, reduction of cardiac-specific drug treatment, cardiac-specific re-interventions), recurrence of findings, need for other treatments, need for hospitalization beyond the intervention related hospitalizations) at one, two and three years. Function / quality of life (impact on health related QoL; disease-specific QoL; return to work; return to previous living conditions; on activities of daily living) and patient satisfaction.

Presenting and analyzing results

The results of the analysis have been reported as relative risks (RR) or as odds ratios (OR) based on an intention to treat-analysis. The surrounding confidence interval (CI) indicates the precision of the estimate. The goal was to perform pre-specified subgroup analyses wherever possible.

As it turned out, subgroup analyses were only possible for type of DES (sirolimus or paclitaxel). Otherwise, the data in the individual studies were not reported in a format that would have allowed pooling in clinically relevant subgroups. Only an individual patient data–meta-analysis would provide answers on the treatment effect in specific subgroups.

The literature search identified a total of 120 trials, 95 of which were excluded as irrelevant based on abstract or title, 25 full text publications were assessed, of which 8 were excluded because of too short follow up (n=3) or subgroup analyses of already included trials (n=5). The study population consisted of 17 primary trials including more than 8200 patients at one year. (The list of trials is available in appendix B). Twelve trials reported two year data, and 9 trials reported 3 year data on mortality.

In the following, we use the structure of the core model to report the results

Assessment elements

Mortality

In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce overall mortality at one, two and three years?

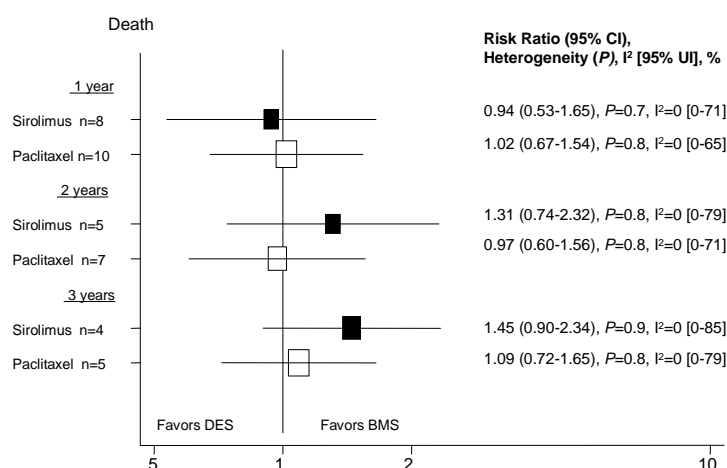
Results

The first analysis looked at *overall* mortality. **At one year**, eight studies were available for the comparison with sirolimus. The relative risk (RR) for overall mortality for sirolimus-coated stents was 0.94 (95% CI: 0.53 – 1.65). Ten studies were available for the comparison with paclitaxel-

coated stents. Here the RR for overall mortality was 1.02 (95% CI: 0.67 – 1.54). The combined RR for mortality was 0.99 (0.71 – 1.39). **At two years**, 5 trials on sirolimus-coated stents were available, for which the RR for overall mortality was 1.31 (95% CI: 0.74 – 2.32). Seven trials reported on overall mortality for paclitaxel-coated stents, which demonstrated a RR of 0.97 (95% CI: 0.60 – 1.56). The combined RR for mortality was 1.10 (0.76 – 1.58). **At three years**, the 4 trials reporting on overall mortality for sirolimus-coated stents detected a RR of 1.45 (95% CI: 0.90 – 2.34), compared to the RR of 1.09 (95% CI: 0.72 – 1.65) for paclitaxel-coated stents, based on 5 trials. The combined RR for mortality was 1.23 (0.90 – 1.69). The results were highly homogeneous ($I^2 = 0$).

There was no significant difference between DES and BMS in either comparison nor was there a difference between the two drugs. However, there was a non-significant trend for an increase in mortality for sirolimus-coated stents over the years, with a RR of 0.94 at year one, a RR of 1.31 at year 2 and a RR of 1.45 at year 3.

Figure 1: Drug Eluting Stents and mortality at 1, 2 and 3 years



In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce cardiac mortality at one, two and three years?

Results

The first sub-analysis on mortality looked at *cardiac* mortality. **At one year**, 8 studies were available for the comparison with sirolimus. The relative risk for *cardiac* mortality for sirolimus-coated stents was 0.81 (95% CI: 0.36 – 1.80). Ten studies were available for the comparison with paclitaxel-coated stents. Here, the RR for *cardiac* mortality for paclitaxel-coated stents was 0.93 (95% CI: 0.54 – 1.60). The combined RR for cardiac mortality was 0.89 (0.57 – 1.40). **At two years**, 5 trials on sirolimus-coated stents were available, for which the RR for *cardiac* mortality was 0.71 (95% CI: 0.29 – 1.74). Seven trials reported on the overall mortality for paclitaxel-coated stents, which found an RR of 0.78 (95% CI: 0.41 – 1.49) for paclitaxel-coated stents. The combined

RR for cardiac mortality was 0.76 (0.45 – 1.28). **At three years**, 4 trials reporting on overall mortality for sirolimus-coated stents detected an RR of 1.14 (95% CI: 0.57 – 2.20), compared to the RR of 0.86 (95% CI: 0.44 – 1.69) for paclitaxel-coated stents, based on 5 trials. The combined RR for cardiac mortality was 0.99 (0.62 – 1.59). All results were highly homogeneous ($I^2 = 0$). There was no difference between DES and BMS in either comparison nor was there a difference between the two drugs.

What is the effect of the intervention on the mortality due to other causes than the target disease at one, two and three years?

In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce non-cardiac mortality at one, two and three years?

Results

The second sub-analysis on mortality looked at *non-cardiac* mortality. **At one year**, 8 studies were available for the comparison with sirolimus. The RR for non-cardiac mortality for sirolimus-coated stents was 1.06 (95% CI: 0.49 – 2.30). Ten studies were available for the comparison with paclitaxel-coated stents. Here, the RR for non-cardiac mortality for paclitaxel-coated stents was 1.16 (95% CI: 0.59 – 2.28). The combined RR for non-cardiac mortality was 1.11 (0.67 – 1.85). **At two years**, 5 trials on sirolimus-encoated stents were available. Here, the pooled analysis showed a trend for an increased non-cardiac mortality (RR 2.13 (95% CI: 0.94 – 4.82) which was not seen in the 7 trials on paclitaxel-coated stents (RR 1.22; (95% CI: 0.61 – 2.45). The combined RR for non-cardiac mortality was 1.54 (0.91 – 2.62). **At three years**, the trend for increased non-cardiac mortality for the 4 trials on sirolimus-coated stents remained 1.95 (95% CI: 0.92 – 4.12), while - based on 5 trials - no such increase was observed in paclitaxel-coated stents (RR 1.12 (95% CI: 0.65 – 1.96)). The combined RR for non-cardiac mortality was 1.37 (0.87 – 2.13). Again, all results were highly homogeneous ($I^2 = 0$)

Morbidity

In patients with CHD, does the insertion of DES compared to BMS modify the overall severity and frequency of cardiac specific symptoms (angina)?

Comment

The studies did not report the impact of DES compared to BMS on overall severity and frequency of angina symptoms – independent of the target lesion. Although some studies (e.g. Weisz et al. JACC 2006) reported “clinically driven repeat percutaneous intervention of the target lesion”, thereby taking into account clinical symptoms of the patients to initiate the actual study end point “*repeat percutaneous intervention of the target lesion*”, those results do not report the overall benefit on symptoms to the patients.

In patients with CHD, does the insertion of DES compared to BMS modify the results of tests (often surrogate measures such as ECHO)?

Comment

Studies reported test results such as ECHO to describe left ventricular function in their baseline variables, but they did not report the impact of DES compared with BMS on those tests.

How does the intervention modify the progression of disease?

The core model addresses 4 aspects of progression of disease: recurrence of the target stenosis; clinical progression of disease (such as non-fatal myocardial infarction); impact on drug treatment for cardiac disease; impact of cardiac specific re-treatment such as CABG. The studies did not provide data for all issues that the core model had identified as clinically relevant.

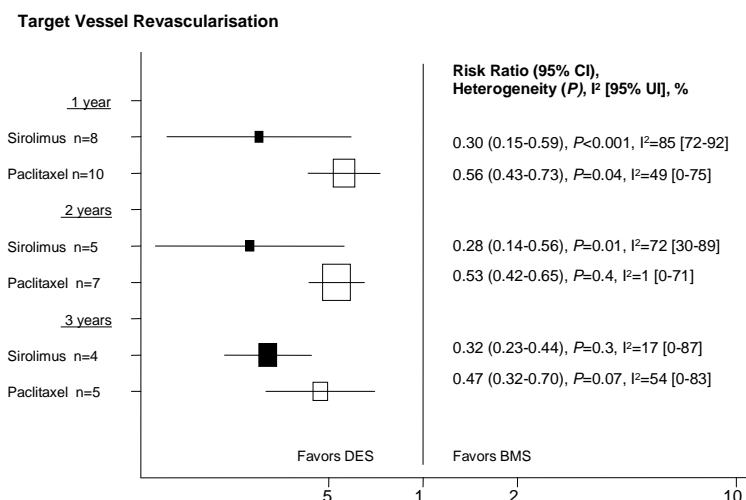
In patients with CHD, does the insertion of DES compared to BMS improve the recurrence of the target stenosis as assessed by re-vascularisation of the target vessel at one, two and three years?

Results

The first analysis on progression of disease looked at *recurrence of target stenosis*, which is commonly used as endpoint in the DES-trials. **At one year**, 8 studies were available for the comparison with sirolimus, which showed a significant reduction in target vessel revascularization (TVR), RR 0.30 (95% CI: 0.15 – 0.59). A similar but less pronounced effect was observed in the 10 studies comparing paclitaxel-coated stents. Here, the RR was 0.56 (95% CI: 0.43 – 0.73) for paclitaxel-coated stents when compared to BMS. The combined RR for TVR was 0.46 (0.34 – 0.61). **At two years**, the reduction in TVR was maintained in the 5 trials on sirolimus-coated stents RR 0.28 (95% CI: 0.14 – 0.56), compared to the 7 trials on paclitaxel-coated stents which showed a decrease in TVR of RR 0.53 (95% CI: 0.42 – 0.65). The combined RR for TVR was 0.43 (0.32 – 0.59). **At three years**, the impact of sirolimus-coated stents in TVR was sustained in the 4 trials, the RR was 0.32 (95% CI: 0.23 – 0.44), as was the reduction of TVR observed in paclitaxel-coated stents (RR 0.47 (95% CI: 0.32 – 0.70) based on 5 trials. The combined RR for TVR was 0.39 (0.29 – 0.52).

Overall, there was a significant improvement in TVR for both, sirolimus-coated and paclitaxel-coated stents. At year 1 and 2, the effect was more pronounced for sirolimus-coated stents, but here, the estimates were highly heterogeneous ($I^2 = 85$ and $I^2 = 72$ respectively) while they were less heterogeneous for the paclitaxel-coated stents ($I^2 = 49$ and $I^2 = 1$ respectively). The difference in treatment effect between the different DES subsided at year 3.

Figure 2: Drug Eluting Stents and target vessel revascularisation at 1, 2 and 3 years

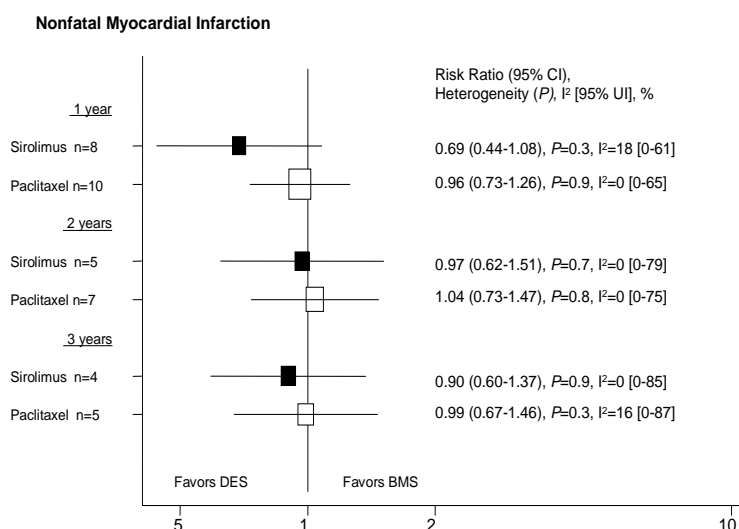


In patients with CHD, does the insertion of DES compared to BMS slow down the clinical progression of the disease, such as the occurrence of non-fatal myocardial infarction?

Results

The second analysis on progression of disease looked at *non-fatal myocardial infarction*. **At one year**, 8 studies were available for the comparison with sirolimus, which did not show a significant reduction in non-fatal MI; RR 0.69 (95% CI: 0.44 – 1.08), neither did the pooled estimate on the 10 studies comparing paclitaxel-coated stents. Here, the RR was 0.96 (95% CI: 0.73 – 1.26) when compared to BMS. The combined RR for non-fatal myocardial infarction was 0.87 (0.69 – 1.08). **Neither at two years, nor at three years** did either stent reduce the occurrence of non-fatal MI (RR for sirolimus-coated stents 0.97 (95% CI: 0.62 – 1.51) and RR for paclitaxel-coated stents 1.04 (95% CI: 0.73 – 1.47); combined RR 1.01 (0.77 – 1.33) at 2 years; RR for sirolimus-coated stents 0.90 (95% CI: 0.60 – 1.37) and RR for paclitaxel-coated stents 0.99 (95% CI: 0.67 – 1.46); combined RR 0.95 (0.73 – 1.24) at 3 years). All pooled estimates were highly homogeneous (range for I² (0 to 18)).

Figure 3: Drug Eluting Stents and non-fatal myocardial infarction at 1, 2 and 3 years



In patients with CHD, does the insertion of DES compared to BMS lower cardiac specific drug treatment?

Comment

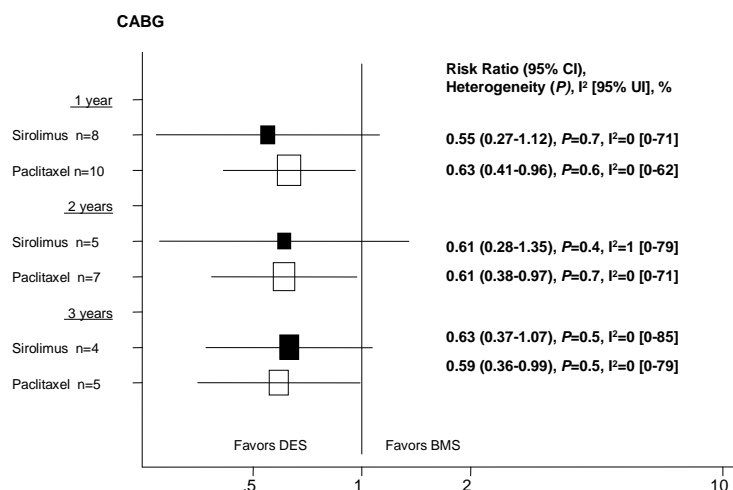
The third issue on progression of disease looked at the impact of DES on cardiac specific drug treatment compared to BMS. None of the studies we reviewed addressed this question.

In patients with CHD, does the insertion of DES compared to BMS lower cardiac specific re-treatment, such as CABG?

Results

The fourth analysis on progression of disease looked at the effect of CABG-operations. The estimate on CABG operations was based on the same number of studies as in the previous comparisons. The pooled estimate showed that the impact was similar across the two different types of stents and across the observation period of three years. The relative risk ranged between 0.55 and 0.63 and the estimates are highly homogeneous ($I^2 = 0$). Despite similar point estimates, the results turned only significant for all paclitaxel trials but remained non-significant for the sirolimus trials. This lack of significance, however, is most likely due to a lack of power rather than a non-existing effect.

Figure 4: Drug Eluting Stents and CABG at 1, 2 and 3 years



In patients with CHD, does the insertion of DES compared to BMS retard or even prevent the recurrence of cardiac specific symptoms (angina)?

Comment

Some studies (e.g. Weisz JACC 2006) reported on “clinically driven” repeat percutaneous intervention of the target lesion, where patient symptoms was one parameter among functional invasive or non-invasive tests. None of the studies reported patient symptoms as a separate outcome.

In patients with CHD, does the insertion of DES compared to BMS modify the need for other treatment?

Comment

In the context of the core HTA on DES, this issue has already been addressed by the question about the progression of disease where the need for PCI or other interventions were the hard endpoints for progression of disease (see above).

In patients with CHD, does the insertion of DES compared to BMS lower the need for hospitalization for CHD?

Comment

The studies reported indirectly the need for hospitalization in the context of repeated PCI or CABG, but they did not report on hospitalization for coronary heart disease unrelated to cardiac re-interventions (e.g. admission for heart failure) or overall hospitalization.

Function / Health Related Quality of Life

In patients with CHD, does the insertion of DES compared to BMS leads to global improvement of function?

Comment

None of the studies assessed whether DES compared to BMS generated an impact on global improvement of function or quality of life.

In patients with CHD, does the insertion of DES compared to BMS improve health-related quality of life?

Comment

None of the studies investigated whether DES compared to BMS affected health related quality of life.

In patients with CHD, does the insertion of DES compared to BMS improve cardiac specific quality of life?

Comment

None of the studies reported whether DES compared to BMS affected cardiac specific quality of life.

In patients with CHD, does the insertion of DES compared to BMS affect return to work?

Comment

None of the studies investigated whether DES compared to BMS affected the patients' general living conditions, such as return to work.

In patients with CHD, does the insertion of DES compared to BMS affect return to previous living conditions?

Comment

None of the studies investigated whether DES compared to BMS affected the patients' general living conditions,

In patients with CHD, does the insertion of DES compared to BMS affect activities of daily living?

Comment

None of the studies reported whether DES compared to BMS affected the patients' activity of daily living.

Patient satisfaction

Do patients with CHD feel that the insertion of DES compared to BMS was worth the effort, the anxiety and pain?

Comment

None of the studies reported about the patients' perspective whether DES compared to BMS made a difference on the patient's emotional wellbeing.

Would patients with CHD who had DES rather than BMS inserted, be willing to select DES (rather than BMS) again?

Comment

None of the studies reported data on patients' perspective.

Discussion

In our work on the core model in the domain of effectiveness, we found four generic topics (mortality, morbidity, function/QoL, patient satisfaction) which were sufficiently general to be applied across a broad range of interventions. We further subdivided the four generic topics to issues. We were able to reach consensus on the importance and transferability of issues relevant to this particular disease-technology pair. We conclude that the method of starting with the research question according to PICO (see core model on effectiveness), creating a generic check list of potentially relevant issues based on generic topics and selecting those with critical importance and

determining importance and transferability of these issues in the context of drug eluting stents is feasible.

In this assessment about the impact of DES compared to BMS in a broad range of outcome areas (“topics” and “issues”) there is a time trend over an observation period of 3 years towards higher overall mortality when using drug eluted stents compared to BMS. This increased risk is more visible for sirolimus-coated stents compared to paclitaxel-coated stents. However, the estimates lack precision, i.e. the confidence intervals are broad and include the possibility of no difference between intervention and control.

Separate analyses for cardiac mortality and non-cardiac mortality reveal that this increase in mortality is mainly driven by the significant increase in non-cardiac mortality with sirolimus-coated stents at year 2 and 3 that has not been observed for paclitaxel-coated stents.

Looking at the secondary outcomes, revascularization rate is significantly lower in patients with DES compared to BMS and sirolimus seems to have overall larger benefit compared to paclitaxel stents, although the difference has never been significant and is moving closer in the third year of observation. However, these estimates show a high degree of unexplained heterogeneity.

Re-vascularisation by CABG is homogeneously reduced by 45% to 55%, independent of the kind of stent. However, only the comparisons using paclitaxel turn significant while the confidence intervals for sirolimus consistently cross 1 and thereby remain non-significant. Nevertheless, we believe that the likely cause for the missing significance is lack of power rather than a non-existing effect. Neither of the DES had a statistically significant impact on a reduction of non-fatal myocardial infarction across the three years.

Limitations: We did not detect any studies with those morbidity outcomes that we had pre-specified as important such as impact on severity and frequency of symptoms (or their recurrence), impact on test findings, or the impact on the conservative cardiac management, i.e. treatment with cardiac specific drugs.

Furthermore, the studies we included did not cover any aspects of function and quality of life or patient satisfaction. However, we regard it as unlikely that such studies will be performed for the comparison DES versus BMS unless complaints or case reports raise a suspicion that the type of stent (rather than alternative approaches such as stenting versus CABG or medical treatment) could make a difference to function and quality of life or patient satisfaction.

Long-term efficacy and safety: recent data and (preliminary) conclusions

In recent months new data on long-term efficacy and safety of DES vs. BMS became available. These were not yet included in this draft chapter on efficacy and safety of the core HTA but will be included in the next version. This new information is summarized below.

Important potential side-effects, some of which typically related to the action of antiproliferative agents, have drawn particular attention of clinicians when using DES. In some cases, endovascular healing was completely inhibited, preventing endothelialisation of the stent and sometimes inducing incomplete apposition of the stent against the vessel wall. Very late stent thrombosis (LST) has been reported and constitutes a major problem because it can lead to increased mortality.¹ Unlike restenosis, thrombosis is a rare but potentially life-threatening complication of coronary stents. The

clinical consequences are often catastrophic, including short-term mortality rates of up to 25 % and major myocardial infarction in 60 % to 70 % of cases.² Stent thrombosis usually occurs before reendothelialization has been completed. It rarely occurs beyond 2 to 4 weeks for BMS³ but is a matter of concern in DES because of the delayed endothelialization. It is likely that occurrence of LST is related to a delayed healing of the injury caused by the mechanical dilatation of the coronary vessel and a continued presence of a foreign body predisposes to thrombus formation. This thrombotic tendency can be more pronounced in complex coronary lesions, but also in patients who stopped one or both of the antiplatelet drugs that were instituted following the DES implant. LST and mortality have been the subject of long-term follow-up reports of previous trials and in real-world registries of unselected patient groups. Premature antiplatelet therapy discontinuation has been shown to be one of several risk factors for LST. The early RCTs with follow-up often limited to 1 year, suggested that thrombosis following DES placement is not more frequent than following BMS at up to one year after the procedure. But, in an observational study within the BASKET trial, Pfisterer et al noticed that the discontinuation of clopidogrel six months after DES implant later on was followed by a doubling of documented LST in DES (2.6 %) vs. BMS (1.3 %).⁴ In a prospective observational study, with follow-up at 9 months after DES implant, stent thrombosis occurred in 29 of 2229 patients (1.3%).⁵ LST occurred in 5 of 17 patients (29%) who prematurely discontinued dual antiplatelet therapy. Other independent predictors of stent thrombosis were renal failure, bifurcation lesions, diabetes and a low ejection fraction.

At the Barcelona meeting of the World Congress of Cardiology in Sep 2006, two separate meta-analyses caused great concern. Those studies have since been published.^{6,7} Nordmann et al. conducted a systematic review on mortality outcomes in randomized trials that compared DES with BMS.⁶ They not only included peer-reviewed publications but also incorporated unpublished results from long-term follow-up of existing studies presented at scientific meetings and follow-up information obtained directly from the principal investigators and manufacturers. They concluded that DES implantation does not reduce total mortality when compared with BMS. In addition to cardiac adverse effects, the Nordmann study also hinted at the possibility of an increase in non-cardiac late mortality with sirolimus eluting stents.⁶ In the meta-analysis by Camenzind et al. a small but significant increase in the risk of death or Q-wave MI was found throughout a period of 3 years after implantation of a sirolimus eluting stent.

In reaction to those alarming reports from academic and clinical researchers, conflicting data from meta analyses and registries, the FDA issued a statement on Sept 14, 2006 warning that data available at that time were not sufficient to fully characterize the mechanisms, risk, and incidence of drug eluting stent associated thrombosis.⁸ In December 2006 the FDA convened a meeting with the various stakeholders to discuss efficacy and safety issues.⁹ As a result of this meeting an updated statement was issued by the FDA, and new criteria for the definition of stent thrombosis were agreed as proposed by the Academic Research Consortium (ARC).^{10, 11} Other controversies included the off-label use of drug eluting stents, i.e. use in categories of patients that were not included in the trials. Since in the US it is estimated that more than 60 % of drug eluting stents are used off-label,¹² which is an important aspect.

More importantly even, meta-analyses of follow-up up to 4 years, and based on individual patient data from the original pivotal trials finally became available in March 2007.^{13, 10, 11, 14} From an effectiveness point of view, these meta-analyses confirm earlier observations that DES are successful in reducing target vessel revascularisation rates, mainly in the first year of follow-up but with a sustained difference up to 4 years later, without however reducing the rates of MI or cardiac death. Those meta-analyses also indicate that the cumulative incidence of stent thrombosis at 4 years does not differ significantly between patients with DES and those with BMS, but also that the

studies were not powered to detect even moderate clinically significant differences in the true rate of stent thrombosis.¹² Time trends however seem to indicate that more events occur later after DES implantation, possibly related to the timing of discontinuation of dual-antiplatelet therapy. Off-label use is more difficult to assess, since those reports rely on non-randomised observational and registry data.¹⁵⁻¹⁷

Additionally, there is uncertainty about the ideal duration of dual antiplatelet therapy, but premature discontinuation of such therapy appears to be associated with an increased risk of stent thrombosis. Patients should therefore also be evaluated for bleeding risk before DES-stenting in order to assess whether long term thienopyridine treatment (at least 12 months) and lifelong aspirin treatment can be envisaged. Patients who cannot comply with extended dual antiplatelet therapy or who have planned procedures requiring early discontinuation of antiplatelet therapy may therefore not be good candidates for drug eluting stents.¹⁸

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of DES Yes / No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
D0001	Effectiveness	Mortality	What is the effect of the intervention on overall mortality?	Yes	In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce overall mortality?	3	3
D0002	Effectiveness	Mortality	What is the effect of the intervention on the mortality caused by the target disease?	Yes	In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce <i>cardiac</i> mortality?	3	3
D0003	Effectiveness	Mortality	What is the effect of the intervention on the mortality due to other causes than the target disease?	Yes	In patients with coronary heart disease CHD, does the insertion of DES compared to BMS reduce non-cardiac mortality?	2	3
D0004	Effectiveness	Mortality	What is the mortality related to the intervention studied?	Yes	In patients with CHD, does the insertion of DES compared to BMS increase intervention-related mortality, e.g. early stent thrombosis or mortality in immediate temporal connection with the catheterisation [related to safety]?	3	3
D0005	Effectiveness	Morbidity	How does the intervention modify the severity and frequency of symptoms and findings?	Yes	In patients with CHD, does the insertion of DES compared to BMS modify the severity and frequency of cardiac specific symptoms (angina)?	3	2
D0005	Effectiveness	Morbidity	How does the intervention modify the severity of symptoms and findings?	Yes	In patients with CHD, does the insertion of DES compared to BMS modify the results of tests (often surrogate measures such as ECG-changes or ECHO)?	2	3
D0006	Effectiveness	Morbidity	How does the intervention modify the progression of disease?	Yes	In patients with CHD, does the insertion of DES compared to BMS improve the recurrence of the target stenosis ?	3	3
D0006	Effectiveness	Morbidity	How does the intervention modify the progression of disease?	Yes	In patients with CHD, does the insertion of DES compared to BMS slow down the clinical progression of the disease?	3	3
D0006	Effectiveness	Morbidity	How does the intervention modify the progression of disease?	Yes	In patients with CHD, does the insertion of DES compared to BMS lower cardiac specific drug treatment?	2	2
D0006	Effectiveness	Morbidity	How does the intervention modify the progression of disease?	Yes	In patients with CHD, does the insertion of DES compared to BMS lower cardiac specific re-treatment, such as PCI or CABG?	3	2

EUnetHTA WP4 - Core HTA on drug eluting stents (DES)
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

D0007	Effectiveness	Morbidity	How does the intervention modify the recurrence of symptoms and findings?	Yes	In patients with CHD, does the insertion of DES compared to BMS retard or even prevent the recurrence of cardiac specific symptoms (angina)?	3	2
D0008	Effectiveness	Morbidity	What is the morbidity related to the intervention?	Yes	In patients with CHD, does the insertion of DES compared to BMS reduce complications related to the intervention [safety]?	3	3
D0009	Effectiveness	Morbidity	What other treatments do patients need?	Yes	In patients with CHD, does the insertion of DES compared to BMS modify the need for other treatment?		
D0010	Effectiveness	Morbidity	How does the intervention modify the need for hospitalization?	Yes	In patients with CHD, does the insertion of DES compared to BMS lower the need for hospitalization for CHD?	2	2
D0011	Effectiveness	Function / HRQL (Health-related quality of life)	What is the effect of the intervention on global improvement of function?	Yes	In patients with CHD, does the insertion of DES compared to BMS leads to global improvement of function ?	3	2
D0012	Effectiveness	Function / HRQL	What is the effect of the intervention on health-related quality of life?	Yes	In patients with CHD, does the insertion of DES compared to BMS improve health-related quality of life?	3	3
D0013	Effectiveness	Function / HRQL	What is the effect of the intervention on disease specific quality of life?	Yes	In patients with CHD, does the insertion of DES compared to BMS improve cardiac specific quality of life?	3	2
D0014	Effectiveness	Function / HRQL	What is the effect of the intervention on return to work?	Yes	In patients with CHD, does the insertion of DES compared to BMS affect return to work?	2	2
D0015	Effectiveness	Function / HRQL	What is the effect of the intervention on return to previous living conditions?	Yes	In patients with CHD, does the insertion of DES compared to BMS affect return to previous living conditions	2	2
D0016	Effectiveness	Function / HRQL	How does the intervention affect activities of daily living?	Yes	In patients with CHD, does the insertion of DES compared to BMS affect activities of daily living?	2	3
D0017	Effectiveness	Patient satisfaction	Was the intervention worth it?	Yes	Do patients with CHD feel that the insertion of DES compared to BMS was worth the effort, the anxiety and pain?	3	2
D0018	Effectiveness	Patient satisfaction	Would the patient be willing to have the intervention again?	Yes	Would patients with CHD who had DES rather than BMS inserted, be willing to select DES (rather than BMS) again ?	3	2

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Costs and Economic Evaluation

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Introduction

It has been shown that drug-eluting stents (DES) decrease angiographic restenosis rates and the subsequent need for repeat revascularisation procedures in the short to medium term as compared to BMS (Brophy, 2005). However DES is more costly than BMS. At the moment there is inconsistent evidence of whether DES would be a cost-effective option compared to BMS.

In the economic evaluation part of this Core HTA, our aim is to assess the cost-effectiveness of DES as compared with BMS in patients with coronary heart disease who undergo percutaneous coronary intervention (PCI).

The costs and economic evaluation domain consists of five topics: cost-effectiveness, resource utilisation, unit costs, indirect costs and outcomes/consequences. In each topic there are one or two issues, altogether six issues (Appendix 1).

Methodology

We have chosen the following framing of the economic analysis:

Target population	Patient with coronary artery disease
Intervention	Drug-eluting stents (DES) used during a percutaneous coronary intervention (PCI).
Comparators	Bare metal stents (BMS) used during a percutaneous coronary intervention (PCI).
Outcomes	Quality-adjusted life years (QALY)
Time frame	Two years from date of procedure
Perspective	Consequence and costs are assessed from the perspective of a hospital.

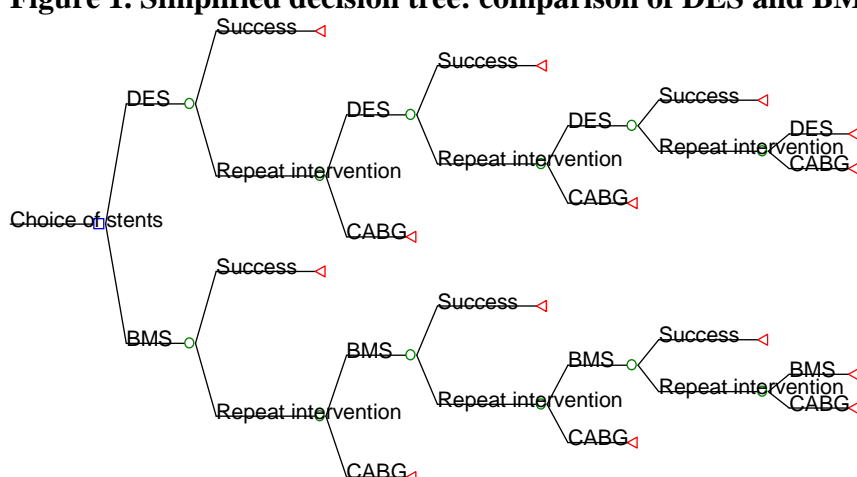
To compare DES with BMS, the data have to be taken from several sources. In the previous work of FinOHTA (Kuukasjärvi et al. 2007), a systematic review of literature was conducted using electronic databases (Cochrane Database of Systematic Reviews; DARE, HTA, EED (NHS CRD); MEDLINE® In-Process, Other Non-Indexed Citations, MEDLINE®) from January 2004 to

January 2006. The following MeSH terms were used: Stents, Paclitaxel, Sirolimus, Costs and cost analysis, Stents/economics. References of the papers identified were checked. The review included economic evaluations alongside randomised controlled trials (RCT) or model-based cost-effectiveness analyses comparing DES to BMS in patients with coronary artery disease. The methodological quality of the papers was assessed using Drummond's criteria. The systematic review identified 13 good quality economic evaluations that compared the DES to BMS.

The perspective of the analysis is that of a single health care provider (hospital). A decision analysis model was built to evaluate the cost-utility of DES compared to BMS. The model was developed using DATA software (TreeAge version Pro 2006). The model compares the costs and outcomes in terms of QALYs within a time horizon of two years. The probability of avoiding a reintervention is based on meta-analyses made in Norway in 2004 (NOKC 2004), and the risk of reintervention is based on the results by Brophy et al. (2005).

A simplified presentation of the decision model is shown in Figure 1.

Figure 1. Simplified decision tree: comparison of DES and BMS.



The two initial branches of the decision tree represent a choice between BMS and DES for patients undergoing a PCI. If the first stenting does not relieve the symptoms, then the treatment options are either a repeat intervention with the same type of stent, or coronary artery bypass graft surgery (CABG). A maximum of three revascularisations of both treatment scenarios are possible. The clinical pathway was confirmed through discussions with a cardiologist and a thoracic surgeon. The model was designed so that different countries can enter their own parameters.

The cost data are based on direct hospital costs from the Cardiac Centre of Tampere University Hospital (in Finland) and are presented in euros and calculated for the year 2006. The outcomes include expected quality-adjusted life years (QALYs) during two years post initial PCI. The QALY calculation is based on earlier work on PCI and CABG patients' HRQoL (Kattainen et al. 2005).

The used HRQoL instrument was the generic 15D (Sintonen 2001; available at <http://www.15D-instrument.net/15D>). No discounting of effects and costs was carried out, since the time horizon is relatively short.

To account for uncertainty around the model input parameter values, one-way sensitivity analyses were carried out for costs and utility values. For further exploration of uncertainty probabilistic sensitivity analysis was used. The results are given using incremental cost-effectiveness ratios (ICER), mean incremental costs and effects, a cost-effectiveness plane, and cost-effectiveness acceptability curve.

Assessment elements

Resource utilisation

What types of resources are used when delivering DES or BMS?

The used resources and costs in this model are based on a price list from the Cardiac Centre of Tampere University Hospital. The relevant resources include: PCI, equipment used during the operation (including the stent) and length of stay in the hospital (overhead, staff and medical costs).

Comment

Due to perspective of analysis only resources used in hospital were considered.

What amounts of resources are used when delivering DES or BMS?

Results

Following the model seven different resource use combinations are possible in both arms (Table 1).

Table 1. Costs used in the decision tree model.

DES		BMS	
Amount	Costs (€)	Amount	Costs (€)
DES x1	4310	BMS x1	3260
DES x2	8620	BMS x2	6520
DES x3	12930	BMS x3	9780
DES x4	17240	BMS x4	13040
DES x1 + CABG	13434	BMS x1 + CABG	12384
DES x2 + CABG	17744	BMS x2 + CABG	15644
DES x3 + CABG	22054	BMS x3 + CABG	18904

Comment

When looking at a single intervention, there are few differences in resource use between DES and BMS. In this draft, the data came from Finland; it is important to keep in mind that resource use may differ between countries.

The results are based on the decision tree model, not on primary study. Therefore certain items of resources use were not available.

Unit costs

What are the unit costs of resources used when delivering DES or BMS?

Results

The average unit costs of DES and BMS are based on data from the Cardiac Centre of Tampere University Hospital for the year 2006 and are presented in euros.

- BMS €3260 (including PCI, all needed materials and maximum two days in hospital)
- DES €4310 (including PCI, all needed materials and maximum two days in hospital)
- CABG €9124 (including operation, six days in hospital two days of them in intensive care unit)

Comment

Costs can vary markedly between different countries and are thus not transferable from one country to another. The ways of collecting cost information may also vary between countries: calculating all unit costs separately, using standard costs per procedure, or using diagnosis-related group (DRG) payments as the cost basis. In this analysis costs of hospital stay include overhead, staff and medical costs. There are differences in antithrombotic therapy after the stenting, which have not been considered in this study.

Indirect costs

What is the impact of DES and BMS on indirect costs?

Comment

We have chosen not to address indirect costs in this draft. It can be argued that there are no differences in indirect costs between DES and BMS. One could argue that the intervention with the most frequent reinterventions will have an impact on indirect costs. We need more information on the number of days in hospital and recovery at home to be able to calculate these costs.

Outcomes/consequences

What are the incremental health-related quality of life effects of DES relative to BMS?

Results

The HRQoL utility scores used to estimate QALYs were measured by the 15D instrument (Kattainen et al. 2005). The utility scores were 0.730 (95 % CI 0.716 - 0.744) for situation before PCI and 0.824 (95 % CI 0.806 - 0.842) 6 months after. In the CABG group the HRQoL scores were 0.752 (95 % CI 0.743 - 0.761) for situation before CABG and 0.858 (95 % CI 0.844 - 0.872) 6 months after, respectively. In this decision tree model the utility scores were assumed to be the same in both branches. QALYs gained in different treatments options are presented in Table 3. The mean incremental QALY gained by DES was 0.00582 during the two-year time horizon. The probabilities of avoiding revascularisation were based on meta-analysis (NOCK 2004).

Table 3. The QALY values

Number of interventions	QALYs
DES or BMS x1	1,648
DES or BMS x2	1,597
DES or BMS x3	1,585
DES or BMS x4	1,566
DES or BMS x1 + CABG	1,577
DES or BMS x2 + CABG	1,559
DES or BMS x3 + CABG	1,550

Comment

Outcomes depend on the hospital environment, experience of the surgical team, and also selection of patients. In this draft, no comparison to a conservative treatment option was done, neither treatment effects of the high risk patients were evaluated.

Incremental cost-effectiveness of the technology

What is the incremental cost-effectiveness ratio for DES versus BMS?

Results

The ICER of DES versus BMS is about €100 000 per QALY. ICER for avoided revascularisation was approximately 4800 euros. Table 4 shows the costs and QALYs gained in different strategies based on the decision tree model.

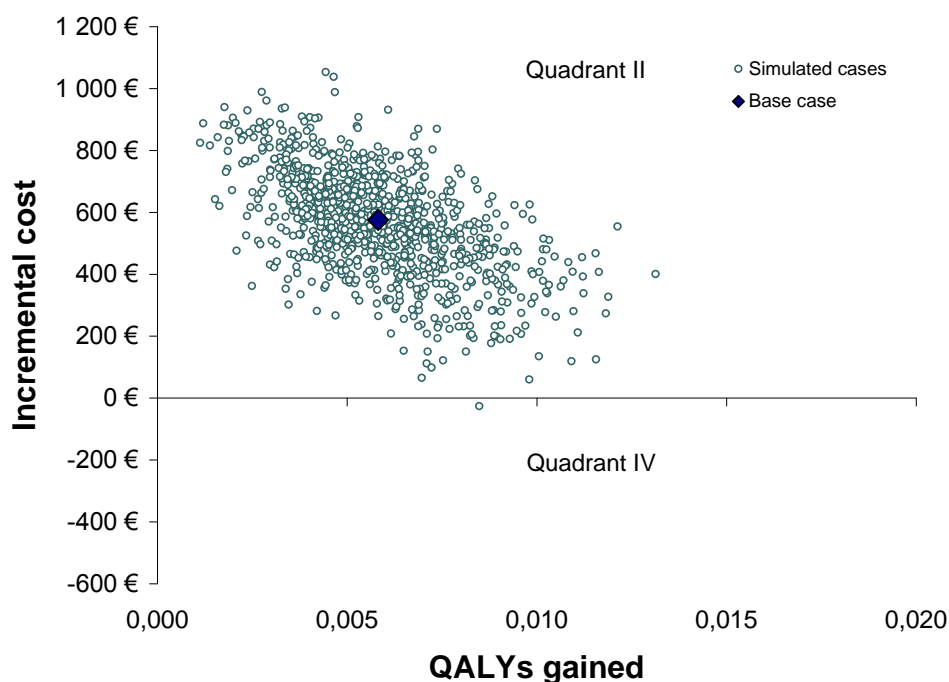
Table 4. The cost-effectiveness results of DES vs. BMS

Strategy	Costs (€)	Incremental costs	QALY	Incremental QALY	C/E (€/QALY)	ICER
BMS	4003,3		1.63942		2442	
DES	4578,7	575,3	1.64524	0.00582	2783	98827

To account for uncertainty both one-way and probabilistic sensitivity analyses were carried out. In the one-way sensitivity analyses the results turned out to be robust to changes in the parameter values except to changes in the cost difference between DES and BMS.

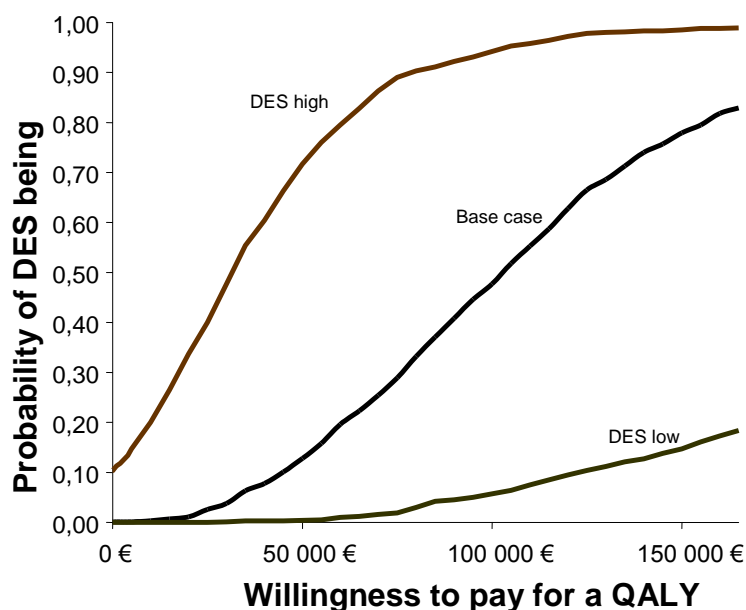
In probabilistic sensitivity analysis of base case DES was almost in all simulated cases both more effective and costly (Quadrant II) and only in few cases less costly and more effective (Quadrant IV) (Figure 2).

Figure 2. Cost-effectiveness plane.



At the threshold level of 50 000 euros per QALY gained the probability of DES (base case) being acceptable is 13 %, where the difference between DES and BMS probabilities of repeated intervention was 0.12 in favour of DES. When the difference was assumed to be 0.188 (DES high) and 0.062 (DES low), the probability of DES being acceptable was 71.7 % and 0.4 %, respectively. (Figure 3)

Figure 3. Cost-effectiveness acceptability curve for DES.



Discussion

It is important to keep in mind that in this analysis the cost and HRQoL values are based on Finnish data and therefore may not be directly transferable to other countries. However, the model constructed here can well be used by changing the input data to reflect the situation elsewhere.

Due to lack of long-term HRQoL data, the model does not examine the cost-utility beyond two years. As DES is quite a new technology, a long-term analysis would require more follow-up data on both effectiveness and costs. The strength of this economic analysis is that the HRQoL data were available from a real world patient population.

The results of the systematic literature review showed that there are no consensus about cost-effectiveness of DES vs. BMS. In two of included articles based on RCTs DES was found cost-effective compared to BMS (Cohen 2004, van Hout 2005). In 6 studies it was concluded that DES might probably be a cost-effective strategy in some circumstances, but not as a single strategy (Bowen 2005, Brophy 2005, Kaiser 2005, Mittman 2005, MSAC 2005, Shivre 2005). Four studies concluded that DES is not cost-effective compared to BMS (Bagust 2005, Hill 2004, NOCK 2004, Oliva 2004). One study did not draw a clear conclusion (Kong 2004). The results of our simplified model indicate that the QALY gain is small and the incremental cost per extra QALY is high.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)
E0001	Costs and economic evaluation	Resource utilization	What types of resources are used when delivering the assessed technology and its comparators?	yes	What types of resources are used when delivering DES and BMS?
E0002	Costs and economic evaluation	Resource utilization	What amounts of resources are used when delivering the assessed technology and its comparators?	yes	What amounts of resources are used when delivering DES or BMS?
E0003	Costs and economic evaluation	Unit costs	What are the unit costs of the resources used when delivering the assessed technology and its comparators?	yes	What are the unit costs of resources used when delivering DES and BMS?
E0004	Costs and economic evaluation	Indirect Costs	What is the impact of the technology on indirect costs?	No	What is the impact of DES and BMS on indirect costs?
E0005	Costs and economic evaluation	Outcomes/consequences	What are the incremental effects of the technology relative to its comparator(s)?	Yes	What are the incremental health-related quality-of-life effects of DES relative to BMS?
E0006	Costs and economic evaluation	Incremental cost-effectiveness of the technology	What is the incremental cost-effectiveness ratio?	yes	What is the incremental cost-effectiveness ratio for DES versus BMS?

Ethical analysis

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Introduction

Ethical analysis within an HTA aims at analysing the moral questions raised by the technology itself and by the consequences of implementing / not implementing a health technology as well as ethical issues that are inherent in the HTA process. In principle, this maybe accomplished by systematically eliciting (by primary research or through literature and document analysis) values which are placed on a technology and / or its implementation by different stakeholders. These different values are then analysed for congruency and compatibility with each other as well as with prevalent morals in the respective societies. The results of the analyses should be integrated into the overall conclusions of the HTA report in such a way that they are helpful for decision-making. Ideally, ethical analysis should not be a „one session“ task, but rather accompany and advise the whole HTA process from prioritising topics, defining research questions, choosing methodology to summarizing results and drawing conclusions.

In some instances, for practical, resource or conceptual reasons this is not feasible (- for example in the ongoing assessment of drug eluting stents -). For these cases, in the HTA Core model a catalogue of questions, based primarily on the work of Hofmann (2005), was suggested that guides value analysis referring to the technology and its implementation as well as discussing compatibility and congruency with prevalent societal moral values.

Methods

The description of the stakeholder perspectives and the completion of the assessment elements are performed by using information from the ongoing assessment as well as data from the published literature. For time and resource reasons there was no opportunity to elicit primary information (e. g. patients perspectives on outcomes used in clinical trials).

Literature searches

A four part literature search was applied:

1. Search for existing HTA reports in the CRD Databases: 28 references to relevant HTA reports were retrieved. Seven were not available in English or German language, two contained no comparison of DES and BMS, six were publications of protocols and two were not accessible. Altogether there were ten fulltext documents available in English language (see reference list).
2. Database searches for articles on “ethical” topics relating to drug eluting stents. The searches were performed in Pubmed as well as in two databases specified for Bioethics literature (BELIT and ETHMED)

- a) a search strategy for Pubmed was constructed using a search module for “ethics” literature as suggested by Droste et al., 2003 and combining it with a module of search terms for “drug eluting stents”. Furthermore the Pubmed subset “bioethics” was searched using the single search term “stent”. The Pubmed searches retrieved 60 references altogether.
- b) The BELIT database of the German Reference Center for ethics in the biosciences and the ETHMED database of the U.S. National Reference Center for Bioethics literature were searched using the single search term “stent”. 28 publications were retrieved from these two databases.
3. Additional references were taken from reference lists of retrieved publications as well as recently published journal articles (e. g. debate on DES in The Lancet, Feb. 2007).
4. Focussed searches relating to the specific issues were performed in Pubmed.

Information selection

HTA-reports: Screening the executive summaries and tables of content of the ten HTA reports revealed that except for the report from AETMIS (Brophy, 2004) none contained a section or chapter dealing with the ethical implications of drug eluting stents.

Journal articles: The search strategies 1-4 yielded 88 references from scientific journals. Titles and Abstracts were screened, whether they contained information that may be useful to answer the research questions, with no regard to methodology of the information collection.

38 references fulfilled the inclusion criterion and were further roughly categorized by topic in order to allocate them to the relevant issues:

Topic	Number of publications
Informed Consent	12
Recent publication on benefit / harm relationship	6
Management of innovations	5
Equity	4
Quality of Life	3
General ethical aspects	2
Professional practice	2
Role of Industry	2
Legal aspects	1
Off Label Use	1

During working on the issues a further 14 publications were deleted from the list because they yielded no information of relevance. A list of all excluded publication with reasons for exclusion can be found in the appendix.

Assessment of study / publication quality

No assessment of methodological study quality was undertaken.

Assessment elements

Going through the retrieved literature soon revealed that the following assessment elements of ethical analysis could not be answered in the suggested proceeding: describing methodology, results and commenting. The answers themselves are rather discussions of the issue questions, which draw on information from the other chapters of the report as well as from statements and facts presented in the literature. The latter are given with their respective references.

Principal questions about the ethical aspects of technology

Are DES intended to be an innovative mode of care, an "add on on" to a standard mode of care or a replacement of a standard?

Results

The application of Drug Eluting Stents (DES) is one form of percutaneous coronary intervention (PCI) for patients with specified forms of coronary artery disease (CAD). By supporting revascularisation of myocardial tissue it primarily aims at reducing CAD related morbidity and mortality. DES is a further development of the bare metal stent (BMS) technology by introducing the "drug eluting" component, which, by inhibiting neointimal growth after the stenting procedure, is supposed to reduce the restenosis rates observed after bare metal stenting and thereby improve relevant outcomes (morbidity, mortality, Quality of life). In order to prevent in-stent thrombosis, dual antiplatelet therapy (ASS + Clopidogrel) is recommended by manufacturers for 3 months (sirolimus eluting stents) or 6 months (paclitaxel eluting stents) after the procedure (Maisel W, 2007). Furthermore recommendations of manufacturers as well as the FDA limit the use of DES to patients with:

- stable or instable angina, or silent but documented ischemia
- with discrete and relatively short lesions (up to 28 mm for one stent, up to 30mm in the other)
- in small native blood vessels (2.5 to 3.5 mm in diameter) (FDA statement, 14.9.2006).

In that sense, DES is intended to be the replacement of a standard mode of care (BMS) for patients with the specified type of disease / lesions.

Can DES challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?

Results

Since placement of DES requires dual anti-platelet therapy for (at least) three to six months after the procedure, it poses patients to an increased risk of bleeding. This may, for example in the case of emergency surgery, lead to the need for blood transfusion or application of other blood products. For some religious groups, e. g. Jehova's witnesses, this is unacceptable. Furthermore, within a country there may exist some religious or cultural groups which do not accept implantable devices

or devices that have drug eluting character. Clarification of these commitments may usually be performed during the informed consent procedure.

What can be the hidden or unintended consequences of DES and its application to the different stakeholders?

Results

The intended use (in whom, how, with what benefits / harms to expect) of DES is specified by manufacturers and through documents (safety data, trial results) required and accepted as prerequisite for market admission by regulatory bodies (e. g. FDA, EMEA). Nevertheless, monitoring and registry data have shown, that at least 50% of the devices are being used “off-label” in patients, that are not specified by the “intended purpose” (e.g. Win et al., 2007; Beohar et al., 2007, Zahn et al., 2004). As specified in these publications, patients treated off-label typically suffer from a more severe form of CHD than those specified in the intended purpose. At the same time, the data suggest that complication rates (esp. late stent thrombosis) maybe higher in this population and therefore yield a less favourable benefit / harm ratio.

Autonomy

Does the implementation or use of DES challenge patient autonomy?

Results

DES seems not to impose major challenges to patients’ autonomy. A minor point might be, that in order to avoid stent thrombosis adherence to dual platelet therapy after the procedure is necessary for a yet to be specified time. Some patients might find the necessity to use a drug as interfering with their autonomy. This point may also be clarified during the informed consent procedure.

Is DES used for patients that are especially vulnerable?

Results

In this issue “vulnerability” means that patients in the situation of treatment do not have the full capabilities of decisionmaking, due to critical illness, age (children!) or mental disturbances. Cardiac patients may belong to this group when presenting in an emergency situation (acute cardiac syndromes: unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction).

Although there is no direct evidence on decisionmaking capabilities concerning consenting to a treatment option, there is indirect evidence from research investigating consenting capabilities to be included into clinical trials while suffering from acute myocardial infarction. These results show,

that in the acute situation in many patients the capabilities of understanding complicated facts are very limited, and that there is a tendency towards the attitude that “the doctor should decide” what should be done (Agard et al., 2001). It seems very doubtful, that in an acute situation all patients will be able to understand the different risk / benefit profiles of DES and BMS and make – together with the treating physician - an informed decision which procedure to prefer. This is even more problematic since the risk profile of DES seems to be more pronounced in high risk patients which therefore require more thorough explanations (Win et al., 2007).

Does DES have special challenges/risks that the patient needs to be informed of?

Results

For a description of formal requirements of an “informed consent” procedure see Chapter “Legal Aspects”.

Recently published “real life” data (Pfisterer et al., 2006; Lagerqvist et al., 2007) suggest, that stent thromboses as a possible late complication are seen more often in patients treated with DES as compared to patients treated with BMS. This especially holds for patients who discontinued antiplatelet therapy early and for patients with advanced disease (Off-label patients). These are non-controlled registry observations however. On the other hand, meta-analyses and medium-term clinical trial results demonstrate that the rate of late thromboses and especially deaths from the consequences are comparable (Mauri et al., 2007; Spaulding et al., 2007). Within the scientific community these results are discussed controversially because they might be afflicted with severe selection and ascertainment bias (RME, 2007). At the moment it seems not to be clear, what the long-term benefit / harm ratio for patients treated with DES rather than with BMS will be. This especially holds for Off-label patients with advanced disease for whom not even data from randomized controlled trials are available demonstrating short-term benefits. Estimation of benefit for this patient population is based on extrapolation of results from trials in less severely afflicted populations (Hodgson et al., 2004).

Against this background all candidate DES patients need to be informed of the unclear long-term benefit / harm ratio of DES application as well as the necessity to take antiplatelet medication for a yet to be determined period of time. Off-label patients furthermore need to be informed that they will be undergoing a treatment that has for their indication not been tested in randomized controlled trial, and that expectations of benefit are derived from data observed in patients with lesser disease severity.

As stated in the issue above, it seems doubtful that patients in an emergency situation will be able to comprehensively understand all implications of DES use. Even if it is legally acceptable and mandatory to initiate therapy in an emergency situation (see Chapter “Legal aspects”) it seems morally doubtful to apply DES instead of BMS in this type of situation.

Does the implementation of DES challenge or change professional roles?

Results

The off-label use of DES in current practice suggests that there is a discrepancy between regulatory statements and the value attributed to the technology by the professions. Indeed physicians' statements expressed the hope that DES "... appear very effective in traditionally high-restenosis-risk subgroups ... and that their availability might eventually prompt expansion of the types of patients that could be treated with PCI..." At the same time it is stated "... that it is important to note that no long-term controlled data currently exist for such applications ..."(Hodgson et al., 2003). Implementation of DES is, as data from registries as well as utilization data demonstrate, readily accepted by the professions. On the other hand, concerns are expressed:

- the reduction of bypass surgery and increase in stenting procedures (on unsecure scientific grounds)
- the technical difficulties
- economic / financial concerns leading to changes in practice patterns
- lag behind competitors
- malpractice litigations (restenosis after BMS).

The Drug Eluting Stent Task Force of the Society for Cardiac Angiography and Interventions (Hodgson et al., 2004) outlines the conflict for the profession by stating that "Concern about litigation and competitors' practices should not be reasons for using DESs. Evidence of benefit should be the primary consideration; where no data exist, a reasoned judgement must be made. In all cases, the potential benefit to patient is the foremost consideration."

Human Dignity

Does the implementation or use of DES rather than BMS affect human dignity?

Results

There were no publications encountered in the literature searches that discussed violation of human dignity (challenging the intrinsic value of a person) in the context of DES implementation. In some guidelines (e. g. Canada: Heart and Stroke foundation, 2005; UK, NICE, 2003), for cost-effectiveness reasons, the application of DES was suggested to be restricted to patients with high risk of restenosis (Groeneveld et al., 2007). This may exclude patients that, from a clinical point of view, still have a potential to benefit.

Does the implementation or use of DES rather than BMS affect human integrity?

Results

The characteristic that differentiates DES from BMS is the drug eluting component and the necessity for antiplatelet therapy after DES implantation. The latter might be a challenge to the self-perception of some patients: the necessity to continue a medication may not be compatible with the hope to be “cured” of the disease after the intervention. Hodgson et al., 2004 pointed out, that there is the widespread perception among CAD patients that placement of a (drug eluting) stent is regarded a cure of coronary artery disease rather than temporary relief of symptoms.

Beneficence/ non-maleficence

What are the benefits and harms for patients and what is the balance between the benefits and harms when implementing and when not implementing DES rather than BMS?

Methods

This issue does not directly apply to the comparison of DES vs. BMS because the technology has been implemented already. When pointing out consequences for patients, two types of patients must be distinguished: CAD patients, who are candidates for receiving DES and “other” patients requiring other modes of health care.

Results

CAD patients:

According to FDA approval and manufacturers advice (Cypher® and Taxus® stents) DES is licensed for use in specified patients only (see above, first issue), but as also stated above (third issue), international utilization data shows that more than 50% of DES are used “off label”. Probably suffering from the disease and the expectations towards the effects of a novel treatment is more pronounced in the second group.

Evidence of short-term benefit may be taken from clinical trials comparing the efficacy of DES versus BMS in selected (on-label) patients. This evidence consistently demonstrates lower restenosis rates and reintervention rates in patients treated with DES compared to BMS. So far, there is no evidence that DES has superior effects on cardiovascular or overall mortality (see also Chapter “Effectiveness” of this report). In cost-effectiveness models indirect evidence (composed of data on QoL impairment in patients suffering from restenosis after PCI and requiring reintervention and data on reduced reintervention rates after DES) is used to estimate gains in Quality of life after DES (Groeneveld et al., 2007). For off-label patients so far there is no direct evidence from randomized controlled trials demonstrating benefit of the procedure. Potential harms (late stent thrombosis, risk of bleeding complications) of the technology were discussed above, pointing out

that at the current state of knowledge, the benefit / harm ratio is not quite clear, especially not for patients treated off label.

Other patient groups:

In many health care systems within publicly funded health care human and money resources are budgeted for various specialities. Decision to implement a more costly intervention may ultimately lead to reallocation of resources within cardiac department or to allocation of resources from other patient groups to cardiac patients.

The relation of benefits and harms of DES for patients may be summarized as follows:

Stakeholder	Benefits when proceeding with implementation	Adverse consequences when proceeding	Benefits when refraining from implementation	Adverse consequences when refraining
"On label" CAD patients	reduced rates of repeat revascularisation when compared to BMI (by 45-55%)	unclear – possibly higher rates of late thrombosis; probability of bleeding complications due to antiplatelet therapy; in the case of emergency situations: loss of autonomy by having to make an informed decision while not being able to consider information offered.	no side effects from antiplatelet medication; probability of surplus complications avoided	Rates of revascularisation procedures won't be reduced
"Off label" CAD patients	unclear – no RCT data available	unclear – possibly even higher late thrombosis rates than in on-label patients probability of bleeding complications due to antiplatelet therapy	no side effects from antiplatelet medication; probability of surplus complications avoided	unclear
Other cardiac patients	unclear	In some health care systems with closed budgets for specialties implementing the more costly DEM might diminish resources for other cardiac patients	No additional constraints on budget	unclear
Other patients outside cardiology	unclear	In health care systems with closed overall budgets implementing the more costly DEM might diminish resources for other cardiac patients	No additional constraints on budget	unclear

Who will balance the risks and benefits of preferring DES over BMS in practice and how?

Results

After publication of the unfavourable registry data, regulatory bodies (e. g. FDA statement, 2006) and professional societies (e. g. Silber S for the German Cardiac Society, 2007) have published recommendations. Given the widespread use and availability of DES, it is the individual physician who decides whether to prefer DES stenting over BMS stenting, after obtaining truly informed consent from the patient. In situations where there is no informed consent obtainable, the use of DES seems questionable.

Effects of DES implementation on all patient groups have to be considered when making a decision whether to include DES into the benefit basket of payers. The decision varies, depending on organisation and financing of different health care systems.

Can the implementation of DES rather than BMS harm any of the stakeholders? What are potential benefits and harms of implementing DES rather than BMS for other stakeholders?

Results

Beside patients the relevant stakeholder groups that may directly or indirectly benefit from the use of DES instead of BMS are care providers, the professions, payers, society and manufacturers.

Providers (Hospitals etc):

Implementing DES requires additional financial resources in comparison to BMS. How much and from whom, depend on the regulation of the hospital financing systems in the respective countries. A fee for service systems may offer the chance for extra profits for care providers; whereas in systems with flat rate hospital financing, DES might cause extra costs on health care providers (e. g. Kearney et al., 2006). Patients and society put high value on technically advanced medical technologies; therefore it is attractive for providers to advertise that patients receive the most innovative care in their facilities.

Professions:

DES has been readily accepted by the cardiologists; with special consideration to the favourable short term results, which, in the highly selected patients included in the randomized controlled trials, manifested as a markedly reduced number of reinterventions compared to bare metal stents. This has led in suggestions that every patient who needs stenting should receive drug eluting devices. The high costs of the procedure were regarded the only constraint from universal use (Faxon DP, 2004). Other representatives of the interventional cardiologist profession were cautious and expressed the need for long-term research results as well as systematic research in high-risk populations (Mitka M, 2004) before the uptake of the procedure into routine care. Mainly due to financial constraints uptake rates varied among countries with the highest seen in the United States and Switzerland (up to 90% of all stenting procedures). In countries with unclear reimbursement regulations the uptake rates have been lower. In Germany, where flat rate reimbursement plus extra

fees do not cover the costs of the procedure, uptake rates below 20% are reported for 2005 (Grumann + Bode, 2005).

After publication of long-term follow up data in 2006, which suggest an increase of late stent thrombosis in DES compared to BMS some professional societies recommended restrictions for the use of DES which immediately manifested in a sharp decrease of utilization rates (see Chapter "Current Use").

From the profession of cardiac surgeons it is pointed out that the tendency towards increased use of PCI, including drug eluting stents, in patients with multivessel disease neglects the existing body of evidence that CABG in this particular patient group produces superior long-term results (Taggart DP, 2006). Furthermore, concerns are expressed that in patients with failed (multiple) stent implantations the options for surgical corrections are very limited (IRR, personal communication).

Society:

In health care systems, based on the idea of solidarity, one of the underlying principles for the provision of care is guaranteeing equal access to effective care for those in need. This, given limited resources to be spent on health care leads to the necessity of cost-effectiveness considerations and prioritisation. At the same time, strong beliefs are encountered among patients and general public, that the most modern and advanced technologies will yield optimal results, and that everyone has the right to receive them (Deyo R and Patrick DL, 2005). Concerning DES, study results and media responses elicited the belief that DES is the method of choice to treat coronary heart disease. Patients may perceive the failure to receive a drug eluting stent as a denial of the optimal chance to cure their heart disease (Hodgson et al., 2004).

Manufacturers:

There are a number of companies manufacturing DES.

Manufacturers (first generation):

- Boston Scientific: paclitaxel-eluting "Taxus"® stent
- Johnson & Johnson (Cordis Corporation): sirolimus eluting "Cypher"® stent

Manufacturers (second generation not approved in the US): e.g.

- Medtronics: zotarolimus-eluting stent "Endeavour"®
- Abbott: everolimus-eluting stent "Xience V"®
- Conor Medsystems: paclitaxel-eluting stent "CoStar"®

While the first generation stents are marketed world-wide, the second generation is, due to regulatory circumstances, not marketed in the US.

Among the companies there is an ongoing competition for market shares while publication of unfavourable long-term results in fall 2006 led to sharply declining sales figures (Shuchman, 2007). Against this background an issue of concern could be that manufacturers are the sponsors of most ongoing trials as well as of most clinical registries and databases.

The following table summarizes the most frequently mentioned consequences of DES implementation / non-implementation from the perspective of the different stakeholders:

Stakeholder	Benefits when proceeding with implementation	Adverse consequences when proceeding	Benefits when refraining from implementation	Adverse consequences when refraining
Care providers	Gain in reputation for providing the most advanced care; In systems with fee for service reimbursement opportunity for financial gains; in systems with flat rate reimbursement indirect chance of financial gains through shifts away from more costly CABG procedures (Hodgson et al., 2004)	In systems with flat rate reimbursement additional costs for DES have to be born by providers	Opposite to "benefits when proceeding with implementation"	Opposite to "adverse effects when proceeding with implementation"
Professions	Gain in reputation for providing the most advanced care; Chance of iterative "learning" by proceeding under trial and surveillance conditions performance"	Cardiac surgeons: losing (CABG) patients. Interventional cardiologists: probability of malpractice litigations in off-label use; probability of doing harm to patients while proceeding with an intervention with unclear benefit / harm ratio	Opposite to "benefits when proceeding with implementation";	Opposite to "adverse effects when proceeding with implementation"
Payers	Gain in reputation for providing the most advanced care; indirect financial gains when costly CABG procedures are avoided	Have to bear additional costs for DES; limited resources may create the need to conceptualize measures for rationing / prioritizing	cost neutrality	Opposite to "adverse effects when proceeding with implementation"
Society	Gain in reputation for providing the most advanced care;	Outside the private sector: having to bear the extra costs for the procedure. In societies with a strong private health care market: danger of enforcing "two class health care"	Opposite to "benefits when proceeding with implementation";	Opposite to "adverse effects when proceeding with implementation"
Producers/Industry	financial gains; ability to provide further data on "real life use" by funding registries and data collections	Proceeding with implementation of second and third generation DES in Europe may lead to competition for market shares, especially for manufacturers of first generation DES.	Opposite to "benefits when proceeding with implementation";	Opposite to "adverse effects when proceeding with implementation"

Justice and Equity

What are the consequences of implementing / not implementing DES on justice in the health care system? (Are principles of fairness, justness and solidarity respected?)

Results

This issue implies at least two types of considerations:

The medical one is concerned with the principle, that technologies should be supplied to those who are in need of them in order to improve health. This concept of „need for a technology“ implies that there is evidence, that use of the technology offers a net benefit (meaning that benefit outweighs harms), also in comparison to other available modes of care. Taken into consideration current knowledge, for DES it is unclear whether benefits outweigh harms. Up to now, an evidence-based decision whether a particular patient or a group of patients „need“ DES instead of BMS can not be taken. Taking into consideration the widespread use and especially off-label use of DES the question arises whether for the implementation of DES fairness, justness and solidarity could also mean to efficiently protect patients in who harms might outweigh possible benefits from receiving the technology.

In case we can in future determine a patient group in need of DES, economic considerations might impair the principles of fairness, justness and solidarity. The price of DES varies between countries but is generally higher than that of BMS (see also Chapter Costs and Economic Evaluations). By whom these extra costs are borne, depends on the reimbursement regulation of the respective countries. Taking into consideration the limited availability of resources for the health care sector it will be mandatory to implement transparent and fair allocation procedures along with the technology.

How are technologies presenting with similar (ethical) problems as DES treated in the health care sector?

Results

The main moral problems around the DES result from the fact, that it is unclear whether in the long term net harm or net benefit will result from its implementation. This is especially a problem in the group of more severely ill patients that often present in an emergency situation, with temporarily limited decision making capacities and therefore constitute a particularly vulnerable population. For new technologies in some health care systems (e. g. Interventional Procedures Program, NICE, UK; Switzerland) it is an established procedure that

1. the technology may only be applied under “monitoring conditions”, which could involve a clinical trial or establishment of a registry. It seems worthwhile to note here, that the monitoring condition should preferably be set up independent of funding from manufacturers in order to avoid “conflicts of interests” should unfavourable results arise.

2. implementation of an innovative technology requires thorough explanation of its developmental status as well as the scope of possible benefits and harms to the patients. Qualitative research found that the amount and precision of information that patients want to know before a cardiac intervention is very variable (Beresford et al., 2001). From an ethical point of view, it seems questionable to proceed with an innovative procedure in patients who are not able to or not want to consider the scope of possible benefits / harms of the respective treatment option.

Are there any third parties involved when implementing DES rather than BMS?

Comment

Consequences of DES implementation for different stakeholders have been outlined in the 11th issue (Benefits and Harms for different stakeholders).

Rights

Does the implementation of DES rather than BMS affect the realisation of basic human rights?

Results

In the context of health care (treatment of an illness) the following human rights issues apply:

- The human right to the highest attainable standard of physical and mental health, including reproductive and sexual health.
- The human right to equal access to adequate health care and health-related services, regardless of sex, race, or other status.

(The People's Movement for Human Rights Education; <http://www.pdhre.org/rights/health.html>)

The “adequacy” of applying DES rather than BMS in different patient groups has been discussed above (tenth issue, benefits and harms for patients) as well as aspects of distributive justice in issue twelve.

Furthermore, there is an ongoing debate in the literature whether gender, age or social status limit access to adequate care, though no articles were found that directly apply to the topic of drug eluting stents. There is some evidence though, that advanced modes of care less often applied in elderly or female cardiac patients than younger (male) ones, despite equal evidence for effectiveness in clinical trials (e.g. Bond et al., 2003; Weisz et al., 2003; Avezum et al., 2005). These aspects should also be taken into consideration when establishing criteria / guidelines for the implementation of DES.

Legislation

Is legislation to use DES rather than BMS fair and adequate?

Results

In Europe medical devices (Drug eluting stents falling into the device class MEDDEV III) may be marketed (and implemented) after receiving the CE conformity marking. CE conformity marking is issued when the safety of the device and its ability to fulfill the intended purpose are proven. CE marking does not require comprehensive evidence on its clinical effectiveness or long-term benefit / harm ratio. Coverage for DES procedures is regulated by national (in some countries even regional) law, in some countries with the possibility of „conditional coverage“ linked to the generation of more clinical effectiveness and safety data (for an overview see the work of WP 7, EUNetHTA project). This legislation implies that innovative devices may be implemented which later prove to be ineffective or have an unfavourable benefit / harm ratio. From a moral point of view, the European legislation for medical devices by itself is not efficient to protect the best interest of the patients.

Discussion

From an ethical point of view in, decisionmaking on how to continue with the implementation of DES the following points should be taken into consideration:

- Up to current knowledge, the relation of benefit and harm for patients receiving DES is not quite clear; this holds especially for patients treated off-label. A further source of risk and activity limitation is the necessity to take dual anti-platelet therapy for a still to be determined period of time.
- In order to enable patients to make an autonomous informed decision whether or not to have treatment with DES, this situation has to be thoroughly explained. On the other hand, in the situation of decision patients ability to understand complicated information may be severely compromised by severity of illness. This again, holds especially for off-label patients, treated in an emergency situation.
- From an overindividual perspective, there is clearly a need for more research data on effectiveness and safety of the intervention. These data should preferably be collected avoiding conflicts of interest for any of the stakeholders.
- Although there are no clear data for DES, literature on the utilization of sophisticated cardiac procedures suggests, that patient characteristics like age and gender influence allocation.
- In some health care systems the financing modalities (e.g. closed specialty or overall budgets) allow the introduction of a new costly technology only if resources are taken from another area of intervention / care. In order to help fair allocation of resources these mechanisms need to be made explicit.

The European legislation for the market introduction of innovative medical devices seems not to be able to sufficiently protect patients from ineffective or harmful interventions.

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APPENDIX 1: Assessment elements

Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research Question in the context of DES	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
Ethical aspects	Principal questions about the ethical aspects of technology	Is the technology intended to be an innovative mode of care, an "add on" to a standard mode of care or a replacement of a standard?	Yes	Are DES intended to be an innovative mode of care, an „add on“ to a standard or replacement of a standard?	3	3
Ethical aspects	Principal questions about the ethical aspects of technology	Can the technology challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?	(Yes)	Can DES challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?	3	2
Ethical aspects	Principal questions about the ethical aspects of technology	What can be the hidden or unintended consequences of the technology and it's applications for different stakeholders.	Yes	Can DES challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?	3	2
Ethical aspects	Autonomy	Does the implementation or use of the technology challenge patient	(Yes)	Does the implementation or use of DES challenge patient autonomy?	3	3

EUnetHTA WP4 - Core HTA on drug eluting stents (DES)
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

		autonomy?				
Ethical aspects	Autonomy	Is the technology used for patients that are especially vulnerable?	Yes	Is DES used for patients that are especially vulnerable?	3	3
Ethical aspects	Autonomy	Can the technology have special challenges/risk that the patient needs to be informed of?	Yes	Do DES have special challenges/risks that the patient needs to be informed of?	3	3
Ethical aspects	Autonomy	Does the implementation challenge or change professional roles?	Yes	Does the implementation challenge or change professional roles?	3	2
Ethical aspects	Human Dignity	Does the implementation or use of the technology affect human dignity?	Yes	Does the implementation or use of DES rather than BMS affect human dignity?	3	2
Ethical aspects	Human integrity	Does the implementation or use of the technology affect human integrity?	Yes	Does the implementation or use of DES rather than BMS affect human integrity?	3	2
Ethical aspects	Beneficence/ nonmaleficence	What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing the technology? Who will balance the	Yes	What are the benefits and harms for patients and what is the balance between the benefits and harms when implementing and when not implementing DES rather than BMS? Who will balance the risks and benefits of preferring DES over BMS in practice and how?	3	2

		risks and benefits in practice and how?				
Ethical aspects	Beneficence/ nonmaleficence	Can the technology harm any of the other stakeholders? What are the potential benefits and harms for other stakeholders, what is the balance between them? Who will balance the risks and benefits in practice and how?	Yes	Can the implementation of DES rather than BMS harm any of the stakeholders? What are potential benefits and harms of implementing DES rather than BMS for other stakeholders?	3	2
Ethical aspects	Justice and Equity	What are the consequences of implementing / not implementing the technology on justice in the health care system? Are principles of fairness, justness and solidarity respected?	Yes	What are the consequences of implementing / not implementing DES on justice in the health care system? (Are principles of fairness, justness and solidarity respected?)	3	2
Ethical aspects	Justice and Equity	Are there any third parties involved when implementing the technology?	(Yes)	Are there any third parties involved when implementing DES rather than BMS?	3	2
Ethical aspects	Justice and Equity	How are technologies presenting with similar (ethical)	Yes	How are technologies presenting with similar (ethical) problems as DES treated in the health care sector?	3	2

		problems treated in health care system?				
Ethical aspects	Rights	Does the implementation or use of the technology affect the realisation of basic human rights?	(Yes)	Does the implementation of DES rather than BMS affect the realisation of basic human rights?	3	3
Ethical aspects	Legislation	Is legislation and regulation to use the technology fair and adequate?	Yes	Is legislation to use DES rather than BMS fair and adequate?	2	2

APPENDIX 2: List of excluded publications

Publications not available

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)
F0001	Ethical aspects	Principal questions about the ethical aspects of technology	Is the technology intended to be an innovative mode of care, an "add on" to a standard mode of care or a replacement of a standard?	Yes	Are DES intended to be an innovative mode of care, an „add on“ to a standard or replacement of a standard?
F0002	Ethical aspects	Principal questions about the ethical aspects of technology	Can the technology challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?	(Yes)	Can DES challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?
F0003	Ethical aspects	Principal questions about the ethical aspects of technology	What can be the hidden or unintended consequences of the technology and its applications for different stakeholders.	Yes	Can DES challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?
F0004	Ethical aspects	Autonomy	Does the implementation or use of the technology challenge patient autonomy?	(Yes)	Does the implementation or use of DES challenge patient autonomy?
F0005	Ethical aspects	Autonomy	Is the technology used for patients that are especially vulnerable?	Yes	Is DES used for patients that are especially vulnerable?
F0006	Ethical aspects	Autonomy	Can the technology entail special challenges/risk that the patient needs to be informed of?	Yes	Do DES have special challenges/risks that the patient needs to be informed of?
F0007	Ethical aspects	Autonomy	Does the implementation challenge or change professional roles?	Yes	Does the implementation challenge or change professional roles?
F0008	Ethical aspects	Human Dignity	Does the implementation or use of the technology affect human dignity?	Yes	Does the implementation or use of DES rather than BMS affect human dignity?
F0009	Ethical aspects	Human integrity	Does the implementation or use of the technology affect human integrity?	Yes	Does the implementation or use of DES rather than BMS affect human integrity?
F0010	Ethical aspects	Beneficence/ nonmaleficence	What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing the technology? Who will balance the risks and benefits in practice and how?	Yes	What are the benefits and harms for patients and what is the balance between the benefits and harms when implementing and when not implementing DES rather than BMS? Who will balance the risks and benefits of preferring DES over BMS in practice and how?
F0011	Ethical aspects	Beneficence/ nonmaleficence	Can the technology harm any other stakeholders? What are the potential benefits and harms for other stakeholders, what is the balance between them? Who will balance the risks and benefits in practice and how?	Yes	Can the implementation of DES rather than BMS harm any of the stakeholders? What are potential benefits and harms of implementing DES rather than BMS for other stakeholders?
F0012	Ethical aspects	Justice and Equity	What are the consequences of implementing / not implementing the technology on justice in the health care system? Are principles of fairness, justness and solidarity respected?	Yes	What are the consequences of implementing / not implementing DES on justice in the health care system? (Are principles of fairness, justness and solidarity respected?)

ID	Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research question(s) in the context of DES or Comment (if regarded as a not relevant issue in this context)
F0013	Ethical aspects	Justice and Equity	Are there any third parties involved when implementing the technology?	(Yes)	Are there any third parties involved when implementing DES rather than BMS?
F0014	Ethical aspects	Justice and Equity	How are technologies presenting with similar (ethical) problems treated in health care system?	Yes	How are technologies presenting with similar (ethical) problems as DES treated in the health care sector?
F0015	Ethical aspects	Rights	Does the implementation or use of the technology affect the realisation of basic human rights?	(Yes)	Does the implementation of DES rather than BMS affect the realisation of basic human rights?
F0016	Ethical aspects	Legislation	Is legislation and regulation to use the technology fair and adequate?	Yes	Is legislation to use DES rather than BMS fair and adequate?

Organisational Aspects

Marco Marchetti, Marco Oradei, Mirella Corio, Carmen Furno, Matteo Ruggeri

Introduction

The organisational domain assesses what types of resources (material things, human skills and knowledge, money, etc) must be mobilised and organised when implementing a new technology, and what kinds of changes or consequences the use can cause in an organisation. In this core HTA the new technology is drug eluting stents (DES) and the objective is to assess the organizational effects of DES introduction compared to the use of traditional bare metal stents (BMS).

From an organisational point of view, DES insertion does not represent a major innovation.

Angioplastic procedures are not affected by the new device, unless stents are placed with ecoguide (IVUS, intra vascular ultrasound) or Optical Coherence Tomography (OCT), where extra skills are required from the professionals.

Furthermore, depending on the kind of drug contained in the DES, patients may need antiplatelet therapy, which needs to be monitored. This therapy is longer than BMS post-surgery therapies.

Methodology

Organisational aspects are rarely analysed within clinical studies and HTA reports, so the analysis required several activities. Systematic review of the literature is crucial but not enough to answer the research questions of this domain. Therefore, in this study literature research represents the first step of analysis. The literature review includes grey literature and international guidelines. The search strategy is described in detail below.

Literature search:

Published literature was obtained by searching MEDLINE, CDSR (Cochrane Database of Systematic Reviews), CCRCT (Cochrane Central Register of Controlled Trials), and DARE (Database of Abstracts of Reviews of Effects), all by using EBSCO-HOST as search engine; and HTA Database CRD (Centre of Reviews and Dissemination). As the research objective is to compare the organizational effects of using drug-eluting stents (DES) compared to the traditional stent (BMS), the following keywords were used: "Drug eluting stent" AND "Organization*". Since the studies containing all of the keywords were found only from Medline, the search strategy was modified for the other databases, by using only "Drug eluting stent" as keyword. We limited our search results to studies on humans published in English between June 2002 (publishing date of the first randomized trial- RAVEL - on DES) and March 2007. This search strategy (showed in detail in table 1) resulted in 212 studies and 16 HTA reports.

Table 1: Literature search strategy

DATABASE	LIMITS	KEYWORDS	RESULTS
MEDLINE	Human; English; 2002+	“Drug eluting stent” AND “Organization*”	181
DARE	Human; English; 2002+	“Drug eluting stent”	7
CDSR - CCRCT	Human; English; 2002+	“Drug eluting stent”	24
CRD	Human; English; 2002+	“Drug eluting stent”	16

Selection criteria and method:

A study was eligible for inclusion in the systematic review of organizational evaluation if it met each of the following inclusion criteria:

- Included patients with coronary artery disease;
- Compared: Drug Eluting Stent with Bare Metal Stent;
- Analyzed and reported results of any of the following organizational topics: utilization, work processes, (de)centralization, staff, cooperation and communication, finances, management and controlling, stakeholders.

Study selection was done in two stages: first the studies were screened based on title to remove duplicates. A total of 155 studies were found. Studies identified have been classified according to the study design. The studies were distributed in eight categories as follows:

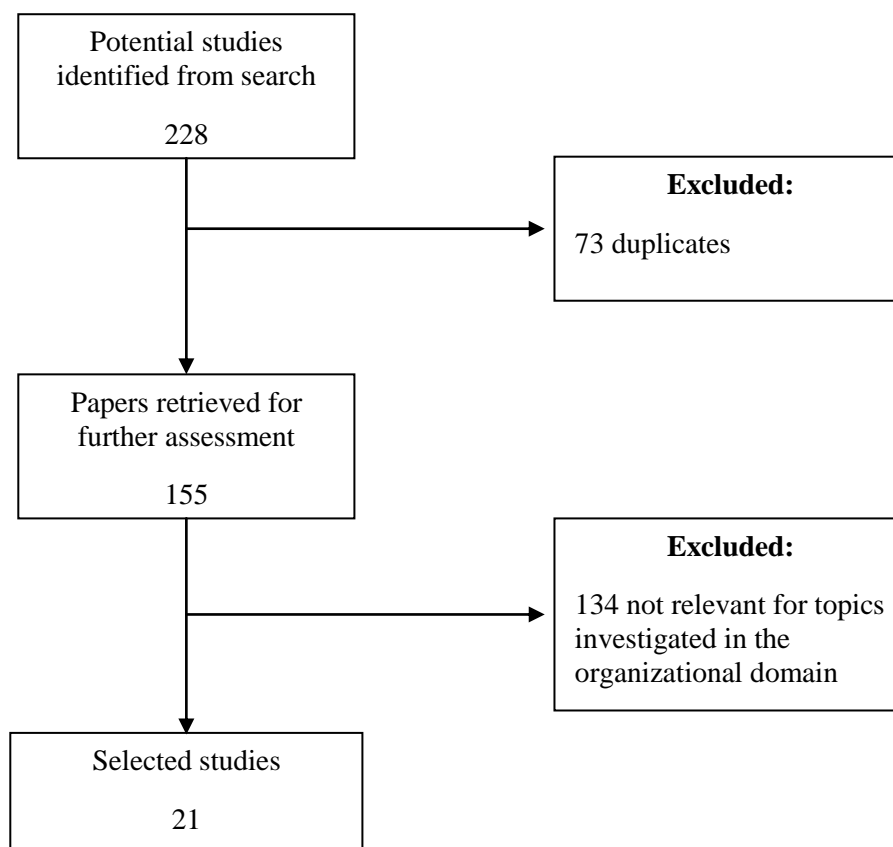
- HTA Reports: 16
- Clinical Trials: 15
- Meta-analysis: 6
- Guidelines: 4
- Reviews: 70
- Comparative Studies: 30
- Evaluation Studies: 2
- Multicenter Studies: 12

Two reviewers independently selected the relevant studies by reading the abstracts. A study was included if it provided useful information to answer the research questions. We identified 20 papers, reported in appendix 1, in the following categories:

- HTA Reports: 2
- Clinical Trials: 2
- Meta-analysis: 0
- Guidelines: 4
- Reviews: 4
- Comparative Studies: 5
- Evaluation Studies: 2
- Multicenter Studies: 1

Figure 1 shows a QUORUM flowchart of study selection¹.

Figure 1: Selection of studies for inclusion



Quality assessment:

Quality assessment using criteria for clinical effectiveness is not pertinent in the investigation of organizational aspects. We are currently not aware of suitable formal instruments or classifications using explicit quality criteria for articles looking at health care organisation.

Integration of literature review:

Since organisational aspects are rarely analysed within clinical studies, which represent the main part of the available content of the databases investigated, we have also integrated grey literature. Based on our review, some issues have not been analysed in literature. Therefore, no scientific evidence was found regarding those issues using our initial search. To complement our search, we reviewed also grey literature using a generic research engine (Google) and consulted websites of manufacturers, regulatory agencies, and health technology assessment agencies. Some issues required the analysis of guidelines established by national and international societies of cardiology (European Society of Cardiology, American College of Cardiology, American Heart Association, Society for Cardiac Angiography and Interventions). All papers on the Joint meeting of the European Society of Cardiology and World Heart Federation in Barcelona 2006 have been included. Furthermore, we have considered documents on DES approval, including recommendations by the US Food and Drug Administration (FDA) for marketing regulations and utilisation in USA, and guidelines by EMEA for regulations on marketing and utilisation in Europe. Since organisational aspects are strictly linked to their own context, it is useful to integrate results with the experience of clinical opinion leaders in this area.

Assessment elements

Utilization

How are DESs accepted by the organisation?

Results

Decisions on introducing new technology in health care organizations are very complex, because they are strongly linked to safety, clinical benefits, and economic aspects. In fact, considering the improvements in medical knowledge, the economic factors have become more and more determinat. So when a new technology is introduced in health care organizations it is necessary to consider the acceptance level of clinicians who are users of technology and also of budget managers who allocate the available resources. In the context of DES it is crucial to study the acceptance level of interventional cardiologists who perform angioplasty procedures, and also of budget managers.

How are DESs accepted by interventional cardiologists of health care organizations?

Methods

Systematic literature review. We found additional information by internet search of grey literature.

Results

Compared to traditional Bare Metal Stents (BMS), Drug Eluting Stents (DES) do not require different implant procedures². DES are functionally similar to their BMS predecessors. Inventory issues (shelf life, sterility, temperature sensitivity, etc.) should be easily addressed. Regarding the acceptance level of DES by interventional cardiologists, we observed original optimism following positive results of first clinical trials published. These studies showed significant reduction of restenosis.

In this first phase, interventional cardiologists suggested wide utilization of DES. Since a meta-analysis presented at the 2006 European Society of Cardiology Annual Meeting/World Congress of Cardiology meeting showed an increased risk of stent thrombosis and MI after 36 months in DES-treated patients, the overall attitude among interventional cardiologists has become careful. The ACC.07/i2 Summit 2007 Joint Symposium: “Drug- Eluting Stent Safety — Hype or Reality?” focused on reports published since findings of two studies indicated that the rates of death and nonfatal myocardial infarction were higher for DES than for BMS.

This uncertainty over stent thrombosis with drug-eluting stents has led to a 20% drop in DES use in early 2007 in the US. Doctor Martin Leon (Columbia University, New York) presented the DES usage data Use of DES peaked in the US during the second half of 2006 at approximately 89%, but has dropped to 70% in early 2007. By contrast, DES usage has fluctuated in the UK and Europe but continues to hover just above 50% on average, while Japan has remained constant, at 72% for the past half year. Leon stressed the importance of careful patient selection; consideration of alternative

options (bare-metal stents, medical therapy), or CABG; clear communication of risks and benefits to patients; awareness of patients' pretreatment history; and optimal implantation techniques³.

How are DESs accepted by financial management of health care organizations?

Methods

Systematic literature review. We found additional information by internet search of grey literature.

Results

In health care organisations, DES introduction can concern managers, because of their high cost may not be covered by reimbursement policies. For example, in several Italian Regions DES receive the same coverage as BMS, though the latter are much cheaper. The adoption levels⁴ of DES in the European countries range from less than 10% to more than 60%. This uptake is mainly constrained by reimbursement policies/incentives. Some regions contemplate the same coverage for both DES and BMS, even though DESs are more expensive than BMS.

How do the patients accept DES?

Methods

Systematic literature review. We found additional information by internet search of grey literature.

Results

Some patients and patients' associations claim that DES should be implanted in every angioplasty intervention⁵. One reason for this is that patients form their own opinions of new technologies based on the information from producers' marketing campaigns and mass media. If they can access scientific literature on the specific technology, they may not fully understand it.

Nowadays, media and advertising are the major sources of information⁶. Most patients do not have access or the necessary training to interpret information provided by scientific literature (HTA reports, articles, scientific papers). Given the overwhelmingly positive results of most of the DES studies reported in peer-reviewed journals and the media response to these results, it is not surprising that patients believe that DES should be used for all patients and for all indications.

Moreover, an information bias was identified: scientific literature and mass media presented adverse effects with less emphasis (high risk of thrombosis related to DES insertion, revealed by BASKET Study - 2005) than the advantages of DES utilization (decreased risk of restenosis revealed in the first studies published).

Signs of changes in this trend are becoming evident, for example the controversies about safety and proper utilization of DES have been introduced in a popular Italian magazine “Panorama”, inviting patients to being more careful in DES implantations decision making⁷.

What kind of technical problems can the implementation of DES produce?

Results

There are no specific technical problems in DES compared with BMS.

Is DES use related with the adoption of new procedures or other instruments?

Methods

Systematic literature review. We found additional information by internet search of gray literature.

Results

Some papers underline the need to use intravascular ultrasound (IVUS) procedures in association with DES, in order to achieve a more correct placing for the stent⁸⁻⁹⁻¹⁰⁻¹¹⁻¹². IVUS is recommended for at least 20% of stent implantations. Another technology was recently introduced in cardiovascular field: The Optical Coherence Tomography (OCT) is a new non-contact, light-based imaging modality providing in situ images of tissues at near histological resolution. As shown in various preclinical and clinical reports, OCT allows the identification of mural as well as luminal morphology including lumen dimensions, plaques, thrombi, dissections, tissue flaps as well as information on stent geometry, including apposition and symmetry¹³⁻¹⁴.

Comment

The high costs of the IVUS and OCT procedures are not included in the reimbursement provided by the public insurance systems in some European countries, so that hospitals are not encouraged to use this procedure.

Work processes

What kinds of changes are required in work processes when implementing DES?

Methods

Systematic literature review. Semi-structured interview with expert physicians in cardiology, purchase managers.

Results

DES implantation, as compared with BMS, doesn't require adoption of new or different work processes. Nevertheless stent use (no matter if DES or traditional) depends on the context in which the interventional procedure is performed. Primary PTCAs should be performed within 1–2 hours (rescue angioplasty), or 20–30 minutes (primary angioplasty)¹⁵⁻¹⁶. Thus a hospital should guarantee surgical cardiology service on a 24-hour basis. Finally a high rate of effectiveness for DES is associated with a decrease of CABG procedures¹⁷⁻¹⁸, so that the organisational characteristics for heart surgical procedures could change.

What kind of changes are required in patient path when implementing DES?

Methods

Systematic literature review.

Results

DES intervention techniques do not differ from coronary angioplasty (PTCA) with traditional stents (BMS). One of the main problems in BMS interventions is restenosis of the lesion treated. It occurs in a variable percentage of cases¹⁹ (in about 20% of patients with simple lesions and more than 50% of patients with more complex conditions), depending on patient characteristics, lesion treated and BMS used. DESs reduce restenosis, even though recent studies highlighted risks of late thrombosis, especially in patients implanted for off-label conditions. In order to reduce such risks, both FDA and NHS recommended therapy with aspirin and an antiplatelet drug (clopidogrel) for 12 months after the implant. In case of BMS implant, the same therapy is recommended for only 4 weeks²⁰⁻²¹⁻²². Patient follow-up is not determined by type of stent implanted but is based on monitoring of cardiovascular disease, and occurs with ambulatory access or hospital admission in cardiovascular department depending on diagnostic tool utilized (ECG, cardiomyography, or other).

Comment

Available scientific evidence is limited since studies didn't compare DES with the latest, technically improved BMS generation.

What kind of changes can the implementation of DES generate in the quality of care ?

Methods

Systematic literature review.

Results

There are numerous definitions of quality in health care. The most widely quoted definition is that of the Institute of Medicine (Institute of Medicine in Washington, D.C., is part of the National

Academy of Sciences): “Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge²³.”

Quality of health care has several dimensions. Quite often reference is made to the following three elements of quality first proposed by Avedis Donabedian: structure, process, and outcome. Quality of health care related to the structure refers to the quality of the facilities and the environment in which health care is provided: buildings, equipment, degree of training of health care professionals and so on. Process quality refers to the correctness and appropriateness of the actual care that is provided: decisions concerning an indication to operate, how the operation was carried out, etc. Quality of health care outcomes refers to the actual result of care: improved health, patient satisfaction, reduced pain and so on.

Therefore from an organisational perspective, DES seems not to influence process quality since the interventional procedure (implantation) remains the same as in BMS.

Comment

Relevant information about quality of care is provided in the domain about effectiveness.

(De)centralization

Where will DES be placed (primary - secondary - tertiary care)?

Methods

Systematic literature review.

Results

DES technology is used in a hospital-based surgical procedure (PTCA), so that the utilization context is the secondary or tertiary care.

Comment

A debate on hospital requirements to perform PTCA is ongoing. In particular in Zavala et al.²⁴ and in Richardson et al.²⁵ the more controversial issue is about the availability of cardiosurgery services. Thus, the structural requirements seem to overshadow other requirements.

How is accessibility taken into account?

Methods

Systematic literature review.

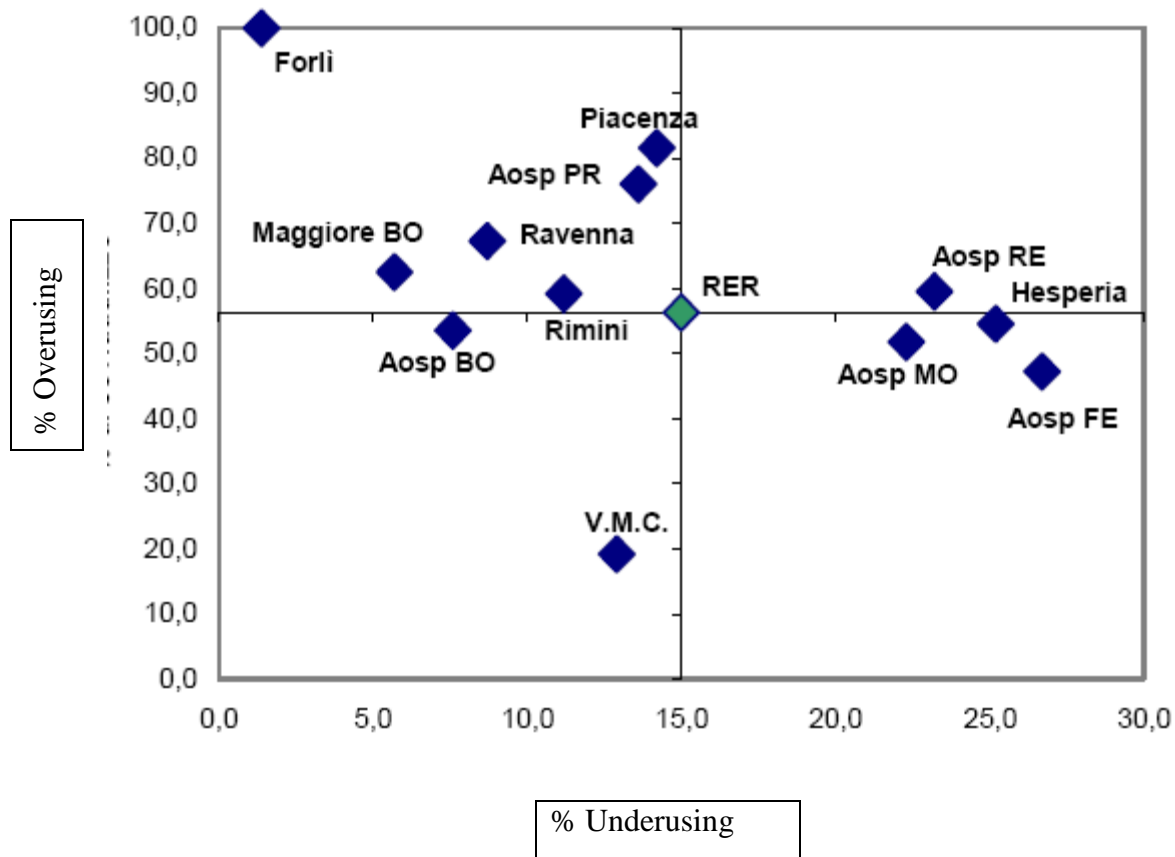
Results

Introducing medical stents implies the same problems as introducing any new technologies in medicine: it is crucial to assess their impact on clinical practice in relation with the type of patients (compared to selected patients enrolled in clinical trials, ordinary patients may present heterogeneous clinical characteristics). DES dissemination in Europe varies from 14% (of total stents) in Germany to 65% in Portugal (2006)⁴. These differences can be partly explained by a lack of structured guidelines and by the high costs of the technology. The European Society of Cardiology organised a workshop involving clinicians, health economists and HTA experts, in order to discuss the equity of patient access to new technologies, including DES. The outcome of the meeting is published in the European Heart Journal. Participants concluded that the European guidelines have little practical influence, and that they should be systematically translated, explained, disseminated and updated by cardiologists. Also at national level the dissemination of DES is heterogeneous, while at a regional level there are some noteworthy experiences, such as the one of Emilia Romagna, where a committee of cardiologists developed its own guidelines, restraining the use of DES at 30% of the total PTCA procedures. This voluntary limit is based on future forecast of use according to patients' clinical characteristics. This shows that institutional decisions may influence patient access to the new technology.

Comment

Variations in using DES, both between and within health care organizations can occur due to different clinical opinions. Such variability resulted in this experience in Emilia-Romagna²⁶, a region of Italy with 4 million residents, where cardiac care is directed through a regional hub-and-spoke model that includes both public and private facilities. Each centre (hub) is assigned a catchment area that includes a network of cardiology departments and wards (spokes). A regional commission of clinicians from both public and private hospitals defined guidelines on DES utilisation for the area and developed organizational and clinical appropriateness criteria. Nonetheless the 12 regional centres applied the guidelines very differently (see Figure below).

DES over- and underutilisation among cardiac Centres of Emilia Romagna



Source : VARIOUS AUTHORS. Stent a rilascio di farmaco per gli interventi di angioplastica coronarica Impatto clinico ed economico. Dossier 91-2004 Agenzia Sanitaria Regionale Emilia Romagna.

Unpublished data of an hospital with high intensive angioplasty activities highlights that in some cases cardiologists have different opinions in implanting a DES stent in single patients, with a range of variation from 20% to 40%.

How can the organisation ensure the accessibility of DES?

Methods

Systematic literature review.

Results

Because of their high cost and unavailability of data regarding long term follow up, access to DES may be limited. Under current conditions, selective use of DES in high-risk patients seems the most acceptable strategy in terms of cost-effectiveness²⁷. The main issue is the appropriate use of DES, in

order to submit eligible patients to the procedure, according to the guidelines developed. Therefore it becomes imperative to standardise processes, by defining shared health care profiles, which must be based on the same guidelines.

What are the economies of scale in (de)centralization?

Methods

Systematic literature review.

Results

From the point of view of the organisations acquiring DES, it is possible to achieve economies of scale through centralised purchasing, as happens in two Italian regions (Emilia Romagna and Sicily). Price is negotiated between Regions and producers, and since products are purchased in big quantities, the prices are lower than to single centres.

Staff

What kinds of experts are involved in DES? What kind of training is needed?

Methods

Systematic literature review. Semi-structured interview with expert physicians in cardiology, purchase managers.

Results

Expertise for DES implantation is not much different from that needed for BMS, because the expertise and training are connected to the angioplasty procedure, regardless of stent type. If IVUS diagnostics are used, special training should be recommended.

Comment

The rate of IVUS utilisation is not equal worldwide. In USA IVUS was used in about 20% of patients during PTCA, while in Europe there was a relatively lower use of IVUS.

What kind of incentive structures (financial, concerning career, work-processes etc.) might be established for staff when implementing DES?

Methods

Systematic literature review and a semistructured interview with physicians in an Italian Hospital.

Results

The literature search highlighted a rising trend in DES use, also outside the indications in the guidelines established. Overuse in some American states may be explained with the fact that cardiologists receive 800\$ for each DES implant²⁸, unlike in Italy. The research did not highlight forms of incentives, despite DES can be overused. An analysis of unpublished data of a hospital with high intensive angioplasty activity suggests that it is crucial to plan incentives for an appropriate DES use. Cardiologists must not only follow the agreed procedures, but also apply appropriate procedures to each patient depending on patient characteristics.

What effect can DES have on job satisfaction?

Methods

Systematic literature review and a semistructured interview with physicians in Italian Hospitals.

Results

The literature search did not identify information on cardiologists' satisfaction in implanting DES. A survey submitted to 140 American cardiologists before DES approval highlighted an enthusiastic attitude of the specialists, who forecasted a significant use of DES in the next few years. This proves that a lack of data on long term follow up was not a restraint for cardiologists²⁹. This attitude has been named "technological imperative" by Victor Fuchs³⁰.

Similar conclusions emerged in a study carried out in the Duke Hospital in 2004³¹. Cardiologists' initial enthusiasm decreased after the Barcelona International Meeting in 2006, where studies were presented, which demonstrated a major risk of late thrombosis in patients implanted with DES. BASKET-LATE study monitored more than 826 patients (545 treated with DES and 281 with BMS) for an 18-month follow-up period³².

The risk of thrombosis and other adverse events increased in patients implanted with DES stents, who stopped using clopidogrel. An internal audit in an Italian hospital showed doctors would be much more satisfied, if they could use new technologies with the procedure, such as IVUS or OCT. Furthermore, using new technologies can be an opportunity to carry out clinical studies, produce new publications and increase professional prestige of both cardiologists and the organisation.

Figure 1: Rate of late-stent thrombosis (adaptation from Basket –Late study)

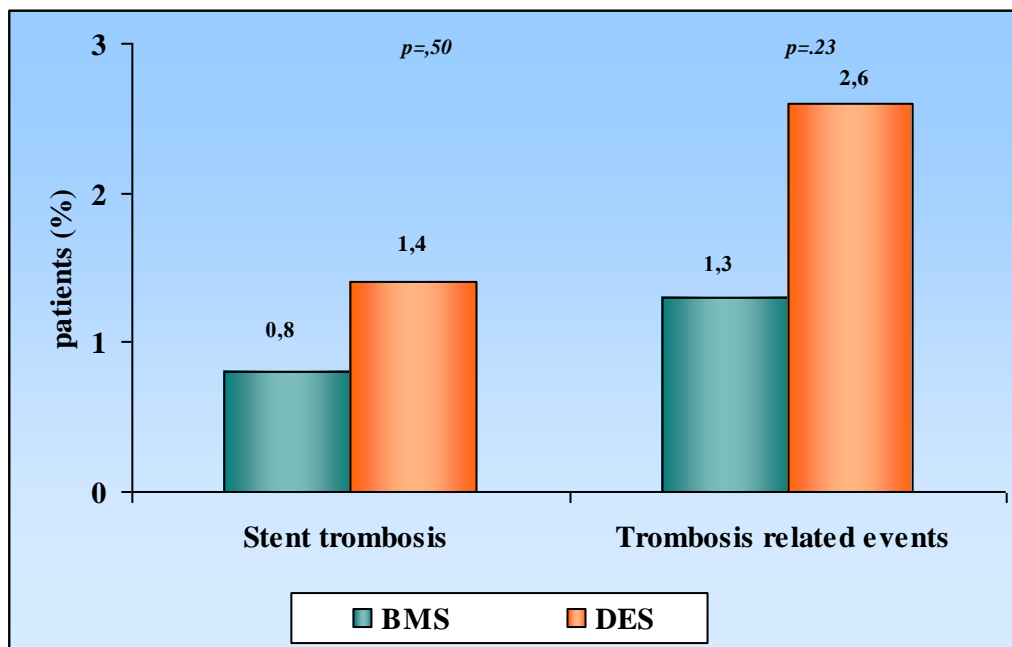
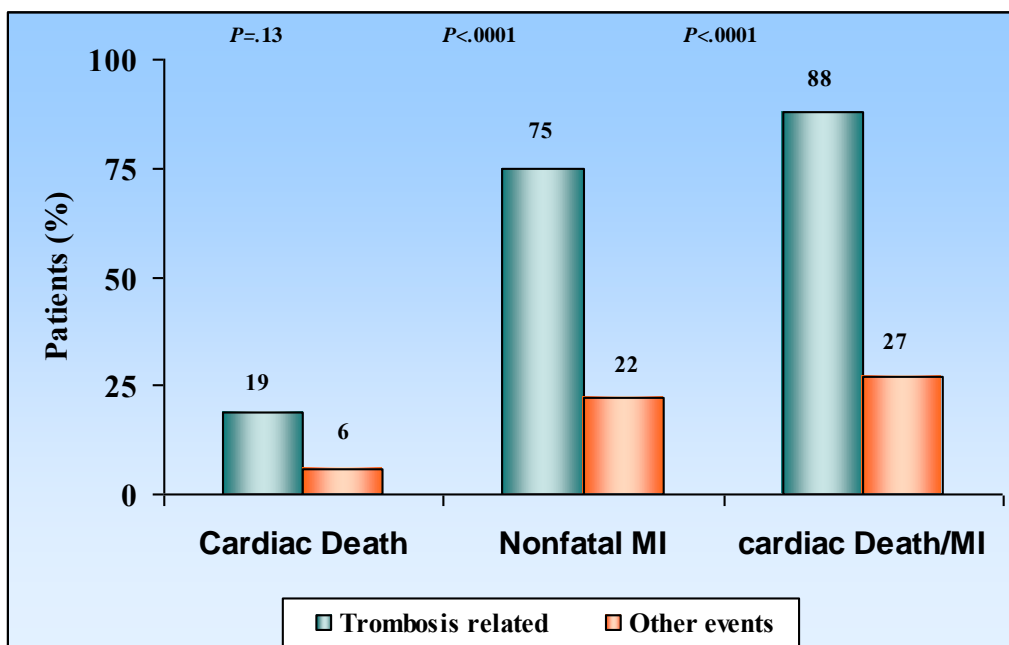


Figure 2: Outcomes related to late-stent thrombosis (adaptation from Basket –Late study)



How will know-how of a new technology be spread out among the staff?

Methods

A semistructured interview has been made with opinion leaders in interventional cardiology

Results

An interview to the specialists pinpointed that DES implants do not require additional know-how with respect to BMS (traditional technology). On the other hand, it may become necessary to acquire new competencies if DES implants are performed with technologies such as IVUS and OCT.

Co-operation and communication

What kind of coordination and communication of activities does DES require?

Methods

A semistructured interview has been made with opinion leaders in interventional cardiology.

Results

DES stents do not require any additional forms of communication and cooperation between hospital units, neither outpatient services nor hospital structures, because implant procedures are the same as for BMS (traditional technology).

What kind of information is given to the patients about the DES?

Methods

Systematic literature review.

Results

There is the clinical priority to provide patients (and often their relatives) with adequate information about the proposed procedure, in order to let them appropriately decide whether to continue the procedure or not. It is crucial that they understand the whole procedure and the risks involved, as well as all other treatment options available. In seeking patient consent, legislation is similar in cardiological and other medical procedures³³.

Generally speaking, when informed consent is required, some recommendations must be followed. For example in Italy, guidelines from the Ministry of Health are as follows:

1. To make sure that in the text to be signed by patients the information is concise, simple and understandable, without specific medical words;
2. to accompany written text with exhaustive and detailed explanations; and
3. if possible, to involve the general practitioner³⁴.

A literature search on international websites confirms that much information is available for patients, provided by the manufacturers (Boston Scientific³⁵ and Cordis³⁶), and institutions, (i.e. information provided to patients by Queensland Government or by UK National Health Service)³⁷.

However such information should be provided by cardiologists who perform the procedure.

For a fully informed consent of the patient, the format designed by Queensland Government, requires that the doctor explains to the patient his/her medical conditions and the procedure to follow, in order to make the patient aware of the risks involved, both general and specific, and the possible outcomes. The doctor should also present other therapeutic options and their risks and introduce the prognosis and the risks of not following the procedure³⁸. An FDA report outlines that patients do not receive adequate informed consent after diagnosis and before the intervention³⁹.

How is the information controlled in integrated patient path with respect to DES?

Methods

Systematic literature review.

Results

The literature search did not find guidelines or recommendations about the timing for communication and about who is in charge of giving the correct information to patients. Several studies underline the importance of having an adequate communication level between physicians and patients. In particular a case study on 199 patients⁴⁰ examined the outcome of improved communication aimed at empowering patients to be more effective participants in rehabilitation after surgery. In the intervention group, hospital stay was shorter (by 1 day), incidence of post-surgery tachyarrhythmia was reduced (by 15%), transfer to less intensive care levels was faster and patient ratings for communicative quality of care by doctors and nurses were improved.

Comment

The personnel in charge of informing patients should be predefined. Information should preferably be provided by the cardiologist in charge of the patient, in order to provide enough time to understand and decide. This issue has some common areas with the “ethics” domain.

Finances

What kinds of investments are needed (material or premises)?

Methods

A semistructured interview has been made with purchasing managers who prepare all purchase orders.

Results

Introduction of DES doesn't require changes in investments as compared to BMS.

How does the costs of DES influence to the purchasing decision?

Methods

A semistructured interview has been made with budget managers and opinion leaders in interventional cardiology.

Results

Since DES are high cost technologies, the purchasing decisions are influenced by budget constraint. It is possible that purchasing managers of health care organizations can acquire fewer DESs than required by users. A negotiation between clinicians and budget managers may be needed to obtain a correct trade-off between clinical and budget needs.

Is the number of DESs purchased influenced by cost?

Methods

Systematic literature review. Semi-structured interviews conducted with cardiologists, regional policy makers, hospital general management, and purchasers in Italian context. We found additional information by internet search of gray literature.

Results

The new technology costs are higher than the traditional ones²⁵⁻⁴¹⁻⁴²⁻⁴³. This difference varies across countries and in most cases DES technology costs twice the traditional BMS. Financing systems can limit the use of DES. For example, until 2006 in Italy⁴⁴ the reimbursement system (based on DRG) paid hospitals for a stent implantation the same amount of money for DES and for the traditional BMS, as a consequence DES use was not encouraged. Some Italian regions applied different reimbursement for DES. Since 2006 a new specific DRG was applied at a national level.

Comment

This issue has some overlapping areas with the domain “Costs and economic evaluation”

Which organizations participate in payment arrangements (investments and running costs)?

Methods

Systematic literature review.

Results

Within the Italian Health Service, investments in new technologies are made directly by hospitals. Because of the high costs of DES, some Italian Regions have attempted to decrease costs through forms of centralised purchasing.

What is the relevance of DES (in financial matters) to other activities of the hospital?

Methods

A semistructured interview has been made with opinion leaders in interventional cardiology

Results

Within the organizations which operate with fixed annual budgets, the number of procedures with DES, (three times more expensive than BMS), highly impact the allocation of available resources.

DES impact on overall expenditure for PTCA with stent insertion could increase from 20% to 300% assuming DES utilization from 10% to 80% correspondingly on overall of stent insertions. The 10% - 80% range represents the EU countries' variation range in stent implantation.

What is the likely budget impact of DES for the government?

Methods

Systematic literature review.

Results

As all innovative technologies, also DES have both an economic and a clinical impact. An Italian region (Sicily) assessed the economic impact of introducing DES in health organizations, local hospitals, and the Regional Health Service.

Five main changes were observed:

1. The costs of PTCA increased (DES are more expensive than BMS);
2. The number of PTCAs increased, because the number of patients treated as an alternative to bypass operations increased;
3. The number of bypass operations decreased. From the analysis made by Boston Scientific, using GISE 2001 data, with respect to PTCA and hospital discharge records 2001, it emerged that PTCA/CABG ratio in Sicily is 2.26 and was lower than regional best performers (Piemonte 3.31, Toscana 3.14, Veneto 2.85). Therefore, Sicily Region can optimise its PTCA/CABG ratio in favour of PTCA;
4. The number of reinterventions decreased, since restenosis rates decreased;
5. The social advantages of reintroducing patients in working environments, without a need for rehabilitation or convalescence (general post-bypass time of rehabilitation is 2 months, post-PTCA 3-7 days).

Similar conclusions have been drawn by NHS R&D HTA Programme, which in the report *Coronary artery stents: rapid systematic review & economic evaluation*, in 2003 forecast an increasing impact of total costs for NHS, due to three main factors:

1. increasing DES costs,
2. DES target population (DES are cost effective for patients at high risk of restenosis), and
3. offset costs level, which comes from reducing needs for revascularization, associated with the use of DES.

Moreover, the final impact of sirolimus-eluting stents on Canadian Health Care budget, even after allowing for savings from a reduction in repeated revascularizations, may reach \$35 million in Quebec only, and \$75 million in Canada. Therefore, this single technology may consume up to 4% of the \$2.1 billion of the funds provided by federal and provincial governments per year.

Management and control

Who sets the overall objectives and goals at the national, regional and organisational levels? Who follows the achievement of goals? Who makes the decisions of investments of DES?

Methods

Analysis of selected studies

Results

Recommendations on DES utilization have been established by regulatory authorities (FDA) and by scientific societies (ESC European society of cardiology, ACC/AHA American College of

Cardiology, American Heart Association). Examples of a systematic implementation on a regional bases of monitoring and management system on DES utilization come from in two Italian regions (Emilia Romagna and Sicily), where regional registers have been established.

Investment decision on DES utilization can be related to two levels of decision making:

- Macro level: government authorities can support the diffusion of DES through favourable reimbursement system. For example in some cases a specific DRG on DES insertion has been established.
- Meso level: in health care organizations there may be a trade-off between physicians' needs, favouring DES introduction, and budget constraint. Thus investment on DES can be influenced by budget negotiations between management and physicians.

Who decides which patients receive DES treatment and on what basis?

Methods

Analysis of selected studies

Results

Cardiologists, on the basis of a diagnostic exam (coronary angiography), should be the main decision makers for a stent implantation procedure. They should decide this based on the kind of lesion and its length. Patients with diabetes, in whom restenosis is more frequent, should be usually treated with DES.

Who will handle management and information responsibility?

Results

Data for formulating recommendations on the use of DES, are managed, assessed and disseminated in guidelines produced by clinical scientific societies or HTA agencies. Moreover, several regulatory authorities (FDA, NICE) have given recommendations on DES appropriate utilization.

What management competences are needed at all levels?

Results

DES management requires:

- Clinical skill to manage DES in clinical practice;
- Multidisciplinary competence for assessment activities (clinical, economical and organizational skills are required).

Who is responsible for sanctioning at all levels?

Results

In European public health care systems sanctioning usually is linked to denied funding. So the responsibility is committed to governmental authorities.

Stakeholders

How will the other interest groups of DES be taken into account in the planning / implementation of the new technology?

Methods

Systematic literature review.

Results

Different stakeholders' perspectives on introducing DES have been summarized (Regulatory Authority, Healthcare Organization, Patients Organization, and Pharmaceutical Industry).

Regulatory Authorities are responsible for regulating both the introduction of new technologies (through approval procedures) and their use, by monitoring adverse events related to them. With regard to monitoring activities, on the basis of the results of recent studies, (where the follow up time of patients enrolled was longer than in the previous studies, an higher risk of late thrombosis, in case of off label DES, was highlighted), FDA recommends the use of DES only for approved indications (not off-label use)⁴⁶. In Europe, the European Society of Cardiology (ESC) provided guidelines for DES utilization⁸. In Italy, in particular, the Emilia Romagna Committee limited DES utilisation to patients with specific clinical characteristics (diabetes, specified length and width of lesions)²⁵.

National/Regional government: In health systems where interventions are reimbursed according to agreed rates, policymakers' decisions (at national/regional level) on DES and BMS rates highly influence stent utilization (incentive – disincentive)⁴⁹.

In Italy most Regional Health Services do not specify diagnosis-related groups (DRGs) for DES; DES are reimbursed at the same rates of traditional stents, even though they are more expensive. This discourages DES utilisation in hospitals²⁵.

In USA, new DRGs for DES with (DRG 526) and without (DRG 527) acute myocardial infarction, have been created by the Centers for Medicare and Medicaid Services, but these DRGs may not be sufficient to cover the acquisition costs of the DES compared with the DRGs for bare metal stents (DRGs 516 and 517)⁵⁰.

Patient Perspective: Most patients do not have the training necessary to interpret this level of scientific data and must base their assessment on other sources. In the modern era, the media and direct patient advertising provide the major sources of this information. Given the positive results of most DES studies reported in peer-reviewed journals and the media response to these results, it is

not surprising that patients believe that DES should be used for all patients and for all indications. In conclusion, from the patient's perspective, optimal utilization is nearly 100%. This is based on the belief that the DES is equally beneficial in all settings and that it provides a lasting cure rather than a treatment for symptoms.

A literature search highlighted that government authorities, in developing recommendations on the appropriate use of devices, involve patient representatives.

In USA, in the FDA Patient Representative Program, the Patient Representative's role is to provide the advisory committee and FDA insight on issues, problems, and questions pertinent to the viewpoint of patients and family members living with a specific serious or life-threatening disease. Representatives serve as voting or non-voting members of the advisory committee⁵¹.

In UK, The Patient and Public Involvement Programme (PPIP) at NICE is dedicated to developing and supporting opportunities to involve patients, in shaping NICE policy⁵².

Also in Canada COMPUS (Canadian Optimal Medication Prescribing & Utilization Service) gathers information from different stakeholders, including patients and consumers, health care providers and pharmaceutical manufacturers⁵³.

Discussion

The objective of organizational domain was to assess what kinds of resources (material things, human skills and knowledge, money, etc) need to be mobilised and organised when implementing DES procedure, and what kinds of changes or consequences the use can further cause in the organisation. The investigation of DES impact on management and structure of organization was very complex, because organisational aspects are rarely analysed within clinical studies and HTA reports. A traditional systematic literature review was not completely suitable to obtain full information on organisational aspects, and it was necessary complete the search with analysis of other sources.

It is the opinion of the authors that lack of information on organizational aspects means there were no relevant changes depending on type of stent used. In fact the patient path is determined by type of procedures (bypass or angioplasty).

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Appendix 1 - Characteristics of studies included in systematic review

Study	Authors	Source	Study design	Inclusion criteria
A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization.	Morice M: et al.	N Engl J Med. 2002 Jun 6; 346 (23):1773-80.	Clinical trial	Relevant for utilization topic
DRUG-ELUTING STENT TASK FORCE: Final Report and Recommendations of the Working Committees on Cost Effectiveness/Economics, Access to Care, and Medicolegal Issues,	Hodgson John McB. et al.	Catheterization and cardiovascular interventions, 2004: 62: 1-17	Review	Relevant to utilization topic
Cost-effectiveness of drug-eluting coronary stents in Quebec, Canada.	Brophy J.M. et al.	Int. J. Of Technology Assessment In Health Care 21:3, 2005	Comparative study	Relevant to utilization topic
Economic Evaluation of Drug Eluting Stents.	Various Authors	CCOHTA, Technology report. Issue 53. February 2005.	Health Technology Assessment report	Relevant to utilization topic
Guidelines for Percutaneous Coronary Interventions: The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology.	Sigmund Silber, et al.	Eur Heart J 2005 26: 804-847.	Guideline	Relevant o utilization topic
TASK FORCE MEMBERS: ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention— Summary Article A Report of the American College of Cardiology/American Heart Association .	Elliott M. Antman et al.	Circulation. 2006; 113:156-175.	Guideline	Relevant to utilization topic
TASK FORCE MEMBERS: ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines)	Sidney C. Smith et al.	Circulation 2001;103;3019-3041	Guideline	Relevant to utilization topic
Relationship between Procedure Indications and Outcomes of Percutaneous Coronary Interventions by American College of Cardiology/American Heart Association Task Force Guidelines.	H. Vernon Anderson et al.	Circulation 2005;112;2786-2791	Guideline	Relevant to utilization topic

Optical Coherence Tomography (OCT). Potential of a new high-resolution intracoronary imaging technique.	Gerckens U. et al.	Herz. 2003 Sep;28(6):496-500	Comparative study	Relevant to utilization topic
Drug-Eluting Stents and the Future of Coronary Artery Bypass Surgery: Facts and Fiction,	Shahzad G. Raja	Ann Thorac Surg 2006;81:1162-71	Review	Relevant to work process topic
Stent Thrombosis Redux — The FDA Perspective, 987.	Farb A. et al.	N Engl J Med 2007 356;10:984-	Review	Relevant to work process topic
Final Appraisal Determination, Coronary artery stents, available on	Various Authors	NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE	Health Technology Assessment report	Relevant to work process topic
Safety of elective--including "high risk"--percutaneous coronary interventions without on-site cardiac surgery.	Zavala A. E. et al.	Am Heart J. 2004 Oct; 148(4):676-83.	Multi centre study	Relevant to work process topic
Management of acute coronary occlusion during percutaneous transluminal coronary angioplasty: experience of complications in a hospital without on site facilities for cardiac surgery.	Richardson SG. Et al.	BMJ. 1990 Feb 10; 300(6721):355-8.	Comparative study	Relevant to work process topic
Effect of Hospital ownership status and payment structure on the adoption and use of drug-eluting stents for percutaneous coronary interventions.	Grilli R. et al.	CMAJ 2007, 16; 176-185.	Comparative study	Relevant f to (De)centralization topic
Coronary artery stents: rapid systematic review & economic evaluation,	Various Authors.	NICE	Review	Relevant to Staff topic
Economic impact of Drug eluting stents on Hospital Systems: a disease-state model.	Kong D.F. et al.	Am Heart Journal; 2004; 147 (3): 449-56.	Evaluation study	Relevant to Staff topic
Consent in cardiology: there may be trouble ahead?	Curzen N. et al.	Heart 2005;91:977-980	Evaluation study	Relevant to Cooperation and communication topic
Does physician–patient communication that aims at empowering patients improve clinical outcome? A case study.	Trummer U. et al.	Patient Education and Counselling 61 300 (2006) 299–306.	Clinical trial	Relevant to Cooperation and communication topic
Economics of Sirolimus-Eluting Stents: Drug-Eluting Stents Have Really Arrived	Weintraub S. W.	Circulation 2004;110;472-474	Comparative study	Relevant to Stakeholder topic

Appendix 2 - Characteristics of references of grey literature used

Reference	Authors	Source	Publication Types	Inclusion criteria
American College of cardiology, Scientific session news. I2 summit 2007.	Various Authors	http://www.acc07.acc.org/ssn/Sun_SSN.pdf	Newsletter of ACC 07 Scientific session	Relevant to utilization topic
Improving patient access to novel medical technologies in Europe.	Kerney P. et al l.	Eur Heart Journal, 2006 Apr;27(7):882-5	Congresses	Relevant to utilization topic
Can we afford to eliminate restenosis? Can we afford not to?	Greenberg D. et al.	Am Coll Cardiol 2004; 43: 513-518.	Comment	Relevant to utilization topic
Processo agli stent.	Codignola A.	Panorama 2007 (18): 221.	Comment	Relevant to utilization topic
Stent a rilascio di farmaco per gli interventi di angioplastica coronarica Impatto clinico ed economico.	Various Authors	Dossier 91-2004 Agenzia Sanitaria Regionale Emilia Romagna http://asr.regione.emilia-romagna.it/	Dossier	Relevant to utilization topic
Cost effectiveness of eluting stents versus other treatments “	M. Oradei, C. Marano, M. Marchetti.	HTA annual meeting 2004, Krakov June 2004,	Oral Presentation	Relevant to utilization topic
Stent a rilascio di farmaco: dai risultati degli studi clinici ai modelli di impatto economico-sanitario nella realtà italiana.	Sangiorgi et al.	Ital Heart J Suppl 2005; 6: 145-156.	Evaluation study	Relevant to utilization topic
Primary coronary intervention in acute myocardial infarction,	Kim C. X. et al	Ital Heart J 2004; 5 (Suppl 6): 76S-82S)	Evaluation study	Relevant to work process topic
Medicare: A Strategy for Quality Assurance.	Lohr KN	Volume I. Institute of Medicine. Washington, DC: National Academy Press; 1990	Books	Relevant to work process topic
Stent coronarici a rilascio di farmaco,	Various Authors	Ministero della salute CUD (Commissione Unica Dispositivi,	Dossier	Relevant to work process topic
Guideline for the use of clopidogrel in combination with aspirin in Coronary Heart Disease (CHD)	Various Authors	NHS Bedfordshire and Hertfordshire Cardiac Network,	Dossier	Relevant to work process topic
DMS Project discovers excessive surgery rates	Blodget K,	The darmount.com news	comment	Relevant to work process topic
Who shall live? Health economics and	Fuchs, V.R	Basic Books, (1974), New York	Books	Relevant to

social choice.				(De)centralization topic
BASKET-LATE: Late Clinical Events Related to Late Stent Thrombosis After Stopping Clopidogrel: Drug-Eluting vs Bare-Metal Stenting:	Gruberg L.	http://www.medscape.com/viewarticle/	Comment	Relevant to (De)centralization topic
Sperimentazione controllata e randomizzata (RCT)	Various Authors	Bollettino di informazione sui farmaci	Comment	Relevant to Staff topic
TAXUS® Express2™ Paclitaxel-Eluting Coronary Stent System.	Various Author	Boston scientific.	Patient information guide	Relevant to Cooperation and communication topic
CYPHER® Sirolimus-eluting Coronary Stent,	Various Author	Cordis (Johnson & Johnson).	Patient information guide	Relevant to Cooperation and communication topic
Recovering from coronary angioplasty and stent insertion,	Various Authors	NHS trusts. Trust New Castle	Patient information guide	Relevant to Cooperation and communication topic
Protecting Patients Through Informed Consent and Appropriate Therapy.	Grover F.	http://www.fda.gov/ohrms/dockets/AC/06/slides/2006-4253oph2_22_Grover.pdf	Oral presentation	Relevant to Cooperation and communication topic
TAXUS® FDA approval	Various Authors	http://www.fda.gov/cdrh/pdf3/POO0026a.pdf	FDA approval	Relevant to Stakeholder topic
CYPHER® FDA approval	Various Authors	http://www.fda.gov/cdrh/pdf3/PO30025a.pdf	FDA approval	Relevant to Stakeholder topic
Boston Scientific Becomes Only Company With Two Drug-eluting Stent Platforms	Various Authors	www.medicalnewstoday.com/medicalnews.php?newsid=54565	News	Relevant to Stakeholder topic
Medtronic stent begins FDA pre-market approval process	Various Authors	www.bizjournals.com/phoenix/stories/2005/10/10/daily1.html	News	Relevant to Stakeholder topic
Update to FDA Statement on Coronary Drug-Eluting Stents	Various Authors	http://www.fda.gov/cdrh/news/010407.html	Appraisal	Relevant to Stakeholder topic
FDA Patient Representative Program,	Various Authors	http://www.fda.gov/oashi/patrep/patientrep.html	Appraisal	Relevant to Stakeholder topic
NICE Patient and Public Involvement Programme	Various Authors	www.nice.org.uk/page.aspx?o=PatientPublic	Guideline	Relevant to Stakeholder topic
CADTH COMPUS (Canadian Optimal Medication Prescribing & Utilization Service).	Various Authors	http://www.cadth.ca/index.php/en/compus/about/procedures	Guideline	Relevant to Stakeholder topic

APPENDIX 3: Table template for translating assessment elements

Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research question(s) in the context of DES	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
Organisational aspects	Utilization	How is the new technology accepted by the organisation?	YES	<i>How are DES accepted by interventional cardiologists of health care organizations?</i>	3,2,2,3,2,2,3 2	3,1,2,2,2,2,2 2
Organisational aspects	Utilization	How is the new technology accepted by the organisation?	YES	<i>How are DES accepted by Financial Management of Health Care Organizations of health care organizations?</i>	3,2,2,3,2,2,3 2	3,1,2,2,2,2,2 2
Organisational aspects	Utilization	How do the patients accept the new technology?	YES		3,2,2,3,2,2,2 2	3,1,2,2,2,2,2 2
Organisational aspects	Utilization	What kind of technical problems can the implementation of a new technology produce?	YES	<i>Are the DES use related with the adoption of new procedures or other instruments?</i>	1,2,3,3,3,2,3 3	3,3,2,3,2,1,2 2
Organisational aspects	Work processes	What kinds of changes are required in the work processes when implementing new technology?	NO because DES implantation compared with BMS doesn't need the adoption of new or different work processes.		2,3,3,3,3,2,3 3	3,1,2,2,2,2,2 2
Organisational aspects	Work processes	What kinds of changes are required in the patient path when implementing new technology?	No because DES interventions techniques do not differ from coronary angioplasty (PTCA) with traditional stents (BMS).		1,2,3,2,3,2,2 2	2,1,2,2,2,1,2 2

EUnetHTA WP4 - Core HTA on drug eluting stents (DES)
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

Organisational aspects	Work processes	What kind of changes can the implementation of a new technology generate in the quality of care?	NO because DES does not influence the quality of process since the interventional procedure (implantation) still remains the same.		3,2,3,2,3,2,3 3	2,2,2,2,2,2 2
Organisational aspects	(De)centralisation	Where will the new technology be placed (primary - secondary - tertiary care)?	YES		3,3,3,3,2,3 3	1,2,1,2,2,2 2
Organisational aspects	(De)centralisation	How is the accessibility taken into account? How can the organisation ensure the accessibility of a new technology?	YES		2,3,2,3,2,2,3 2	2,1,2,1,1,1,1 1
Organisational aspects	(De)centralisation	What are the economies of scale and quality of scale of the (de)centralisation?	YES		1,1,2,2,2,2,2 2	3,1,1,1,1,1,1 1
Organisational aspects	Staff	What kinds of experts are involved in the new technology? What kind of training is needed?	NO because Expertise for DES implantation is not much different from the one needed for the BMS		3,3,3,3,3,3,3 3	2,2,2,2,2,2,2 2
Organisational aspects	Staff	What kind of incentive structures (financial, career-wise, work-process-wise, treatment-wise etc.) might be established for staff when implementing a new technology?	YES		3,3,1,2,2,1,2 2	3,2,1,2,2,1,1 2
Organisational aspects	Staff	What kind of meaning can a new technology have in relation to job satisfaction?	YES		1,1,1,1,1,1,1 1	2,1,2,1,2,1,1 2
Organisational aspects	Staff	How will know-how of a new technology be spread out among the staff?	NO because DES implant doesn't need further know how with respect to BMS		2,2,2,2,2,2,2 2	3,2,2,2,2,2,2 2
Organisational aspects	Co-operation and communication	What kind of co-ordination and communication of activities does the new technology require?	NO because DES doesn't require any additional forms of cooperation and communication between hospital units.		2,2,2,3,2,2,2 2	3,2,2,2,2,2,2 2
Organisational aspects	Co-operation and communication	What kind of information is given to the patients about the new technology?	YES		1,3,3,2,2,2,3 2	3,2,2,2,2,2,2 2
Organisational aspects	Co-operation and communication	How is the information controlled in integrated patient path with respect to a new technology?	YES		3,3,3,3,3,3,3 3	3,3,2,3,2,2,2 2

EUnetHTA WP4 - Core HTA on drug eluting stents (DES)
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

Organisational aspects	Finances	What kinds of investments are needed (material or premises)?	NO because Introduction of DES doesn't require changes in investments matter compared to BMS.		3	2
Organisational aspects	Finances	How does the costs of the new technology influence to the purchasing decision?	YES		2	2
Organisational aspects	Finances	How does the costs of the new technology influence to the purchasing decision?	YES	<i>Is number of DES purchased influenced by their higher costs?</i>	2	2
Organisational aspects	Finances	Which organisations participate in the payment arrangements (investments and running costs)?	YES		1,2,2,2,1,2 2	2,2,1,1,1,1,1 1
Organisational aspects	Finances	What kind of relevance has the new technology (in financial matter) to other activities of the hospital?	YES		1,2,2,2,2,2 2	2,2,1,1,1,1,1 1
Organisational aspects	Finances	What is the likely budget impact of the technology for the government?	YES		3	1
Organisational aspects	Management and controlling	Who makes the overall objectives in national / regional / organisational level? Who is setting goals? Who will follow up on goal achievement? Who makes the decisions of investments of a new technology?	YES		2,2,2,2,2 2	1,1,1,1,1,1 1
Organisational aspects	Management and controlling	Who decides which patients are to undergo a treatment and on what basis?	YES		2,3,2,3,3,3 3	2,2,2,2,1 2
Organisational aspects	Management and controlling	Who will handle management, responsibility and evaluation of information?	YES		1,3,2,2,3,3 3	1,1,1,1,1,1 1
Organisational aspects	Management and controlling	What management competences are needed at all levels?	YES		2,2,2,2,2 2	3,2,2,2,1 2
Organisational aspects	Management and controlling	Who is responsible for sanctioning at all levels?	YES		1,1,1,1,1,1 1	1,1,1,1,1,1 1
Organisational aspects	Stakeholders	How will the other interest groups of the new technology be taken into account in the planning / implementation of the new	YES		1,3,3,2,3,2,3 3	2,1,1,1,1,1,2 1

		technology?				
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Social aspects

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Introduction

Coronary disorders can not be cured by any current treatment. Regardless of the chosen treatment (e.g. revascularisation with DES or BMS or treatment with drugs) the coronary disease progresses individually. Also patients' commitment to changes in life-style may have a major effect on the outcome. The symptoms of coronary disease requiring medical intervention can thus reoccur. In many cases repeated interventions (re-stenting or coronary by-pass surgery) may be required.

The social consequences of using DES or BMS can be expected to be the same for both technologies, as the only difference between these two technologies lies in the addition of drug to the stent. Thus we analyzed the social consequences of using any type of stent: drug eluting stents (DES) or bare metal stents (BMS).

Methodology

We conducted a literature search to find systematic reviews or primary studies on social issues related to the use of stents. We decided to include every empirical study that concerns some of the social issues and analysed what kind of information the studies provide concerning issues defined according to the translation model.

In addition, to explore the differences between DES and BMS, we consulted a content expert in thoracic and cardiovascular surgery (Pekka Kuukasjärvi, senior medical officer, Finohta). In a two hour interview the expert was asked to evaluate the consequences and differences of using DESs compared to BMSs in relation to social issues. One researcher wrote down his answers.

Translating the issues to study questions

The two main questions in the social analysis are:

1) What kind of resources (people, support, money etc.) must be mobilized and organized when using DES or BMS after the hospital stay in order to produce satisfactory results.

Issues:

- Support needed by the patient (from health care professionals, family and other related people, and services, systems and polices)
- Arrangements needed at work place, at home or in any daily activities

2) What kind of changes or consequences can the use of DES or BMS produce in the various life spheres of patients/citizens?

Issues:

- Access to health care
- Working life
- Economy of a citizen
- Family life
- Social relations
- Attitudes and self-conception

We translated the issues to specific study questions simply by changing the word "technology" in the issues to "DES or BMS" (Appendix A).

Locating and selecting the studies

We searched systematic reviews and empirical studies from databases of

- 1) social sciences: Sociological Abstracts, Social Services Abstracts, Social Care on line/Caredata, SocINDEX,
- 2) medicine: Medline, EBM-databases (Cochrane, DARE, ACP Journal Club), Cinahl, Medic, SweMed+ ;
- 3) other databases: Assia, Ageline, PsycINFO, ERIC, Academic Search Elite, and
- 4) full text databases: Sage premier, SpringerLink, Blackwell Synergy, Science direct from the time of their inception to to March 2007.

Information scientists at STAKES planned the literature searches for the various databases. The following search terms were used for searches in Medline: *stent\$, coronary stenosis, transluminal, percutaneous, coronary, coronary disease, coronary artery bypass, myocardial infarction, coronar\$, angioplasty, heart, cardiac\$, cardiol\$, myocardi\$, social welfare, social work, social security, social support, social, socio\$, societal\$, health services accessibility, access\$, health resources, health priorities, patient selection, candidate\$, resource\$, equit\$, unequit\$, allocate\$, reallocate\$, gender, age factors, professional-family relations, professional-patient relations, family relations, famil\$, patient\$, nurse\$, doctor\$, physician\$, staff\$, personnel, relations\$, work capacity evaluation, work simplification, work\$, job\$, profession, return\$, capacity\$, facit\$, ability\$, workload, rehabilitation, vocational, attitude to health, patient\$, attitude\$, belie\$, expect\$, percept\$, perceive\$, experience\$, asaptation, psychological, orientation, self concept, self efficacy, cope, soping, empowerment, social adjustment*. In the other databases the search term was "stent*" in keywords or free text. The search strategies are attached (to be added in appendix B).

Studies were eligible if they:

- included patients with coronary artery disease,
- investigated stents (drug-eluting sirolimus or paclitaxel stents or BMS or other type of stents)
- consider patients outside the treating hospital (before or after hospital stay)
- analyzed and reported results of any of the following social issues: access to health care, patient group selection, support, working life, economy of the citizen, family life, social life, values, attitudes, self-concept
- study designs: systematic reviews or any kind of empirical studies that studied some of the social issues

Two researchers (HA, PRM) separately screened all search results by titles and abstracts to select the articles to be ordered. One researcher (JK) evaluated the full text articles for inclusion criteria. Unclear cases were discussed and solved in consensus by the three researchers.

Assessing study quality

There are several different models for assessing the quality of empirical studies other than randomized controlled trials. Due to time limits we were not able to assess study quality.

Collecting data from individual studies

The following study characteristics will be tabulated of the empirical studies:

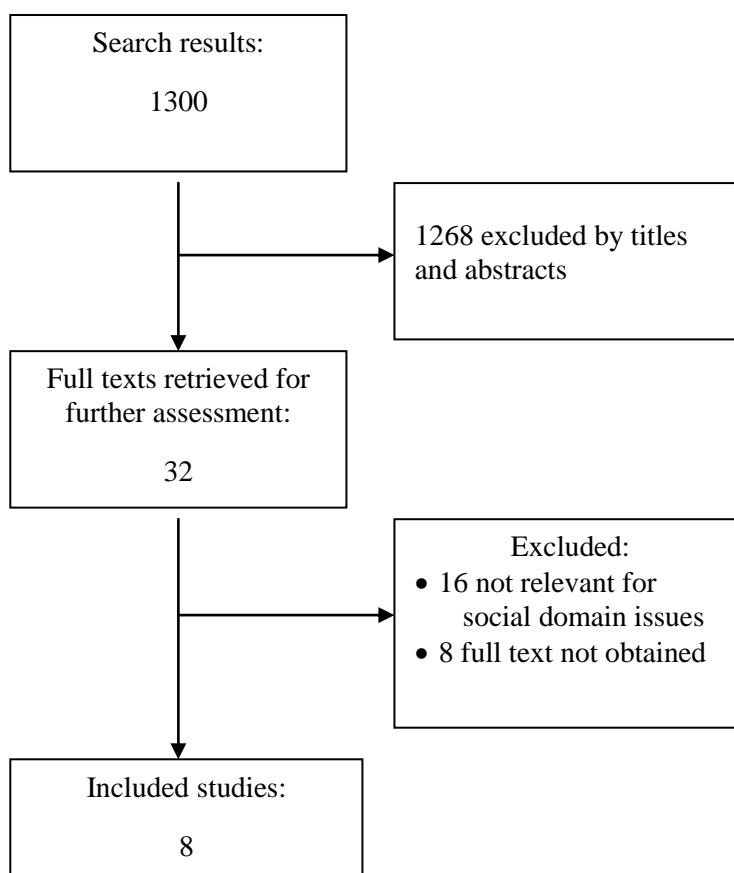
- *Publication details*: authors, year, social issue,
- *Nature of the study*: aims/objectives of the study, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model, study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods
- *Participant characteristics*: gender, age, ethnicity, types of practitioners, policy makers or patients
- *Features of the studied intervention* (when applicable): aim of the intervention, country, location/setting, intervention process (description of how the intervention/service was delivered) and
- *Outcomes and results*: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.

Presenting and analyzing results

We made a narrative synthesis and analysed the results with the help of the themes that arose from the selected studies.

The literature searches yielded 1300 references; of which 32 were ordered for closer consideration of the inclusion criteria (Figure 1). Eight full text articles were not obtained until week 21 in May 2007 and thus had to be excluded. Sixteen studies were excluded by the full text as they did not address the social domain issues (appendix C). Eight studies were included, and they were categorized to the social issues as follows: access to health care (n=2), support (n=5), working life (n=1) (1-8). Full details of the included studies are in appendix D. No studies were identified on the other issues. Thus the analysis of these issues is based on the expert interview only, which addressed solely the differences between BMS and DES.

Figure 1: Selection of studies for inclusion



Assessment elements

Access to health care

What kind of changes can the implementation of DES or BMS produce in the access to health care?

Results

We identified two studies focusing on patients' access to health care. Bond et al. (1) analysed equity in access by age group to cardiac procedures. The observational study was based on a retrospective case note analysis of 712 patients (388 males, 324 females) with diagnosed cardiovascular disease. Eligible patients were inpatients with a cardiac ICD-code (120-25) recorded on the patient administration system covering ischaemic heart disease, acute myocardial infarction or angina

pectoris (n=447) and a sample of 265 cardiac outpatient attendees. The analysis tracked each case backwards and forwards by 12 months from patient's study entry date. The primary outcome was whether the patient received the targeted interventions, e.g. exercise tolerance testing, cardiac catheterisation and angiography or revascularisation when indicated.

Forty eight percent of the study patients were under 65 years, 31% were between 65- 75 years, 10% between 75-80 years and 11% over 80 years. The analysis showed that older hospital patients with ischemic heart disease, and with indication for further investigation, were less likely to be referred for exercise tolerance tests and cardiac catheterisation and angiography than younger people. This was independent of both the gender and the severity of condition. The patients who underwent cardiac catheterisation and angiography were analysed in relation to their subsequent receipt of revascularisation. Of the 107 patients 31% were referred for revascularisation. Of these patients 27% were under 65 years and 34% between 65-75 years. Two of the four people aged over 75 years underwent revascularisation.

Rates of indicated interventions were relatively low for all the age groups, and lowest for the oldest patients. The patients did not appear to be discriminated in receiving the indicated treatments, except in the case of revascularisation, where older patients were more likely to be filtered out at the investigation stage. The study population was limited only to one district hospital in eastern London. There might also be some underestimation of the denominator population due to lack of information how many patients with cardiac problems were not given a cardiac diagnosis on death and discharge.

Rao et al. (2) study focused on the use of DES in clinical practice. The multicenter data from the ACC-NCDR registry included the information of 408,033 percutaneous coronary intervention procedures. Of those, 353,242 procedures (86.6%) involved stent placement. The initial part of the study examined the use of the Cypher stent. After the Taxus stent became available, the later part of the study examined the use of either stent. The primary outcomes were the occurrence of in-hospital mortality, adjusted in hospital mortality, post procedure MI, unplanned coronary artery bypass grafting and procedural success.

During the study period of 21 months the proportion of procedures using DES increased from 19.7% to 78.2%. There were significant patient-level and hospital-level differences in DES use. Although DES use increased in all patient groups and hospital types, adoption was slower among older patients and those without health insurance. There was a progressive decrease in the odds of DES use as age increased. White race, female sex, presence of insurance, diabetes mellitus, PCI of de novo lesion, PCI at a suburban hospital and PCI at a high volume center were significant predictors of DES use. To determine if the differences persisted after the introduction of the Taxus stent, the analysis was repeated after dividing the study period into 2 phases: before and after the availability of the Taxus stent. The same patient, clinical, and hospital characteristics were associated with DES use in both phases. The adjusted odds ratios and 95% confidence intervals were nearly identical in both phases. The analysis of data demonstrates that there was rationing of DES to certain patients subgroups. Non white patients and patients without health insurance appear to be much less likely to receive DES. The use of DES was higher at high-volume hospitals than at low-volume hospitals. These patterns persisted even after the introduction of a second DES product.

Expert interview:

At this moment the clinical criteria for implementing BMS or DES are the same. Based on the effectiveness and cost-effectiveness studies we need to have clear indications for the use of DES. The consequences of patient selection for stents need to be evaluated.

The cost of DES is ca. 1.5 times the cost of BMS. The decision to use DES instead of BMS will require a budget increase as the amount of patients needing stents remains the same. This will have major consequences on the reallocation of resources. The major question here is whether these resources will be taken from other patient groups in the cardiac unit or from any other patient group within the health care. At the end the funding of other interventional approaches (e.g. preventive measures) might be challenged. In the long run the costs may be balanced if the need of reoperations decreases when using DES. The major issue would then be how the released resources would be used. Will those be reallocated to areas that suffered when implementing DES or will it be kept within coronary units. How open and transparent these decisions are made will have consequences with relation to the public opinion.

An increase in the use of DES may lead to limiting resources available for coronary patients who do not fulfil the criteria for these stents. It is most probable that patients needing a stent will receive it. The consequent limitation in resources (personal money) may also affect other patient groups.

Comment

The change in the available resources could produce changes in the access to health care that may differ between organisations.

Support

What kind of services, systems and policies do the patients with DES or BMS need after the hospital stay?

Results

We identified two studies addressing patient service needs after the hospital stay. Caulin-Glaser et al. (3) assessed gender differences for in-hospital secondary prevention instruction and physician referral to cardiac rehabilitation (CR). A matched case, observational survey design was used to assess the referral for phase II outpatient cardiac rehabilitation based on gender at the hospital and/or follow-up physician visit after a cardiac revascularization procedure. Study subjects consisted of 80 patients (40 men, 40 women) who had been revascularized (50% balloon angioplasty/coronary stenting, and 50% CABG). No patient had previously undergone a revascularization procedure. The patients were 45 years old or older and English speaking, and geographically distributed throughout New Haven County. They completed a survey addressing information and referral to cardiac rehabilitation during their hospitalization and at the follow-up physician office visit.

The study results inform that women were less likely to be instructed on secondary prevention strategies and CR or referral to CR compared to men despite being matched for age and undergoing the same procedure. The data demonstrate a gender difference in hospital teaching and referral information for CR after revascularization. The instruction of patients concerning secondary prevention and CR postrevascularization procedure is poor. Within that group, women were far less

likely to have CR discussed or referrals made by healthcare professionals. The study demonstrates that all healthcare providers need education on the comprehensive nature and benefits of cardiac rehabilitation, with a particular emphasis on women.

Edelman et al. (4) reports a qualitative analysis on the feedback provided by cardiac disease patients who attended a group cognitive behaviour therapy (CBT). The aims of the program were to reduce anxiety, depression and hostility. Eligible participants were males who had undergone stent surgery at one of the two major hospitals in Sydney. The participants were randomized to either a group CBT intervention or a "standard care" control group. Participants attended eight weekly group sessions, with 6 to 10 patients per group. The groups were led by a clinical psychologist. Evaluation of the program was mostly positive; mean scores (out of 5) on the questions "How much did you enjoy the program?", how helpful did you find the program?", and "How well did the leader facilitate the group?" were 4.73, 4.45, and 4.79 respectively. Ninety-six percent of the responses were above the indifference point (of 3). However, the intervention process was not followed, evaluated and analysed. Thus the results give only scarce knowledge of the functioning of the group CBT program.

An interesting finding of the study was that the value that participants placed upon interacting with other patients who had had similar experiences with cardiac disease. This was the aspect of the program that most participants enjoyed. It was also nominated frequently as a perceived benefit of the program. This finding suggests that while the content of a structured group CBT program is often perceived as beneficial, the social environment in which it is delivered may be the most highly valued aspect of the intervention. The findings call for studies that analyse the interaction of peers and the meaning of support from peers after the in-hospital time.

Expert interview: No major difference. After implanting DES the need for antithrombotic prophylaxis is slightly longer. DES requires a higher resource allocation.

What kinds of support do the patients with DES or BMS need from health professionals after the hospital stay?

Results

We identified three studies addressing patients' needs from health professionals. Higgins et al. (5) described participants' perceptions of recovery after angioplasty. Coronary angioplasty and stent placement is associated with short hospital days. Patients are expected to recover at home, alone, following limited care time with nurses. The study used a grounded theory design. Data were gathered from semi-structured, taped interviews designed to explore the recovery experiences of coronary angioplasty patients. The participants were eight men and three women. Selection criteria included men and women over the age of 18 from all cultural groups who could communicate in English. Participants, who resided in the Australian metropolitan area and had undergone elective PTCA, were selected.

The study results describe the recovery phase. Awareness of problems in the recovery phase was associated with 'relief from chest pain' for most participants. In contrast, anxiety continued and was associated with 'uncertainty over future health'. Participants described coping responses of 'taking control of their life again' by undertaking both physical and psychological strategies. Finally, the situation was appraised to be either a 'good' or a 'bad' recovery. This appraisal was based on considerations of the absence of chest pain, improvement in well-being and energy levels. The

results of this study highlight patients' concerns and support the need for greater emphasis on their psychosocial needs. This care must be provided within the time constraints of short hospital stays. Nurses must also consider providing support to patients in the pre-admission and recover phases. Nurses have the potential to extend their support to the post discharge recovery phase. Participants in the study felt that psychological support was very important. This may be achieved by follow-up calls by nurses, or establishing phone help so that the patient could call and discuss any feelings or concerns. It could also provide an avenue for families to gain access to nursing support.

In another report Higgins et al. (6) provided insight into the same patients' perceptions of their experiences during the admission phase of the angioplasty process. The results indicate that the admission period before the PTCA may be anxiety provoking. Data analysis revealed three major categories: awareness of the problem or situation, coping responses and appraisal of the situation. The patients were described to go through a problem solving process in response to the perceived health threat. Continuing chest pain and fear of the unknown were identified as themes within the first category. Anxiety was reported in relation to fear of the unknown and was experienced also those patients who had earlier experience with angioplasty. Only three participants reported little anxiety.

The coping responses included acquiring knowledge of the angioplasty, confidence in the skill of the doctor, support from family and gearing up psychologically. Doctors were perceived the most important source of information. Some patients were disappointed with the reliance on pamphlets rather than human interaction with nurses. Information from experienced patients who had undergone the angioplasty was perceived valuable. Support from family members was identified important coping mechanism during the whole angioplasty process. Patients' appraisal of their situation and decisions to go ahead with or delay the procedure seemed to be based on the success of the coping responses. Participants' experiences indicate that psychosocial aspects of nursing care are an important component of the care of angioplasty patients and provide information in order to change and advance nursing practises.

Eastwood (7) described the rationale and influences behind the decisions of four male patients to change or not to change their risk factor behaviour three months after a percutaneous transluminal coronary angioplasty/intracoronary stent procedure. Three months period was thought to be long enough to allow patients to either incorporate rehabilitative changes into their lifestyles or to return to pre-procedure behaviour. The data was collected by single semi-structured interview. The participants in the study were English-speaking males who had not previously had cardiac surgery or been involved with a cardiac rehabilitation program.

Of the four participants, only one had implemented a noticeable degree of lifestyle pattern change following the procedure. The results suggested that psychological, social, family-related and work-related issues had impact on decisions concerning possible lifestyle pattern change. Some of the patients viewed that the procedure had fixed their health problem and were unaware of the need to change and maintain new lifestyle patterns in order to prevent future cardiac complications. The short period of hospitalization was also thought to have impact on dismissing the severity of their cardiac condition. Two participants emphasize the value of the family members receiving counselling to improve their understanding about patient's condition. The ability to maintain exercise routines was affected by the nature of the work, work rosters and inflexible work schedules. The benefits regarding working life were increased feelings of self-worth, renewed ability to socialize and the feeling of a return to normality.

Despite the information concerning the benefits of lifestyle change being received during hospitalization there was a reluctance to attend cardiac rehabilitation program activities. Two out of four patients believed that the information they received and their own knowledge base was sufficient to maintain healthy lifestyle. Only one of the four participants took part in structured cardiac rehabilitation. He also showed the greatest awareness of cardiac risk factors and implemented the greater degree of lifestyle pattern change. The nurses, who spend the greatest amount of time with patients during the hospitalization period, are in an important position to provide relevant information concerning healthy lifestyle patterns. Because of the small sample size and the descriptive methodology generalisation of the study results is not possible.

Expert interview: Some people having an implanted stent may have psychological problems due to fear of complications. The fears may slightly vary as the side-effect profiles are slightly different between DES and BMS. After implanting DES the need for antithrombotic prophylaxis is longer.

What kind of physical and emotional support do the patients with DES or BMS need from family or other related people?

Results

No studies were identified in the literature search.

Expert interview:

No difference between DES and BMS. The patients with DES and BMS probably need as much and the same type of help and support from family or other related people.

Working life

What kind of arrangements does the use of DES or BMS require at the workplace?

Results

No studies were identified in the literature search.

Expert interview:

The use of a stent itself does not require reorganization or adjustments at work - the primary disease/s (coronary disorder) and the requirements of the work are the major limiting factors in working capacity. What about differences in side-effects and medication? If stents (DES or BMS) reduce the symptoms of cardiovascular disease (e.g. the grade of angina) an improvement in working capacity can be expected. Thus previous adaptations at workplace may no longer be necessary.

What kind of changes in the working capacity/life can the implementation of DES or BMS mean for the patients?

Results

We identified one study addressing working life after stent installation. Abbas et al. (8) conducted an analysis of the frequency and variables associated with early (after 1 month) and late (after 6 months) return to work after percutaneous coronary intervention for acute myocardial infarction. The patients (n=450) had been randomized in the Stent Primary Angioplasty in Myocardial Infarction trial. The international study compared primary angioplasty with and without stenting with a heparin-coated Palmaz-Schatz stent in patients who had electrocardiographic or angiographic evidence of AMI. This study examines the demographic, clinical, and angiographic characteristics of patients who returned to employment 1 and 6 months after percutaneous coronary intervention for AMI. The frequency and variables associated with return to work at 1 and 6 months were analyzed.

Of 450 patients who were employed before the acute myocardial infarction, 230 (51%) returned to work within 1 month with no increases in in-hospital and 1-or 6-month event rates compared with those who did not return to work. Predictors of early return to work were employment in the United States, no history of smoking, and single-vessel coronary disease. At 6 months, 353 of 435 patients (78%) had returned to work; and predictors of late return to work were employment in the United States and absence of angina.

The study suggests that regional differences play an important role in determining return to work after percutaneous coronary intervention for AMI. Being a US employee was the single most important predictor of early (1 month) and late (6 months) resumption of employment. Early return to work was also determined by the number of narrowed coronary arteries and history of tobacco use but appeared to have no adverse effect on rates of mortality, stroke, or reinfarction at 6 months. By 6 months, >75% of the patients had returned to work and they were less likely to complain on angina. However, even in patients who remained unemployed, symptoms were mild in most of them (only 3.8% had class 3 to 4 angina). In addition, with no difference in clinical events in the previous 6 months, regional and geographic influences seem to supersede functional class and clinical events in determining late return to employment.

The study highlights the importance of regional rather than clinical factors in determining reemployment after percutaneous coronary intervention for AMI. The reason for this is unclear but definitely reflects geographic, ethnic, and regional influences on return to employment after AMI. However, the qualitative analysis of recovery and return process is missing from the study, thus the results give only scarce knowledge of return process.

Expert interview: After BMS there is a higher risk for the need of reoperations, preceded by signs of angina pectoris. DES might thus allow a slightly higher probability of better working capacity. The mortality data shows, however, a slightly higher mortality 2 to 3 years after implanting DES.

Economy of a citizen

What effect can the implementation of DES or BMS have on patients' economy?

Results

No studies were identified in the literature search.

Expert interview:

The patients' costs of implanting a BMS or DES may vary depending on the social security system of the country and cost-sharing policies. The length of hospital stay and sick leave are the same for both stent types. The costs of medication after implementing DES are slightly higher due to longer prophylactic antithrombotic medication. The differences in need of reoperations and complication rate may cause different economic burden favouring the use of DES as compared to other therapeutic alternatives.

Family life

What kind of special arrangements does the use of DES or BMS require at home?

Results

No studies were identified in the literature search.

Expert interview: BMS or DES do not require special rearrangements at home; no difference between the stents.

Social relations

What kind of changes can the use of DES or BMS produce to the patients' social relations?

Results

No studies were identified in the literature search.

Expert interview: No big difference between BMS and DES. The stents allow normal social life. The coronary symptoms decrease similarly after both treatments (DES and BMS). However, after DES the symptoms reoccur slightly later and every tenth DES patient increases their movement capacity more than BMS patients.

Comment

Life-style changes recommended are related to coronary disease regardless of therapeutical approach.

Attitudes and self-conception

What kind of changes can the implementation of DES or BMS produce in the patients' or other peoples's attitudes and patients self-conception?

Results

No studies were identified in the literature search.

Expert interview: As DES are more expensive than BMS, patients receiving BMS might think that they are not "worthy" of receiving DES. In contrast to open heart surgery (scar) the stents are invisible and a person with a stent is not recognized as "heart diseased". It is well known that new and advanced technologies can have a substantial symbolic value. To the extent that the difference between BMS and DES are known to patients, the latter can turn out to have a higher social status than the former. As new technology is sometimes promoted by producers and health care professionals as "advanced methods" and "high-tech", other kinds of technology can come to symbolize "low-tech" or low standard treatment.

Discussion

We evaluated the social aspects of revascularization treatment in patients with coronary disease. A comprehensive literature search identified only eight studies addressing social issues. The identified studies focus on the following four issues: access to health care; support from services, systems and policies; support from health professionals; and working life. No studies were identified on support from family or other related people, working capacity, arrangements needed at workplace or home, patients' economy, social relations, and attitudes and self-perception. However, due to tight time constraints of the project, a few studies that possibly address social aspects could not be retrieved in time. These studies may reveal additional social aspects, and they will be evaluated for inclusion criteria later.

This analysis has some limitations. It is possible, that we have not identified all existing qualitative studies in the search. As these studies often describe local circumstances they have a scarce international interest and are thus usually published only in each country's own language. Locating these studies would require searching national databases and interpretation of the studies would require versatile language skills. Even then the transferability of these studies may be questionable. Another limitation of our analysis is that we did not conduct any quality assessment of the included studies. The study methods were of such variety that no single quality assessment approach could be applied. The study designs and characteristics are described and their limitations are discussed in the data extraction sheets.

The identified eighth studies differed in design, size and patient characteristics: retrospective analysis of case notes (n=712, ischemic heart disease, acute myocardial infarction, angina pectoris) (1), register data (n=408,033, of which 86.6% stent patients) (2), matched case observational survey (n=80, of which 50% balloon/stent patients) (3), randomised controlled trial (n=38, cardiac disease) (4), qualitative study with grounded theory design (n=11, angioplasty patients) (5,6), semi-

structured interview (n=4, PTCA/stent patients) (7), regression analysis of RCT patients (n=470, percutaneous coronary intervention patients) (8).

Our results on coronary patients' access to health care services are based on two studies (1,2). In one British hospital most patients seemed to receive the indicated cardiac intervention, except some older people, who were filtered out already at the investigation stage (1). One American register study (2) revealed rationing of DES (both Cypher and Taxus stents) to certain patients subgroups. Non-white patients and patients without health insurance were less likely to receive DES. Also the use of DES was higher at high-volume hospitals than at low-volume hospitals. These findings may not be transfereble to other settings, as different countries may have different service access limits for the coronary artery patients.

Two studies assessed patients views on support needed from services, systems and policies (3,4). According to the results of an American survey, women are less likely than men to have cardiac rehabilitation discussed and referred by health professionals (3). An Australian randomised controlled trial found that group cognitive behaviour therapy, that provides interaction with peers, may help the cardiac patients to reduce anxiety, depression and hostility compared to no such therapy (4). Three studies were found on patients' support needs from health professionals (5-7). According to an Australian qualitative study on patients' needs after a stenting procedure, more psychological support after hospital stay may be needed e.g. in form of follow-up calls by nurses (5). The same patients experienced that the admission period before the PTCA may be anxiety provoking. Their coping responses included acquiring knowledge of the angioplasty, confidence in the skill of the doctor, support from family and gearing up psychologically (6). Another Australian small study suggested that psychological, social, family-related and work-related issues have impact on the patients' decisions concerning possible lifestyle pattern change (7). Thus, there are some findings of various patient needs before and after the hospital stay. However, no studies exist on how these needs could be met in these patients, except the only cognitive behaviour therapy intervention study.

One study was classified to the issues of working life (8). This American study reveals that regional rather than clinical factors determine reemployment after percutaneous coronary intervention for AMI. The reason remains unclear, but results reflect geographic, ethnic, and regional influences on return to employment after AMI. These environmental factors may be caused from formal or informal structures, services or systems in the community or society. No studies were found on what kind of services related to the work environment e.g. on the arrangements needed for working place to help the patients' reemployment after the revascularization.

None of the studies were made according to the translational model, i.e. analyzed and evaluated the actual use processes of the technology in question where different resources needed are mobilized and that may produce further changes in the different life spheres of the patients. Thus, this analysis tells a little of the patients' life when returning home from hospital after a revascularization treatment. Future research may provide more information on the patients' resource needs before and after the hospital stay, as well as on the consequences of use of stents to patients' family life, social relations, attitudes and self-conception.

In conclusion, the included studies highlight some Australian, British and American patients' needs with coronary artery disease. Based on this literature review we have no information on what kind of community activities, or services would be needed and no information of informal social networks, attitudes and ideologies of the patients. Disability after a revascularization procedure at

hospital can be characterized as a complex relationship between an individual's health condition, personal and environmental factors. Different sociomaterial networks may mould the same individual with a coronary artery disease very differently. The local sociomaterial conditions hinder patients' performance either by creating barriers, or it does not provide facilitators. Future studies should focus on patients' needs in different settings and evaluate what kind of services could be helpful to meet these needs.

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Assessment elements table

Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research question(s) in the context of DES	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
Social aspects	Access to health care	What kind of changes can the implementation of the technology produce in the access to health care?	Yes	What kind of changes can the implementation of DES or BMS produce in the access to health care?	3	2
Social aspects	Support	What kind of services, systems and policies should be organized to support the use of the technology after the hospital stay?	Yes	What kind of services, systems and policies do the patients with DES or BMS need after the hospital stay?	2	1
Social aspects	Support	What kind of support is needed from the health professionals when using the technology or as a consequence of using the technology?	Yes	What kinds of support do the patients with DES or BMS need from the health professionals after the hospital stay?	2	2
Social aspects	Support	What kind of physical and emotional support for the use of technology is needed from family or other related people?	Yes	What kind of physical and emotional support do the patients with DES or BMS need from family or other related people?	2	2
Social aspects	Working life	What kind of arrangements does the implementation of the technology require at the workplace?	No	What kind of arrangements does the use of DES or BMS require at the workplace?	2	2
Social aspects	Working life	What kind of changes can the implementation of the technology mean in the working capacity/life of a person?	Yes	What kind of changes in the working capacity/life can the implementation of DES or BMS mean for the patients?	3	2
Social aspects	Economy of a citizen	What effect can the implementation of the technology have on patients' economy?	Yes	What effect can the implementation of DES or BMS have on patients' economy?	2	1
Social aspects	Family life	What kind of special arrangements does the use of the technology require at home?	Yes	What kind of special arrangements does the use of DES or BMS require at home?	2	2
Social aspects	Social relations	What kind of changes can the use of the technology produce to patient's social relations?	Yes	What kind of changes can the use of DES or BMS produce to the patients' social relations?	2	2
Social aspects	Attitudes and self-conception	What kind of changes can the implementation of the technology produce in patients' or other people's attitudes and patients self-conception?	Yes	What kind of changes can the implementation of DES or BMS produce in patients and other peoples's attitudes and patients' self-conception?	2	2

Appendix B: Search strategies

Database	Search strategy
CINAHL	<ol style="list-style-type: none"> 1 exp Stents/ (1888) 2 stent\$.tw. (1695) 3 1 or 2 (2226) 4 exp coronary disease/ or exp myocardial infarction/ (18068) 5 exp angioplasty, transluminal, percutaneous coronary/ or exp coronary artery bypass/ (4514) 6 (coronar\$ or angioplasty or stenosis or restenosis).mp. or (heart\$ or cardiol\$ or myocardia\$ or cardiac).ti. (41559) 7 4 or 5 or 6 (44791) 8 3 and 7 (1506) 9 exp social attitudes/ or exp "economic and social security"/ or exp social environment/ or exp social work/ or exp social change/ or exp social class/ or exp sociological theory/ or exp social values/ or exp social welfare/ (33200) 10 (social\$ or socio\$ or societal or communit\$).tw. (92674) 11 9 or 10 (115703) 12 8 and 11 (7) 13 exp HEALTH SERVICES ACCESSIBILITY/ (15023) 14 access\$.mp. [mp=title, subject heading word, abstract, instrumentation] (37246) 15 exp HEALTH RESOURCE UTILIZATION/ (4057) 16 Patient Selection/ (3874) 17 candidate\$.tw. (2826) 18 resource\$.tw. (25404) 19 13 or 14 or 15 or 16 or 17 or 18 (68248) 20 (equit\$ or unequit\$ or allocat\$ or reallocat\$ or gender).mp. [mp=title, subject heading word, abstract, instrumentation] (24227) 21 *age factors/ or minority groups/ or race factors/ or sex factors/ (32991) 22 20 or 21 (50203) 23 19 and 22 (7009) 24 8 and 23 (5) 25 exp professional-client relations/ or exp professional-family relations/ or exp family relations/ or exp patient-family relations/ (20368) 26 ((famil\$ or patient\$ or nurse\$ or physician\$ or staff or personal) adj2 relation\$).mp. [mp=title, subject heading word, abstract, instrumentation] (49646) 27 25 or 26 (58131) 28 8 and 27 (1) 29 Job Re-Entry/ (1903) 30 ((return\$ or capacit\$ or abilit\$) adj2 (work\$ or job? or profession)).mp. [mp=title, subject heading word, abstract, instrumentation] (2315) 31 29 or 30 (3517) 32 8 and 31 (1) 33 patient attitude.mp. [mp=title, subject heading word, abstract, instrumentation] (6654) 34 ((experienc\$ or belief\$ or expect\$ or perception\$) adj2 patient\$).mp. [mp=title, subject heading word, abstract, instrumentation] (9773) 35 (experienc\$ adj2 (thrombo\$ or restenosis)).mp. [mp=title, subject heading word, abstract, instrumentation] (27) 36 34 not 35 (9765) 37 33 or 36 (15603) 38 8 and 37 (14) 39 Coping/ (9296) 40 exp self concept/ or self-efficacy/ (11196) 41 (cope or coping or self concept or self efficacy or empowerment).mp. [mp=title, subject heading word, abstract, instrumentation] (30549) 42 39 or 40 or 41 (31934) 43 8 and 42 (3) 44 SOCIAL ADJUSTMENT/ or (workplace adj 2 adjustment\$).mp. (971) 45 8 and 44 (0) 46 12 or 24 or 28 or 32 or 38 or 43 or 45 (27) 47 from 46 keep 1-27 (27)
Cochrane	<p>#1 (coronary disease):ti,ab,kw and (stents):ti,ab,kw 635</p> <p>#2 (patient experiences):ti,ab,kw or (patient selection):ti,ab,kw or (social support):ti,ab,kw or (interpersonal relations):ti,ab,kw or (workplace adjustments):ti,ab,kw or (empowerment):ti,ab,kw 23851 #3 (#1 AND #2) 36</p>
Medline	<ol style="list-style-type: none"> 1 Stents/ (26118) 2 stent\$.ab.ti. (29887) 3 1 or 2 (34891) 4 exp Coronary Stenosis/ or exp Angioplasty, Transluminal, Percutaneous Coronary/ or exp Coronary Disease/ or exp Coronary Artery Bypass/ (186544) 5 exp Myocardial Infarction/ (111880) 6 (coronar\$ or angioplasty).ab.ti. (211835) 7 (heart\$ or cardiac or cardiol\$ or myocardia\$).ab.ti. (718999) 8 4 or 5 or 6 or 7 (853983)

	<p>9 3 and 8 (15988)</p> <p>10 exp Social Welfare/ or exp Social Work/ or exp Social Security/ or Social Support/ (93021)</p> <p>11 (social or socio\$ or societal\$.ab,ti. (215374)</p> <p>12 10 or 11 (282195)</p> <p>13 9 and 12 (40)</p> <p>14 Health Services Accessibility/ (27386)</p> <p>15 access\$.ab,ti. (145576)</p> <p>16 Health Resources/ or Health Priorities/ (11803)</p> <p>17 Patient Selection/ (26984)</p> <p>18 candidate\$.ab,ti. (76822)</p> <p>19 resource\$.ab,ti. (75268)</p> <p>20 14 or 15 or 16 or 17 or 18 or 19 (336355)</p> <p>21 (equit\$ or unequit\$ or allocat\$ or reallocat\$ or gender).ab,ti. (117814)</p> <p>22 *Age Factors/ (3186)</p> <p>23 exp Minority Groups/ or exp Ethnic Groups/ (75436)</p> <p>24 Sex Factors/ (152559)</p> <p>25 22 or 23 or 24 (223581)</p> <p>26 20 and 25 (9593)</p> <p>27 9 and 26 (10)</p> <p>28 professional-family relations/ or exp professional-patient relations/ (93061)</p> <p>29 exp Family Relations/ (48913)</p> <p>30 ((famil\$ or patient\$ or nurse\$ or doctor\$ or physician\$ or staff\$ or personnel) adj2 relation\$.ab,ti. (17422)</p> <p>31 28 or 29 or 30 (149955)</p> <p>32 9 and 31 (14)</p> <p>33 Work Capacity Evaluation/ or Work Simplification/ (4543)</p> <p>34 (work\$ or job\$ or profession).ab,ti. (508620)</p> <p>35 (return\$ or capacit\$ or facilit\$ or abilit\$.ab,ti. (840710)</p> <p>36 34 and 35 (65568)</p> <p>37 Workload/ (8784)</p> <p>38 Rehabilitation, Vocational/ (7105)</p> <p>39 37 or 38 (15856)</p> <p>40 33 or 36 or 39 (82198)</p> <p>41 9 and 40 (32)</p> <p>42 *Attitude to Health/ (24573)</p> <p>43 (patient\$ adj2 (attitude\$ or belie\$ or expect\$ or percept\$ or perceiv\$ or experience\$)).ab,ti. (43727)</p> <p>44 (experience\$ adj2 (restenosis or thrombo\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (515)</p> <p>45 43 not 44 (43608)</p> <p>46 42 or 45 (66615)</p> <p>47 9 and 46 (196)</p> <p>48 adaptation, psychological/ or orientation/ (66167)</p> <p>49 self concept/ or self efficacy/ (34520)</p> <p>50 (cope or coping or self concept or self efficacy or empowerment).ab,ti. (36100)</p> <p>51 48 or 49 or 50 (115616)</p> <p>52 9 and 51 (6)</p> <p>53 Social Adjustment/ (17084)</p> <p>54 9 and 53 (0)</p> <p>55 13 or 27 or 32 or 41 or 47 or 52 (290)</p>
Medic/Helecon	stent*
ASSIA/CSA Illumina	stent* in keywords
ERIC/CSA Illumina	stent* in keywords
Sociological Abstracts/CSA Illumina	stent* in keywords
Social Services Abstracts/CSA Illumina	stent* in keywords
Social Care Online/ SCIE	stent* in free text
PsyclNFO/EBSCOHost	stent* in Keywords not (stent in Author field or stentor in Keywords)
Academic Search Elite/EBSCOHost	(stents in subject terms) and (coronary* or arterial* or heart* or cardiol* or myocard*) and (economic* or financ* or cost* or resource*)
Academic Search Elite/EBSCOHost	(stents in subject terms) and (coronary* or arterial* or heart* or cardiol* or myocard*) and (access* or patient selection or candidate*)
Academic Search Elite/EBSCOHost	(stents in subject terms) and (coronary* or arterial* or heart* or cardiol* or myocard*) and (work* or occupation or capacity*)
Academic Search Elite/EBSCOHost	(stents in subject terms) and (coronary* or arterial* or heart* or cardiol* or myocard*) and (support* or aid* or auxiliar or help* or guidance*)
Academic Search Elite/EBSCOHost	(stents in default fields) and (coronary* or arterial* or heart* or cardiol* or myocard*) and (socio* or social*)
SocINDEX with Full Text/EBSCOHost	stent* in default fields
Sage Premier/Sage Publications	(stent or stents or stenting) in keywords
SpringerLink/Springer	(stent or stents or stenting) in summary

Publishing	
Blackwell Synergy/Blackwell Publishing	(drug-eluting stent and bare-metal stent) in all fields
Science Direct/Elsevier	"drug-eluting stent" and "bare-metal stent" and (socio or social)
Science Direct/Elsevier	"drug-eluting stent" and "bare-metal stent" and not (socio or social)

Appendix C: Excluded studies (n=24)

Database	Year	First author	Title	Reason for exclusion
PsycInfo via EBSCOHost	2006	Peterson, JC	Living with heart disease after angioplasty. Dissertation Abstracts International: Section B: The Sciences and Engineering 66(10-B):5671, 2006	Full text not obtained
PsycInfo via EBSCOHost	2002	Larney, L	Do depression, anxiety, hostility, coping style and dispositional outlook predict adherence to prescribed rehabilitation program and recovery outcomes for cardiac rehabilitation outpatients? Dissertation Abstracts International: Section B: The Sciences and Engineering 62(7-B):3382, 2002	Full text not obtained
PsycInfo via EBSCOHost	2000	Deaner, SL	Depressive symptoms and problem solving as predictors of adherence to the cardiac medical regimen. Dissertation Abstracts International: Section B: The Sciences and Engineering 60(8-B):4214, 2000	Full text not obtained
Ovid MEDLINE(R)	2005	Korzeniowska-Kubacka, I	Cardiological rehabilitation -- a chance of returning to work (Review) [Polish]. Medyzyna Pracy 56(4):325-7, 2005	Full text not obtained
Ovid MEDLINE(R)	2002	de la Rosa, A	Nurses' participation in heart rehabilitation (review) [Spanish]. Archivos de Cardiologia de Mexico 72 Suppl 1:S247-53, 2002	Full text not obtained
ERIC via CSA Illumina	2004	Cujec, B	The effect of age upon care and outcomes in patients hospitalized for congestive heart failure in Alberta. Canadian Journal on Aging 23(3):255-267, 2004	Full text not obtained
EBSCOHost Academic Search Elite	2006	Floyd, KC	Age-based differences of percutaneous coronary intervention in the drug-eluting stent era. J Int Cardiol 19(5):381-387, 2006	Full text not obtained
SocINDEX with Full Text	1999	Charlson, ME	Improving health behaviour & outcomes after angioplasty (project (RCT), Medicine Weill Medical College of Cornell University, New York, US).	Full text not obtained
PsycInfo via EBSCOHost	2006	Pedersen, SS	Anxiety enhances the detrimental effect of depressive symptoms on health status following percutaneous coronary intervention. J Psychosomatic Research 61(6):783-789, 2006	Examines whether anxiety has incremental value to depressive symptoms in predicting health status in patients undergoing PCI
PsycInfo via EBSCOHost	2006	Pedersen, SS	Risk factors for impaired health status differ in women and men treated with percutaneous coronary intervention in the drug-eluting stent era. J Psychosomatic Research 61(1):11-17, 2006	Compares women's and men's health status 6 and 12 months post-PCI
PsycInfo via EBSCOHost	2006	Trummer, UF	Does physician-patient communication that aims at empowering patients improve clinical outcome? A case study. Patient Education & Counselling 61(2):299-306, 2006	Organizational domain, staff training and reorganization of communication
PsycInfo via EBSCOHost	2000	Ladwig, K-H	Gender differences in emotional disability and negative health perception in cardiac patients 6 months after stent implantation. Journal of Psychosomatic Research 48(4-5):501-8, 2000	Effectiveness -domain
PsycInfo via EBSCOHost	2005	Lehrner, J	Neuropsychosocial outcome 6 months after unilateral carotid stenting. Journal of Clinical and Experimental neuropsychology 27(7):859-866, 2005	Examines neuropsychological outcomes after stenting, effectiveness domain
PsycInfo via EBSCOHost	2003	Sirois, BC	Biomedical and psychological predictors of anginal frequency in patients following angioplasty with and without coronary stenting. Journal of Behavioral Medicine 26(6):535-551, 2003.	Examines the contribution of biomedical and psychological variables in the report of anginal frequency at 6-week and 12 - month follow-up in patients who received angioplasty with or without stent
Ovid MEDLINE(R)	2006	Denollet, J	Social inhibition modulates the effect of negative emotions on cardiac prognosis following percutaneous coronary intervention in the drug-eluting stent era. Eur Heart J 27(2):171-7, 2006	Examines whether social inhibition (inhibited self-expression in social interaction) modulates the effect of negative emotions in clinical outcome following PCI
Ovid MEDLINE ®	1999	Eeckhout, E	Indications for intracoronary stent placement: the European view. Working Group on Coronary Circulation of the European Society of Gardiology. Eur Heart J 20(14):1014-9, 1999	Analyses indications for stent placement, clinical, no social dimension
Ovid MEDLINE ®	1995	Rothlisberger, C	Coronary interventions in Europe 1992. The working group on coronary circulation of the European Society of Cardiology. Eur Heart J 16(7):922-9, 1995	Organizational domain, studies the amount etc. of coronary interventions in European countries
ASSIA/CSA Illumina	2006	Grilli, R	Managing the introduction of expensive medical procedures:	Organizational issue

			use of a registry. <i>Journal of Health Services Research & Policy</i> 11(2):89-93, 2006	
ERIC via CSA Illumina	2005	Straube, BM	How changes in the Medicare coverage process have facilitated the spread of new technologies. <i>Health Affairs</i> 24(1): 5314-5316, 2005	Organizational issue
SocINDEX with Full Text	2000	Mehilli, J	Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. <i>JAMA</i> 284(14):1799-1806, 2000	Examines whether there are sex-based differences in prognostic factors and in early and late outcomes among CAD patients undergoing coronary stent placement
SocINDEX with Full Text	2006	Hashimoto, H	The diffusion of medical technology, local conditions, and technology re-intervention: a comparative case study on coronary stenting. <i>Health Policy</i> 79(2-3):221-230, 2006	Examines the diffusion/implementation of medical technology; organizational domain
CINAHL	2006	Shim, JK	Risk, life extension and the pursuit of medical possibility. <i>Sociol Health Illn</i> 28(4):479-502, 2006	Focus is not on the CM issues
Cochrane	1999	Stables RH	Design of the 'Stent or Surgery' trial (SoS): a randomized controlled trial to compare coronary artery bypass grafting with percutaneous transluminal coronary angioplasty and primary stent implantation in patients with multi-vessel coronary artery disease	Effectiveness domain, trial design presentation
Cochrane	2007	Dawn, AJ	Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents	Clinical effectiveness, gender differences

Appendix D: Characteristics of the included studies (n=8)

First author, year	Bond M et al. (2003)
Issue	Access to health care:
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Objectives: To analyse equity in access by age group to procedures with documented benefits in all age groups: exercise testing, coronary angiography, revascularisation (percutaneous transluminal coronary angioplasty/stent insertion and coronary artery bypass graft surgery) and receipt of thrombolysis, where indicated</p> <p>Country: Great Britain</p> <p>Site: A district hospital in the eastern part of outer London. Primarily responsible for the provision of district hospital services for over 700 000 people.</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Study type and design: An observational study based on a case note analysis of a 12-month census of all inpatients (elective and emergency, survivors and deceased) with a cardiac ICD-10 code (120-25) recorded on the patient administration system (PAS) covering ischaemic heart disease, acute myocardial infarction or angina pectoris (n=447), and a sample of 265 cardiac outpatient attenders (new episodes who attended in date order as recorded on the PAS), attending cardiology clinics (out of the total of 1304 outpatients)</p> <p>Study date and duration: From 1 April 1996 to 31 March 1998, 24 months</p> <p>Sampling/recruitment: Patients were eligible for inclusion in the study if they were admitted or first attended (new episodes) the study hospital between 1 April 1996 and 31 March 1997</p> <p>Methods of data collection:</p> <ul style="list-style-type: none"> - the notes of the outpatient sample were hand-searched from hospital case notes, the total number of case notes included in the study was 712 - the data included: specialty, date of birth, sex, symptoms, diagnoses, results of all recorded tests and investigations, interventions, severity and pattern of disease, co-morbidity, indications for and contraindications to investigations/treatment - repeat tracings of eligible case notes were conducted over 12-month period <p>Analysis methods: Retrospective case note analysis, tracking each case backwards and forwards by 12 months from the patient's date of entry to the study</p> <p>Bivariate analyses included χ^2-tests for trends. Interactions between potentially predictive variables were tested using logistic regression analysis (odds ratios). Age and gender were entered as independent variables in the models on the grounds of theoretical significance. The data for inpatients and outpatients were analysed separately, but as the results were similar they are presented together.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	<p>Gender: Males: 55 % of the study patients, (n=388), Females: 45 % of the study patients, (n=324)</p> <p>Age:</p> <ul style="list-style-type: none"> - 48 % (n=342) under 65 years - 31 % (n=217) between 65 and 75 years - 10 % (n=74) between 75-80 years - 11 % (n=79) 80+ years <p>Thirty-seven per cent (n=265) of all study patients entered through cardiology outpatients, the remaining 635 (n=447) were elective (n=107) or emergency (n=340) admissions. Sixty-two per cent of cases (n=443) had a primary diagnosis of ischaemic heart disease and 38% (n=269) had a primary diagnosis of AMI</p>
Features the studied intervention (when applicable)	NA
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Outcome measures:</p> <ul style="list-style-type: none"> - whether the patient received the targeted interventions when indicated (based on tight internationally approved criteria for intervention, and taking into consideration documented contraindications) <p>Details of findings:</p> <p>Analysis of 712 case notes showed that older hospital patients with ischemic heart disease, and with indication for further investigation, were less likely than younger people to be referred for exercise tolerance tests and cardiac catheterisation and angiography. This was independent of both gender and severity of condition. Older patients did not appear to be discriminated against in relation to receipt of indicated treatments (revascularisation or thrombolysis), although, in the case of revascularisation, older patients were more likely to have been filtered out at the investigation stage (catheterisation and angiography), so selection bias partly explains this finding.</p> <p>Author's conclusions:</p> <p>The current findings from a single hospital are comparable with the results from a broader study of equity to access by age to cardiological interventions in another district hospital in the same region. It appears that age per se causes older cardiac hospital patients to be treated differently.</p> <p>The rates of indicated interventions were relatively low for all age groups, with older patients' rates of intervention the lowest of all.</p>
Reviewers' comments: e.g. remarks of quality issues	<p>Limitations of the study:</p> <ul style="list-style-type: none"> - the possibility that there may have been some underestimation of the denominator population: it is not known how many patients with cardiac problems were not given a cardiac ICD code on death or discharge and were thus not selected for study - this investigation was limited to hospital patients, who represent a relatively small proportion of patients with ischemic heart disease.

Publication details: First author, year	Rao SV et al. (2006)
Issue	<p>Access to health care:</p> <ul style="list-style-type: none"> - limited availability of the stents due to uneven distribution across the country - high cost of DES when compared with BMS - hospital-level characteristics (significantly lower proportion of nonteaching hospitals, low- and medium-volume hospitals, rural hospitals, government hospitals) <p>Patient group selection:</p> <ul style="list-style-type: none"> - technology diffusion as it relates to innovative medical devices; initial underuse in certain patient groups - black patients less likely to receive DES in 2003 (demographic characteristics) - significantly lower proportion of male patients (demographic characteristics) - lower proportion of patients older than 70 years (demographic characteristics) - lower proportion of patients without insurance (socioeconomic characteristics)
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Objective: To determine patterns and outcomes of drug-eluting stents (DES) use in clinical practice (= to examine the use of DES in clinical practice)</p> <p>Country: USA</p> <p>Site: - Multicenter data, PCI procedures at 383 sites</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Study type and design:</p> <ul style="list-style-type: none"> - data from the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) - the initial part of the study examined the use of the Cypher stent (the first phase was the period between the second quarter of 2003 when the Cypher became available and the end of 2003) - in March 2004 the Taxus stent became available and the later part of the study examined the use of either stent (the second phase was the period between the first quarter of 2004 and the fourth quarter of 2004) <p>Date and duration: from April 2003 to December 2004</p> <p>Sampling/recruitment: 408,033 percutaneous coronary intervention (PCI) procedures. Of those, 353,242 procedures (86.6%) involved stent placement.</p> <p>Methods of data collection: - data from the registry</p> <p>Used research tools:</p> <ul style="list-style-type: none"> - categorical variables were compared with the χ^2 test - continuous variables were compared with the nonparametric Kruskal-Wallis test - predictors of DES use were determined by using multivariate logistic regression. Candidate variables: patient level variables, e.g. demographics and medical history, hospital level variables, e.g. PCI volume and teaching affiliation, clinical characteristics, e.g. presence of shock, prior coronary artery bypass surgery (CABG) and acute myocardial infarction (MI) <p>Analysis methods:</p> <ul style="list-style-type: none"> - first the proportion of procedures that involved placement of a BMS, a DES, or both were determined - the proportion of procedures that involved the placement of at least 1 DES during each quarter after the market availability of DES were determined - second the comparison of baseline characteristics between the patients who received only a BMS with those who received at least 1 DES - predictors of DES use were determined <p>To determine the impact of introduction of the Taxus stent on patterns of DES use, the analysis was repeated after dividing the study period into 2 phases.</p> <p>Multivariate predictors of DES use were determined separately for each phase to see if patient, clinical, or hospital characteristics associated with DES use changed after availability of the Taxus stent.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	<p>Gender: males, females</p> <p>Age: from <50 y to >70 y</p> <p>Ethnicity: white, nonwhite</p> <p>Types of practitioners, policy makers or patients: subgroup: patients with diabetes mellitus</p>
Features the studied intervention (when applicable)	NA
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Outcome measures:</p> <p>The primary outcomes considered were</p> <ul style="list-style-type: none"> - the occurrence of in-hospital mortality - adjusted in-hospital mortality (expressed as observed mortality/expected mortality multiplied by the overall mortality rate) - postprocedure MI - unplanned coronary artery bypass grafting - procedural success <p>Details of findings:</p>

	<p>Adoption of DES</p> <ul style="list-style-type: none"> - placement of only a BMS in 127,973 procedures (31.4%) - placement of only a DES in 207,733 procedures (50.7%) - use of both BMS and DES in 18,536 procedures (4.5%) <p>Therefore 225,269 procedures (55.2%) involved the placement of at least 1 DES. The rate of DES use over the study period increased from 19.7% of cases in the second quarter of 2003 to 78.2% of cases in the fourth quarter of 2004.</p> <p>Once available, the use of Taxus stent was higher than that of the Cypher stent throughout the study period.</p> <p>Patient and hospital characteristics by stent type</p> <ul style="list-style-type: none"> - significant differences between procedures during which at least 1 DES was used (n = 225,269) compared with procedures where a DES was not used (n = 127,973) - a significantly lower proportion of male patients (?), patients older than 70 years and patients without insurance represented in the DES procedures - a significantly lower proportion of nonteaching hospitals, low- and medium-volume hospitals, rural hospitals, and government hospitals using DES <p>Predictors of DES use</p> <ul style="list-style-type: none"> - there was a progressive decrease in the odds of DES use as age increased - white race, female sex (?), presence of insurance, diabetes mellitus, PCI of de novo lesion, PCI at a suburban hospital and PCI at a high volume center were significant predictors of DES use. To determine if the differences persisted after the introduction of the Taxus stent, the analysis was repeated after dividing the study period into 2 phases: before and after the availability of the Taxus stent. The same patient, clinical, and hospital characteristics listed above were associated with DES use in both phases. The adjusted odds ratios and 95% confidence intervals were nearly identical in both phases. <p>Outcomes</p> <ul style="list-style-type: none"> - procedural outcomes (procedural success, unplanned CABG, postprocedure MI) and in-hospital mortality were excellent regardless of the stent type - outcomes with either DES platform were slightly better than those with BMS <p>Limitations</p> <ul style="list-style-type: none"> - lack of the detailed angiographic data that could have influenced the choice of stent used - the researchers did not compare restenosis rates or subacute thrombosis rates among patients who did and did not receive DES - the analyses were observational, and the trends identified could be influenced by unmeasured patient, angiographic, or hospital level characteristics <p>Author's conclusions:</p> <p>The analysis of a large multicenter PCI data demonstrates that there was rationing of DES to certain patient subgroups. In particular, nonwhite patients and patients without health insurance appear to be much less likely to receive DES. DES use was higher at high-volume hospitals. These patterns persisted even after the commercial introduction of a second DES product.</p>
Reviewers' comments: e.g. remarks of quality issues	In the results concerning patient characteristics the authors state there were a significantly lower proportion of male patients represented in the DES procedures. The authors' also state female sex was one of the significant predictors of DES use. However, in table 1, the numbers (percentages) regarding patient level characteristics show higher proportion of male patients in both BMS and DES groups.

First author, year	Caulin-Glaser T et al. (2001)
Issue	Support : services, systems and policies needed after hospital stay
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Objectives:</p> <p>The main objectives of the study were to assess whether gender differences exist for in-hospital secondary prevention instruction and physician referral to cardiac rehabilitation after coronary revascularization procedure in patients with cardiovascular disease controlling for age and cardiac procedure.</p> <p>Country, site:</p> <p>Yale New Haven Hospital during 1997 and 1998.</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Design:</p> <p>A matched case, observational survey design was used to assess the referral for phase II outpatient cardiac rehabilitation based on gender at the hospital and/or follow-up physician visit after a cardiac revascularization procedure.</p> <p>Sample:</p> <p>Study subjects consisted of 80 patients (40 men, 40 women) who had been revascularized (balloon angioplasty, coronary stenting, and CABG). No patient had previously undergone a revascularization procedure. Fifty percent of the patients had undergone revascularization by balloon angioplasty/stent, 50 percent had undergone coronary bypass strategy. The patients were 45 years old or older and English speaking. Respondents completed a survey addressing information and referral to cardiac rehabilitation during their hospitalization and at the follow-up physician office visit. Respondents were geographically distributed throughout New Haven County; based on the address zip codes, it was determined that a CR program was within reasonable distance to</p>

	<p>all participants in the study. In the population, 87% of the men and 95% of the women were Caucasian; African Americans comprised the remainder of the group.</p> <p>Data analysis: Descriptive statistics were utilized to summarize data obtained from chart reviews. In order to control for the matching criteria, the Extended Mantel-Haenszel procedure was employed.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	See above.
Features the studied intervention (when applicable)	NA
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Patient questionnaires were employed to evaluate teaching of patients on secondary prevention and the referral patterns of patients to CR. CR instruction included indication for referral program components (such as education, exercise, and behaviour/life-style modification, written literature and the names of the local programs. Subjects were asked if they received any information (written or verbal) about secondary prevention of cardiovascular disease and CR while hospitalized and/or at the follow-up physician visit. Questions addressed information provided by medical personnel, including nurses, CR representatives, medical house staff, cardiology fellows, and attending physicians. The subjects were also asked about potential factors which would have influenced their decision to participate; these factors included (1) written information on CR, (2) physician/healthcare provider encouragement to participate, (3) family and/or friend encouragement to participate, and (4) insurance coverage. In addition, factors which may have influenced referral patterns include hypertension, diabetes mellitus, and prolonged hospitalization after cardiac procedure due to medical or surgical complications were examined.</p> <p>Results: Women were less likely to be instructed on secondary prevention strategies and CR or referral to CR compared to men despite being matched for age and undergoing the same procedure. The data demonstrate a gender difference in hospital teaching and referral information for CR after revascularization.</p> <p>Conclusion: The instruction of patients concerning secondary prevention and CR postrevascularization procedure is poor. Within that group, women were far less likely to have CR discussed or referrals made by healthcare professionals. This study demonstrates the need for education initiatives of all healthcare providers on the comprehensive nature and benefits of CR in the secondary prevention of cardiovascular disease, with a particular emphasis on women.</p>
Reviewers' comments: e.g. remarks of quality issues	In the boundary of organizational and social domains.

First author, year	Edelman S et al. (2003)
Issue	Support: : services, systems and policies needed after hospital stay
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Aims/objectives: - the study reports a qualitative analysis on the feedback provided by cardiac disease patients who attended a group CBT program as part of an ongoing study examining psychological and health outcomes of the intervention; associations between patients' qualitative evaluations and changes in scores on anxiety, depression, and hostility are also reported</p> <p>Country: - Australia, Sydney.</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Study type, recruitment, methods: - participants were randomized to either a group CBT intervention or a "standard care" control group - in order to reduce the interval between recruitment and intervention, additional patients who met all eligibility criteria, except that they had had previous cardiac surgery, were invited to participate as "fillers". 38 patients had completed the program, of whom 13 were randomized to the intervention and 25 were fillers. - anxiety and depression were measured using the Hospital Anxiety and Depression Scale; hostility was measured using the Hostility Scale - the program evaluation included six items; the first three were five-point Likert scale items asking the degree to which participants had enjoyed the program and found it helpful, and how well the leader had facilitated the group; the next three items were open-ended, asking participants to describe any specific benefits that they experienced as a result of doing the program, any aspects of the program that they had particularly liked or found helpful, and any aspects of the program that they did not like or ways in which the program could be improved - Relationships between measured variables and evaluations were tested using repeated measures ANOVA analyses.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	Eligible participants were males who had undergone stent surgery (mechanical expansion of a partially blocked cardiac artery) at one of the two major hospitals in Sydney.
Features the studied intervention (when applicable): aim of the intervention, intervention process (description of how was the intervention/service delivered)	<p>Participants attended eight weekly group sessions, with 6 to 10 patients per group. The groups were led by a clinical psychologist. A participants' manual was provided, with supplementary handouts being added each session. The first tour of each session involved a discussion of homework. Participants were asked to record any stressful situations that occurred during each week and to identify their accompanying thoughts, feelings, and beliefs. Subsequently, they learned how to identify and reframe maladaptive cognitions, and they were asked to write down "disputing statements" and "positive actions" as part of their homework. In the second half of each session, the group leader provided a didactic presentation (10-15 minutes) on the week's topic. This was followed by exercises and discussion aimed at encouraging participants to learn and apply the skills being taught. The theoretical component of each session included training in the principles of Cognitive Behaviour Therapy and</p>

	information on particular topics. Weekly topics included an introduction to CBT, managing anxiety, depression and anger, effective communication, relationships, life-style, and goal-setting.
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Items 1 to 3, Program assessment:</p> <ul style="list-style-type: none"> - evaluation of the program was mostly positive; mean scores (out of 5) on the questions "How much did you enjoy the program?", how helpful did you find the program?", and "How well did the leader facilitate the group?" were 4.73, 4.45, and 4.79 respectively. Ninety-six percent of the responses were above the indifference point (of 3). <p>Item 4: Specific benefits experienced from doing the program:</p> <ul style="list-style-type: none"> - the classification frequency for the category "Learning new skills" was 62% (based on weighted percentage of responses), for "Change in thinking" 22%, for "Disclose/share 18%, for "Improved function" 15%, and for "Feel better" 15%. The less frequent categorization was "Reduced anxiety/depression 6%. <p>Item 5: Positive aspects of the program:</p> <ul style="list-style-type: none"> - the most frequently nominated category was "Disclose/share" which was cited in 44% of evaluations, "Program contents" in 19%, "Useful information" in 12,5%, "Thought provoking" in 12,5% "Social interaction" in 10%, and "Method of delivery" in 6%. - pre/post changes were evident for anxiety, hostility, but not for depression; these changes cannot be interpreted as due to the intervention on the basis of the participant sample alone. - an interesting finding was the value that participants placed upon interacting with other patients who had similar experiences with cardiac disease. This was the aspect of the program that most participants enjoyed. It was also nominated frequently as a perceived benefit of the program. This finding suggests that while the content of a structured group CBT program is often perceived as beneficial, the social environment in which it is delivered may be the most highly valued aspect of the intervention.
Reviewers' comments: e.g. remarks of quality issues	

First author, year	Higgins M et al. (2000)
Issue	Support from the health professionals
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Objectives: Coronary angioplasty and stent placement is associated with short hospital days. Patients are expected to recover at home, alone, following limited care time with nurses. The purpose of this study was to describe participants' perceptions of recovery after angioplasty.</p> <p>Country: Australia Theory: qualitative techniques of grounded theory (see above).</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Study design: The study used a grounded theory design. Data were gathered from semi-structured, taped interviews designed to explore the recovery experiences of coronary angioplasty patients. The purpose of the grounded theory is to understand the concerns, actions and behaviours of a group of individuals and, through their own language, explain those patterns of behaviour at a higher level of abstraction or theory. In-depth interviewing is an appropriate method to gain access to the individual's language and interpretations of social reality.</p> <p>Data collection: The semi-structured interviews allowed the researcher to clarify issues and gain further explanations and information during each interview. In this way, data saturation could be achieved. The interviews were taped and transcribed verbatim, therefore enhancing accuracy and validity of the interview data. The researcher verified each tape recording against the transcript to ensure it was an accurate record of the interview. All participants were assigned a code number and pseudonyms in order to preserve anonymity.</p> <p>Data analysis: The constant comparative method was utilized during the concurrent data collection and analysis to identify and develop recurrent themes and ideas. The aim was to generate theoretical constructs that, along with codes, categories and their properties, formed a theory that encompassed as much behavioural variation as possible. By constantly comparing codes and categories, the researcher identified patterns, similarities and differences. Comparing for similarities enabled the basic properties of a category to be defined, while differences enabled boundaries and relationships between categories to be clarified. These categories were further broken down, conceptualized and put back together in new ways through grounded theory techniques including open and axial coding procedures and memoing.</p> <p>The outcomes of the continuing analysis suggested additional questions to be asked at the upcoming interviews. In this way theoretical sampling of data was achieved through directed questioning. This process enabled constant comparison of patient perceptions to either strengthen or challenge the emerging categories. The constant comparative method also uncovered a depth of range and variation within the categories. By the time the last of 11 interviews were analysed, no new information was identified that did not fit within the previously identified and defined categories. Thus the data was dense, rich and fully saturated.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	The participants included eight men and three women. Selection criteria included men and women over the age of 18 from all cultural groups who could communicate in English. Participants who resided in the metropolitan area and had undergone elective PTCA were selected. Those patients undergoing emergency coronary angioplasty in the setting of acute myocardial infarction were excluded, as their recovery patterns were different to that of elective angioplasty patients and included a longer hospitalisation and a graded cardiac mobilisation.
Features the studied intervention (when applicable)	NA
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study,	<p>Results: Data analysis revealed three major categories: awareness of the problem, coping responses and appraisal of the situation. These were linked via a problem solving process. In step one, the problem was identified. In step two,</p>

author's conclusions.	<p>coping responses were taken up to try and solve the problem. In step three, the results of the coping responses were appraised and evaluated. These categories were further defined by four phases identified as: pre-admission, admission, during the angioplasty and recovery.</p> <p>The results describe the recovery phase. Awareness of the problem in the recovery phase was associated with 'relief from chest pain' for most participants. In contrast, anxiety continued and was associated with 'uncertainty over future health'. Participants described coping responses of 'taking control of their life again' by undertaking both physical and psychological strategies. Finally, the situation was appraised to be either a 'good' or a 'bad' recovery. This appraisal was based on such considerations as the absence of chest pain, improvement in well-being and energy levels. The results of this study highlight patients' concerns and support the need for greater emphasis on their psychosocial needs. This care must be provided within the time constraints of short hospital stays. Nurses must also consider providing support to patients in the pre-admission and recover phases.</p> <p>Implications for nursing practice: Nurses have the potential to extend their support to the post discharge recovery phase. Participants in the study identified that psychological support was very important. This may be achieved by follow up calls by nurses, or establishing phone help that the patient could call to discuss any feelings or concerns. It could also provide an avenue for families to gain access to nursing support.</p> <p>Limitations of the study: Several potential limitations of the study were identified. First, the researcher did not contact the participants after the interview transcript was complete in order to validate interpretation of the data. Second, the interviews were contacted 4 weeks following PTCA, therefore the participants were requested to recall past events. A number of staged interviews whilst the participants were experiencing recovery may have identified different perceptions. Third, the current study was small and specific to the first month following angioplasty. Thus the process described cannot be generalised to include recovery events occurring later than one month after PTCA.</p>
Reviewers' comments: e.g. remarks of quality issues	

First author, year	Higgins M et al. (2001)
Issue	Support from health care professionals
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Objectives: To describe participants' experiences of preparing for angioplasty in situations where patients undergo a short stay admission with limited care time with nurses User involvement in the conducting of study: Eleven patients were interviewed for the study Setting: The participants were selected from the cardiology and intensive units of a private metropolitan hospital. The hospital Ethics Committee granted ethical approval.</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Study type and design: Qualitative study using techniques of grounded theory. Sampling: People from all cultural groups who could communicate in understandable English, were over the age of 18 and were scheduled for elective angioplasty were eligible for the study. Methods of data collection: A single, tape-recorded, semi-structured interview one month after discharge from hospital. Interviews took place at participants' homes. Analysis methods: The grounded theory techniques were used: theoretical sampling, open and axial coding, the constant comparative method.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	<p>Gender: Eight men, three women Ethnicity: Not specified Types of patients: Patients prior to percutaneous transluminal coronary angioplasty (PTCA) and intracoronary stent placement</p>
Features the studied intervention (when applicable): aim of the intervention, intervention process (description of how was the intervention/service delivered)	<p>The aim of the study is to describe patients' experiences before the PTCA procedure (during admission to hospital and preparation for the angioplasty). The potential participants were given a study description sheet and consent form prior the procedure. The interviews took place 1 month after the angioplasty procedure date and were conducted at patients' homes. The tapes were transcribed and data analysis was reviewed by research colleagues. During data collection and analysis the constant comparative method was used to identify different themes. The open coding was used to assign a code to each theme and the codes were clustered into categories. Axial coding was used to connect the categories.</p>
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Details of findings: Three major categories were identified: awareness of the problem or situation, coping responses and appraisal of the situation. Continuing chest pain and fear of the unknown were identified as themes within the category of awareness of the problem. Anxiety was related to fear of unknown and was identified as a central theme. Anxiety was expressed also by those patients who had previous experience with angioplasty. Three participants reported little anxiety. The coping responses included acquiring knowledge of the angioplasty, confidence in the skill of the doctor, support from family and gearing up psychologically. The patients received information from doctors, pamphlets and experienced patients. The doctor was perceived the most important source of information but also other patients experiences were thought to be valuable. Some of the patients perceived the written material helpful but others were disappointed and preferred human interaction. Support from family members was an important coping</p>

	<p>mechanism during the whole angioplasty process. Patients' appraisal of their situation and their decisions to go ahead with or delay the procedure seemed to be based on the success of the coping responses. The common perception was that the admission phase was anxiety provoking.</p> <p>Limitations of the study: The small sample size limits generalisability of the result to other population. The interview was conducted one month after the procedure and participants were recall past events.</p> <p>Author's conclusions: The concepts that emerged from the study provide the potential for changes to nursing practice and further research. The time before the angioplasty was experienced anxiety provoking by most of the patients. In contrast, the high turnover nature of the angioplasty care may cause that nurses view the procedure as a mechanised and routine process. The patients' perceptions indicated that psychological aspects of nursing care are important components of nursing practice for the angioplasty patients.</p>
Reviewers' comments: e.g. remarks of quality issues	

First author, year	Eastwood GM (2001)
Issue	Support from health professionals
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Objectives: What are the rationale and influences behind the decisions of patients to change/not to change their lifestyle patterns 3 months after a percutaneous transluminal coronary angioplasty/intracoronary stent procedure</p> <p>User involvement in the conduct of study: Data collected by interview from the patients Country:Australia</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>Study type and design:Descriptive study utilized naturalistic inquiry approach with the implementation of semi-structured interview</p> <p>Study date and duration: A single interview with each participant three months after PTCA/intracoronary stent procedure</p> <p>Sampling/recruitment: -Identification of potential participants via regular telephone and personal consultations with the cardiac unit coordinator. Consent from the cardiologist responsible for performing the procedure -Non-probability purposive sampling. A sample of four male participants who had undergone a PTCA/stent procedure for the first time - The patients approached by the researcher within the first 36 h following their procedure and ask their interest to participate in the study (plain language statement and consent form)</p> <p>Methods of data collection: Semi-structured interview schedule Data collector:Not specified Research tools:Semi-structured interview, audio-taped, transcribed verbatim</p> <p>Analysis methods: The material of interviews was read, re-read and listened to several times, in sequential order, in order to make the researcher familiar with the collected data and recognise emergent themes. A copy of transcript was sent to each participant to verify the accuracy, interpretation and use of quotations</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	<p>Gender:Males Age:Not specified Ethnicity:Not specified</p> <p>Types of patients:Inclusion criteria: No a serious co-morbid medical diagnosis, no major complication as a result of the procedure, English-speaking, males, no previous cardiac surgery or involved with a cardiac rehabilitation program</p>
Features the studied intervention (when applicable):	NA
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Details of findings: The results suggested that a positive psychological health perspective, family considerations, return to work issues together with a reluctance to participate in cardiac rehabilitation program activities had impact on patients' decision to change/not to change their lifestyle patterns after the procedure:</p> <ul style="list-style-type: none"> -The renewed feelings of well-being, improved quality of life and enhanced physiological outcomes are a consequence of the PCTA/stent procedure. Some of the patients viewed that the procedure has 'fixed' the problem which made apparent that they were unconcerned or unaware of the need to change their lifestyle patterns in order to prevent future cardiac complications. The short period of hospitalization was thought to be another influential factor (three out of the four patients dismiss the significance of their cardiac condition). - The results suggested that participants with dependants (children, elderly relatives) were affected in their ability to instigate change or maintain existing lifestyle patterns. Two participants highlighted the need for and potential value of the family members receiving counselling to promote better understanding of patients' situation. - The ability to maintain exercise routines was affected by the nature of the work, work rosters and inflexible work schedules. The benefits regarding working life were increased feelings of self-worth, renewed ability to socialize and the feeling of a return to normality. - Despite the information concerning the benefits of lifestyle change being received during hospitalization there was a reluctance to attend cardiac rehabilitation program activities. Two out of four patients believed that the information they received and their own knowledge base was sufficient to maintain healthy lifestyle. - The one patient who took part in structured cardiac rehabilitation showed the greatest awareness of cardiac risk factors and implemented the greater degree of lifestyle pattern change.

	<p>Limitation of the study: Due to methodology and a small sample size, the ability to extrapolate the findings of the study to the greater population of PTCA/stent patients is not possible. Due to only one interview it is not possible to detect the long-term influences on lifestyle pattern change.</p> <p>Author's conclusions: The study gave insight into and understanding of the influences affecting lifestyle pattern change. That change is dependent on the individual's psychological, social, familial and work-related circumstances. Nurses spend the greatest amount of time with PTCA/stent patients during hospitalization and have best opportunity to provide relevant information in order to influence the decisions concerning lifestyle pattern change.</p>
Reviewers' comments: e.g. remarks of quality issues	

First author, year	Abbas AE. et al. (2004)
Issue	Working life; meaning of implementation of the technology for the patient's working life
Nature of the study: aims/objectives, user/carer involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.	<p>Aims: The study conducted an analysis of the frequency and variables associated with early (after 1 month) and late (after 6 months) return to work after percutaneous coronary intervention for acute myocardial infarction in patients who had been randomized in the Stent Primary Angioplasty in Myocardial Infarction trial. The study examines the demographic, clinical, and angiographic characteristics of patients who returned to employment 1 and 6 months after percutaneous coronary intervention for AMI:</p>
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods	<p>The frequency and variables associated with return to work at 1 and 6 months were analyzed. Categorical variables were analyzed with the chi-square test, when appropriate. Fisher's exact test, and continuous variables were examined with Wilcoxon's rank test. A p values <0,05 was considered statistically significant. We compared demographics, clinical presentation, angiographic findings, procedural success, anginal index at 1 month, and in-hospital and 1-month events of patients who returned to work at 1 month with those of patients who did not. We also compared 6-month clinical outcomes to determine the safety of early return to employment. In addition, we compared the anginal index and 6-month outcomes in patients who returned to work at 6-months with those in patients who did not.</p> <p>A step-down multivariate logistic regression analysis was completed to determine the best predictors of returning to work at 1 and 6 months. Included in the first step for return to work at 1 month were age >70 years, gender, employment, in the US versus employment elsewhere, multivessel disease, smoking history, final percent stenosis, in-hospital events, 1-month events, lowest systolic blood pressure during hospitalization, and angina at 1 month. Included in the first step for return to work at 6 months were age >70 years, gender, US versus non-US employee, multivessel disease, smoking history, 6-month events, and presence of angina at 6 months. The least significant variable was dropped at each step until only those with a p value <0,05 remained in the final model.</p>
Participant characteristics: gender, age, ethnicity, types of practitioners, policy makers or patients	An analysis was done of all patients (450) who had been randomized in the Stent Primary Angioplasty in Myocardial Infarction study. The international study compared primary angioplasty with and without stenting with a heparin-coated Palmaz-Schatz stent in patients who had electrocardiographic or angiographic evidence of AMI.
Features the studied intervention (when applicable):	NA
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions.	<p>Results: Of 450 patients who were employed before the acute myocardial infarction, 230 (51%) returned to work within 1 month with no increases in in-hospital and 1-or 6-month event rates compared with those who did not return to work. Multivariate analysis showed that predictors of early return to work were employment in the United States, no history of smoking, and single-vessel coronary disease. At 6 months, 353 of 435 patients (78%) had returned to work, and multivariate analysis showed that predictors of late return to work were employment in the United States and absence of angina.</p> <p>The study suggests that regional differences play an important role in determining return to work after percutaneous coronary intervention for AMI: Being a US employee was the single most important predictor of early (1 month) and late (6 months) resumption of employment. Early return to work was also determined by the number of narrowed coronary arteries and history of tobacco use but appeared to have no adverse effect on rates of mortality, stroke, or reinfarction at 6 months. By 6 months, >75% of the patients had returned to work and they were less likely to complain on angina. However, even in patients who remained unemployed, symptoms were mild in most of them (only 3,8% had class 3 to 4 angina). In addition, with no difference in clinical events in the previous 6 months, regional and geographic influences seem to supersede functional class and clinical events in determining late return to employment.</p> <p>The study highlights the importance of regional rather than clinical factors in determining reemployment after percutaneous coronary intervention for AMI. The reason for this is unclear but definitely reflects geographic, ethnic, and regional influences on return to employment after AMI:</p>
Reviewers' comments: e.g. remarks of quality issues	

Legal Aspects

Marco Marchetti, Marco Oradei, Mirella Corio, Carmen Furno, Matteo Ruggeri

Introduction

In this HTA domain will be discussed some legal issues related to DES technology. Some legal issues are directly related to the patient and his/her basic rights, such as autonomy, informed consent, privacy and confidentiality. Other issues are linked to the technology, such as authorisations, patents/licenses, acquisition process, price and reimbursement regulations, product safety, guarantee and liability. European directions do not include specific instructions for DES, but regulate the general devices sector (i.e. CE certification for new devices). DES can not be considered as a new experimental technology; therefore some questions of this domain are not relevant.

One of the legal aspect linked to DES utilization it is a possible increase of litigation cases, either when a DES was not implanted and restenosis occurred, or conversely, if a complication occurred after DES implantation for an unapproved indication.

Questions proposed in this domain partly overlap those in the other domains (i.e social, organizational, ethical, economic domains).

Methodology

According to the guidelines provided by the Corel Model, legal sources were analysed at different levels.

- European Council Level (i.e. Convention on Human Rights and Biomedicine and European Human Rights Convention)
- EU level (medical devices guidelines)
- National level
- Documentation provided by DES producers.

Articles have been searched on medical-legal specialised reviews and ad hoc researches have been made on both generic (e.g. Google) and specialised (e.g. Pubmed) search engines.

Assessment elements

Autonomy of the patient

Is the patient competent to make his/her own health care decisions?

Methods

Analysis of legal sources at the different levels (European and National) and research of articles on scientific journals.

Results

Patient's capacity to make informed decisions on their health is connected to the type of information received and the way it is transferred. The Convention for the protection of Human Rights and Biomedicine (Oviedo 1997), agreed by all States member of European Community, encloses regulations on informed consent, by establishing that each person must give his/her own consent to be submitted to health care treatments(art. 5)¹.

Consent must be personal, expressed, specific, actual, revocable, and informed. Without adequate information, no form of consent, even if undersigned, is valid by laws. If the patient is a minor, the consent is automatically delegated to his/her own parents. The minor has the right to be informed and to express his/her wishes, which must be taken into consideration. If the patient is a major, but he/she **is incapable to decide**, his/her **legal tutor** is responsible for giving consent, even though he/she has the right to be informed and his/her will must be taken into consideration.

The three steps of informed consent:

- 1- The physician transfers to the patient all of the relevant information, on both diagnosis and therapy
- 2- The physician ascertains that the patients comprehended the meaning of the communication
- 3- Patient makes final decisions.

In the case of DES, the patient's capacity to give his/her consent to the treatment can be influenced by the seriousness of his/her clinical conditions. With elective patients all of the three steps of the informed consent process can take place. In emergency situations it may be difficult to obtain truly informed consent from the patient, because:

- a. the patient is considered to be neurologically incompetent, or
- b. although the patient is conscious, clinical and psychological pressure caused by his/her clinical conditions, make him/her incapable to make an aware decision

In these circumstances then the law allows emergency medical treatment to be administered without consent².

Nowadays, relevance of patient decisions on health care procedures has been legally recognised. Regulations provided are clear: physicians must provide patients with clear and complete information and they can proceed only after patient's consent.

Comment

The crucial issue in DES implant procedure is physicians' capacity to inform patients properly. In fact, since DES are a new generation technology (first DES have been merchandised in 2002), only now clinical trials identify medium, long-term effects, which highlight the occurrence of new possible risks, respect to the optimistic forecast of the first trial conducted. Therefore, physicians are not acquainted with all of the effects of a DES procedure on patient's health. This issue undoubtedly overlaps with the ethical domain.

Can the patient understand the implications of using/not using DES?

Methods

Several patients' information papers concerning PTCA (performed either with or without stent insertion), selected by an internet search, have been analysed.

Results

Patients are usually able to understand the meaning of stent insertion and its clinical implications, if correctly explained, and thus legally competent to give his/her own consent. One of the few documents available explaining which information patients undergoing to PTCA (with or without stent implant) must receive, has been produced by Queensland Government³. It states that the doctor must explain to the patient his/her medical conditions and the procedure to follow, in order to make patient aware of the risks involved, both general and specific, and the possible outcome. The doctor should present also other diagnostic options and their risks. Finally, he must introduce to patients the prognosis and the risks of not following the procedure.

Comment

As highlighted in the previous paragraph, in case of a DES implant, information available on medium and long term risks are not sufficient, because there is still poor scientific evidence on this subject.

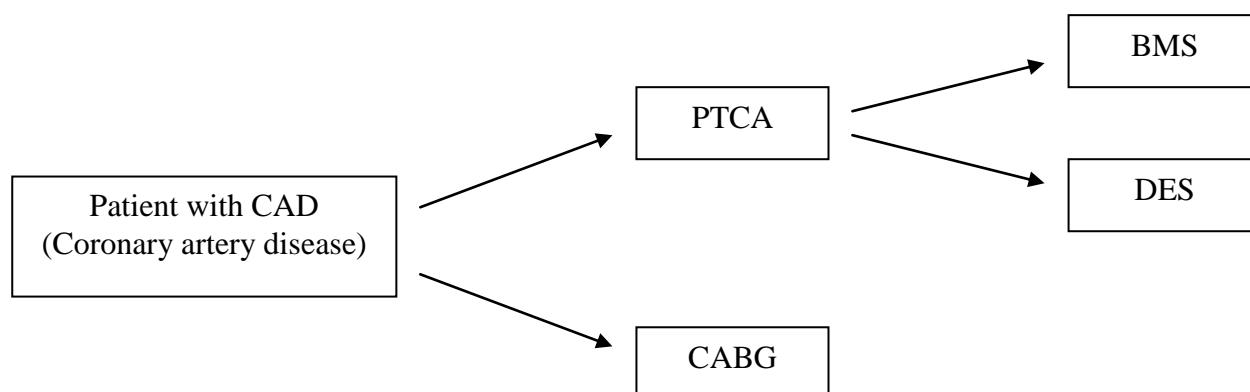
Are there relevant optional technologies that the patient should be allowed to consider?

Methods

Comparative studies on PTCA with DES/BMS insertion versus bypass grafting have been analysed. These studies have been searched by Pubmed, using the follow keywords: "CABG", "PCI", "Bypass", "Stent", "DES" and "BMS". This analysis included only comparative studies published in the last five years.

Results

There are two levels of choices between available technological options:



First level:

There is a relevant choice to stent (both DES and BMS) insertion, consisting in CABG (Coronary Artery Bypass Graft). The issues to be considered here are early and late morbidity and mortality for cardiovascular events^{4,5,6}.

Second level:

Several studies have compared BMS versus DES. In addition to issues listed at the first level of choice, the issue of long-term medication after the intervention must be considered^{7,8}.

Comment

Although coronary artery bypass grafting (CABG) remains the treatment of choice for certain types of coronary artery disease (CAD), percutaneous coronary intervention (PCI)--particularly coronary angioplasty with stenting--has become the most popular interventional treatment approach to CAD. Both CABG and PCI technologies will continue to advance, and longer-term data may change the evaluations.¹⁰

Is it possible to give the patient enough time to consider his/her decision?

Methods

Analysis of legal sources at the different levels (European and National) and research of articles in scientific journals.

Results

As outlined before, angioplasty with stent insertion procedure can be twofold: primary or secondary.

- in case of primary angioplasty (urgent/emergency cases) the patient may not have enough time to decide whether to accept the treatment, due to his/her clinical condition. A primary angioplasty must be performed within 30-40 minutes. For legal implications, please see issue “*Is the patient competent to make his/her own health care decisions?*”

- in case of secondary angioplasty, since it is an elective procedure, it is possible to plan in advance meetings with patients, so that they can receive all of the necessary information to make informed decisions on their health. For legal implications of not following the regulations on the informed consent, please see the issue “*Is the patient competent to make his/her own health care decisions?*”

Comment

Hospitals Clinical/Critical Pathways must take into account the time patients need to consider their decision. Even if clinical conditions of patients do not always allow for enough time to think about PTCI procedures, the time should be built in clinical pathways.

Is it possible to obtain an advance directive on the use of DES?

Results

An advance directive is a legal document that helps ensure that the patient's wishes regarding health care will be respected if he becomes unable to speak or otherwise communicate. In the absence of a written document, sometimes an advance directive may be an oral communication, where patient express his wishes for care verbally to his family members or health care agent. An advance directive may become important if patient are severely injured or develop a serious illness that prevents him from actively participating in decisions about his medical care.

Living wills and medical powers of attorney are types of advance directives.

- A living will documents personal wishes about end-of-life medical treatment in case decision-making or communication abilities are lost such as ventilation, feeding tubes in the event you are in a terminal condition or persistent vegetative state.
- A medical power of attorney is a legal document that lets you appoint someone (usually called a health care agent or health care proxy) to make medical treatment decisions for you not only at the end of life but any time you are unable to speak for yourself¹¹.
-

Convention On Human Rights And Biomedicine¹ (art. 9) establishes that “*The previously expressed wishes relating to a medical intervention by a patient who is not, at the time of the intervention, in a state to express his or her wishes shall be taken into account*”.

Each Country has proper Laws for assigning individuals their rights to decide on their own life, depending on the legal value they assign to “life” as a good. As a consequence, different rights to decide on own life, could affect, in case of life danger, advance directives’ relevance.

The performed search produced no meaningful results that link advance directives with PTCA; it has been thought that it is not necessary to obtain an advance directive on the use of this specific technology. It may be possible find examples of advanced directive written by patients with CAD. In people with CAD, in fact, death often occurs without warning. Death can occur quickly, before any symptoms develop or before they become bothersome. Such a death may result from a heart attack or an abnormal heart rhythm. Or death can occur after a period of chronic illness with ups and downs. Such a death may result from heart failure. Consequently, people with CAD, even those without significant symptoms, should prepare advance directives, stating what kind of care they want at the end of life¹².

A study have been shown that patients want to share in major decisions with their physicians but prefer to be less involved in minor decisions. For some illnesses, such as myocardial infarction, prior experience with the illness increases the patients' desire for participation in decision making¹³.

Privacy of the patient

Is the access to the patient data secured properly?

Methods

Analysis of the norm sources at various levels (European and national) has been performed.

Results

Specific information on managing the data of the patient with PTCA does not exist.

Security and protection of patient health data in most developed countries, are required by law. This is of utmost importance, since patient health data are among the most sensitive personal data. In order to ensure the confidentiality and integrity of such kind of data, they need to be protected against manipulation, unauthorized access and abuse.

Below it will be present some basic definitions of data protection and security that are given in the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data:

- Data protection aims to protect the fundamental rights and freedoms of natural persons and in particular their right to privacy with respect to the processing of personal data.
- Data security aims to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing.

Together, data security and data protection aim to ensure the following five fundamental objectives:

1. Confidentiality means the assurance that patient data are not made available or disclosed to unauthorized individuals.
2. Integrity means to ensure that patient data cannot be changed or deleted by unauthorized individuals or parties.
3. Authentication means the corroboration that a person is the one claimed.
4. Accountability means that the actions of a person, especially the modifications that he/ she performs on data stored in an EPR, can be traced.
5. Availability means that upon demand patient data can be accessed and used by authorized people.

When using, storing and exchanging patient health data, all these fundamental objectives have to be taken into account and their achievement has to be ensured by appropriate methods and tools¹⁴.

Within the European Union several legal regulations shall cover all the different legal aspects.

- The fundamental right to the protection of personal data is essentially based on Article 8 of the European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR) and on Article 8 of the EU Charter of Fundamental Rights. More precise rules are in particular laid own in the EC Data Protection Directive 95/46/EC and in Directive 002/58/EC on privacy and electronic communications.
- Secure data exchange is regulated by means of the European Directive from 1999 on a

Community framework for electronic signatures (Directive 1999/93/EC of the European Parliament and of the Council of 13 December 1999 on a Community framework for electronic signatures).

The latter directive also aims at the creation of a foundation for the legal equality of electronically signed documents and hand-signed documents. All directives have to be implemented in the national legislation of the member states of the European Union.

In EU, processing of personal data is regulated by the articles 7 and 8 of the EU Directive of 1995. Article 7 applies to all forms of personal data, whereas in article 8 specific regulations are laid down that apply to the processing of special categories of data, which amongst others also cover patient health data. By means of the latter article the processing of special categories of data shall be prohibited by the Member States.

When the processing of such personal data relates to a person's health, processing is particularly sensitive and therefore requires special protection.

Article 8 (1)

The definition of special categories of data contained in Article 8 (1) of the Directive reads as follows:

“Member States shall prohibit the processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life.”

This definition also applies to personal data when they have a clear and close link with the description of the health status of a person: data on consumption of medicinal products, alcohol or drugs as well as genetic data are doubtlessly "personal data on health" especially if they are included in a medical file. Also any other data – e.g. administrative data (social security number, date of admission to hospital etc) – contained in the medical documentation of the treatment of a patient will have to be considered as being sensitive: if they were not relevant in the context of the treatment of the patient, they would and should not have been included in a medical file.

Article 8 (1) of the Data Protection Directive 95/46/EC prohibits the processing of personal data concerning health in general. So does Article 6 of the Council of Europe Convention No 108. This special protection contained in Article 8 (1) complements the other provisions of the Directive, in particular Article 6 on the principles relating to data quality and Article 7 on the criteria for making data processing legitimate.

However, considering the importance of using information about a patient in order to medically treat him appropriately, there are exemptions to the general prohibition of processing medical data. The Data Protection Directive provides for **mandatory derogations** laid down in Article 8 (2) and (3) plus an **optional exemption** in Article 8 (4).

All these derogations are **limited, exhaustive** and have to be **construed in a narrow fashion**.

Article 8 (2) (a): “Explicit consent”

According to Article 8 (2) (a) of the Directive:

“Paragraph 1 shall not apply where: (a) the data subject has given his explicit consent to the processing of those data, except where the laws of the Member State provide that the prohibition referred to in paragraph 1 may not be lifted by the data subject's giving his consent;” to be valid, consent – whatever the circumstances are in which it is expressed – must be a *“freely given, specific and informed indication of the data subject's wishes”*, as defined in Article 2(h) of the Directive.

- a) Consent must be given freely: ‘Free’ consent means a voluntary decision, by an individual in possession of all of his faculties, taken in the absence of coercion of any kind, be it social, financial, psychological or other. Any consent given under the threat of non-treatment or

lower quality treatment in a medical situation cannot be considered as ‘free’. Consent given by a data subject who has not had the opportunity to make a genuine choice or has been presented with a *fait accompli* cannot be considered to be valid.

- b) **Consent must be specific:** ‘Specific’ consent must relate to a well-defined, concrete situation in which the processing of medical data is envisaged. Therefore a ‘general agreement’ of the data subject e.g. to the collection of his medical data for an EHR and to subsequent transfers of these medical data of the past and of the future to health professionals involved in treatment would not constitute consent in the terms of Article 2 (h) of the Directive.
- c) **Consent must be informed:** ‘Informed’ consent means consent by the data subject based upon an appreciation and understanding of the facts and implications of an action. The individual concerned must be given, in a clear and understandable manner, accurate and full information of all relevant issues, in particular those specified in Articles 10 and 11 of the Directive, such as the nature of the data processed, purposes of the processing, the recipients of possible transfers, and the rights of the data subject. This includes also an awareness of the consequences of not consenting to the processing in question.

In contrast to the provisions of Article 7 of the Directive, consent in the case of sensitive personal data and therefore in a Health care Record must be **explicit**. Written consent is, however, not required.

Article 8 (2) (c): “vital interests of the data subject”

The processing of sensitive personal data can be justified if it is necessary to protect the vital interests of the data subject or of another person where the data subject is physically or legally incapable of giving his consent.

Article 8 (3): “processing of (medical) data by health professionals”

Article 8 (3) allows for the processing of sensitive personal data under three cumulative conditions: the processing of sensitive personal data must be “*required*”, and *this processing takes place “for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services”* and the personal data in question “*are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy*”.

This derogation only covers processing of personal data for the **specific purpose** of providing health-related services of a preventive, diagnostic, therapeutic or after-care nature and for the purpose of the management of these healthcare services, e.g. invoicing, accounting or statistics.

Article 8 (4): substantial public interest exemptions

A number of provisions of the Directive contain a substantial degree of flexibility, so as to strike the appropriate balance between the protection of the data subject’s rights on the one side, and on the other side the legitimate interests of data controllers, third parties and the public interest which may exist.

Article 29 Working Party¹⁵ provides guidance on the interpretation of the applicable data protection legal framework for health in electronic health records EHR systems and explains some of the general principles. The Working Document also gives indications on the data protection requirements for setting up EHR systems, as well as the applicable safeguards. The Article 29 Working Party first examines the general legal data protection framework for EHR systems. The Article 29 Working Party recalls the general prohibition of the processing of personal data concerning health of Article 8 (1) of the Data Protection Directive 95/46/EC, and then discusses the possible application of the derogations in Article 8 (2), (3) and (4) of the Directive in the context of

EHR systems by stressing the need for interpreting such derogations in a narrow fashion. The Article 29 Working Party also reflects on a suitable legal framework for EHR systems and provides recommendations on eleven topics where special safeguards within HER systems seem particularly necessary in order to guarantee the data protection rights of patients and individuals. These topics are:

1. Respecting self determination
2. Identification and authentication of patients and health care professionals
3. Authorization for accessing EHR in order to read and write in EHR
4. Use of EHR for other purposes
5. Organisational structure of an EHR system
6. Categories of data stored in EHR and modes of their presentation
7. International transfer of medical records
8. Data security
9. Transparency
10. Liability issues
11. Control mechanisms for processing data in EHR

Below – with a focus on consent - a cross sectional overview of main European countries' fitting to EC directive has been reported:

United Kingdom position

The Data Protection Act 1998 does not contain a definition of consent. According to Paul Boyle (the official responsible for data protection at the Department for Constitutional Affairs) this is one of the aspects of UK implementation of the Data Protection Directive which has been queried by the EU Commission.

There are no specific formal requirements (such as consent being in writing).

The Netherlands

The Dutch Data Protection Act reproduces the definitions in the Data Protection Directive and uses consent in similar situations. There are no specific formal requirements in the Dutch Data Protection Act. This is a change to the old Data Protection Act which did require consent to be given in writing. Guidance from the Ministry of Justice does, however, note that written evidence of consent can be helpful.

Spain

The Organic Law 15/99 uses the same definition as the Directive. However, it goes further than the Directive and also requires that consent must be “unequivocal”.

Article 7.2 of the LOPD requires consent to be express and in writing for the processing of information relating to ideology, religion, beliefs and trade union membership. Under Article 7.3 consent for processing of other sensitive personal data needs to be express but does not necessarily need to be in writing.

In accordance with the Spanish Civil Code, minors older than 14 are mature enough to give consent. For minors who have not yet reached 14, consent is to be given by their legal representatives.

Note that the LOPD does not allow data to be processed based on the data controller's “legitimate interests” (i.e. Article 7(f) of the Directive has not been implemented in Spanish law). Accordingly, organizations in Spain must, as a practical matter, make greater use of consent.

One of the exceptions to the principle of consent is where the data is in sources accessible to the public which are solely and exclusively:

- the promotional census (i.e. electoral roll data to be used for direct marketing);

- telephone directories;
- list of members of professional groups; and
- Newspapers, official gazettes and the media.

Belgium

Belgian law follows the Directive's definition of consent.

Articles 6 and 7 of the Belgian Data Protection Act require consent to be in writing to process sensitive and health related personal data. Other than this, there are no requirements for formalities. In addition, Article 39 provides that acts of violence or threats made with the purpose of obtaining a person's consent are illegal and punishable by fine.

Italy

The Italian Data Protection Code (Legislative Decree Number 196/2003) does not contain a specific definition of consent. The requirements of the Data Protection Directive are reproduced in Article 23. In addition, this also provides that consent must be express (i.e. not implicit, for instance, by simply going ahead and using a service) and must be documented in writing or, in the case of sensitive data, actually given in writing. Consent may either be given by the data subject or by the person entitled to act on the data subject's behalf.

Sweden

In the Swedish Personal Data Act (1998:204), section 3, consent is defined as:

"Every kind of voluntary, specific and unambiguous expression of will, by which the registered person, after having received information, accepts processing of personal data concerning him or her." There are no formal requirements, such as consent being in writing.

France

The French Data Protection Act reproduces the definitions in the Data Protection Directive. There are no specific formal requirements in the French Data Protection Act.

The French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés: CNIL*) considers that consent must be given in writing.

Germany

German data protection law defines consent as a free and informed declaration: Section 4a para. 1 sentence 1 Federal Data Protection Act (*Bundesdatenschutzgesetz*), which is applicable to the private sector, requires that consent must be a result of a free decision of the data subject. The data subject must be informed about the purpose of the data collection, processing or use and the consequences of a refusal to give consent if necessary or if the data subject so requests (Section 4a para. 1 sentence 2 Federal Data Protection Act).

To the extent sensitive data are concerned the consent must refer explicitly to such sensitive data (Section 4a para. 3 Federal Data Protection Act).

As regards formal requirements, German law requires (Section 4a para. 1 sentence 3 Federal Data Protection Act) the written form unless another form is appropriate. If consent is included with other provisions, the consent wording must be highlighted (Section 4a para. 1 sentence 4 Federal Data Protection Act).

The information related to Directive and its application in the European countries are from http://www.twobirds.com/english/publications/articles/Use_of_Consent_in_Data_Protection.cfm

Comment

National situation all over the Europe is very similar according to EU directive.

How many people in the care pathway need to get access to the patient information?

Methods

Analysis of the norm sources at various levels (European and national) has been performed.

Results

According to privacy Law the access to patient data must be allowed to health professionals (clinicians and nurses) responsible for patient's care process and to patient's caregivers.

Comment

National situation all over the Europe is very similar according to EU directive.

Equality in health care

Is DES equally accessible to all needing members of society?

Methods

Analysis of the norm sources at various levels (European and national) has been performed. A research on different funding system has been performed by internet tools.

Results

Drug-eluting stents became commercially available in 2002 in Europe and Canada, and in 2003 in the United States. They are now widely used in the treatment of coronary artery disease¹⁶.

The penetration of the coronary stent market by drug-eluting stents from a common launch in 2002 to the third quarter of 2004 is very similar in different countries of Europe. All countries had a very similar market penetration of coronary artery stents, except Switzerland and France. Penetration in Switzerland increased rapidly to a plateau of over 70 percent within 2 years of availability. In France the penetration was slower than elsewhere for the first year of use, but then caught up with the majority. In Denmark the penetration was similar to all the other countries except in 2004, when the rate of increase was much greater than in the others. Consequently, the utilization of DES in the European Countries seems uniform.

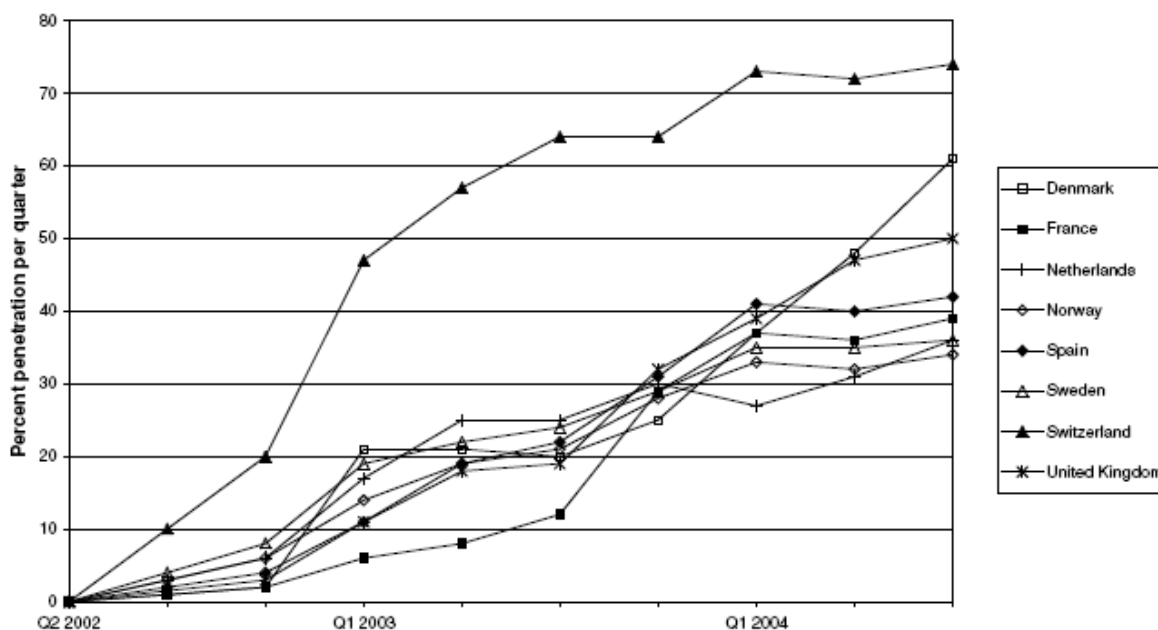


Fig 1 - Penetration of the coronary stent market by drug-eluting stents

A problem related to the safety and appropriateness of this particular technology – and in some way to its equal utilization - is apparent. It is not clear yet which treatment strategy would be optimal, when considering various treatment options.^{17, 18}

Comparing international utilization of stents is naturally not a robust proof of equal societal accessibility. Although national numbers compare well, significant variation may exist within countries and their societal groups. These issues are addressed also in the chapter "Social aspects".

Comment

It is also possible that DES technology is overused in wealthy health care systems. The international scientific and political debate is generally focused on the necessity to increase the appropriate use of DES.

Is DES subsidized by the society?

Methods

Analysis of the norm sources at various levels (European and national) has been performed. A research on different funding system has been performed by internet tools.

Results

Judging from the large number of publications on the cost-effectiveness of drug-eluting stents, the price tag for the commercially available drug-eluting stents is excessive (approximately \$1500 to \$3000 per stent in Canada). Because drug-eluting stents are considerably more expensive than bare-metal stents, with an estimated world market of \$6 billion annually, some health care systems are trying to control their diffusion in clinical practice.¹⁹

Subsidizing policies are related to DES diffusion and the characteristics of the health care system. In particular an above average health expenditure is positively associated with diffusion and cost enhancement. A single state agency controlling expenditure on health care may make it easier to control diffusion compared with multiple insurance schemes, which are likely to favour high-tech innovation. An important means of controlling (both restricting and promoting) diffusion is through a national decision making system²⁰.

In the UK system for example at current UK prices, DESs are not cost-effective compared with conventional stents except for a small minority of patients. Although the technology is clearly effective, general substitution is not justified unless the price premium falls substantially²¹. At the Health Care Organization level it seems that public hospitals have been more selective than private facilities in their use of these stents.

Interestingly, in Italian the private sector has adopted unrestricted use of drug-eluting stents without a change in overall cardiac surgery volumes. Although the number of isolated CABG procedures has decreased in both private and public hospitals, the level of reduction has been significantly greater in the public hospitals. The small reduction in private hospitals suggests reluctance to move from CABG (and the high revenues it generates) to PCI (and its lower revenue margins due to the high cost of drug-eluting stents). The fact that PCI numbers have not decreased, has likely been a business decision to maintain a “high technology veneer” that would appeal to patients and referring physicians²².

Comment

Different subsidizing activities have been performed at different level in European Countries (macro-policy level, institutional meso-level)

Equality in health care

Is there a wide variation in permissibility of the technology across Europe?

Methods

To answer this issue we searched in the European Court of Justice Database, using the keywords “stent” and “permissibility”. We also searched in the Medline database using the keywords “stent” and “permissibility”.

Results

The research in European Court of Justice Database not found anything on stents. Also the search in Medline not found articles with the keywords. The conclusion is that there is nothing specific on stents permissibility.

DES legislation, as far as permissibility is concerned, is ruled by general laws on devices permissibility. The European reference law on this issues is the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices established, in the article 2, that “Member States shall take all necessary steps to ensure that devices may be placed on the market and put into service only if they do not compromise the safety and health of patients, users and, where applicable, other persons

when properly installed, maintained and used in accordance with their intended purpose”. In addition article 17 states that “Devices ... must bear the CE marking of conformity when they are placed on the market”. In Italy this directive has been ratified with Law n. 46 of 24-02-97. On the base of this Law, it doesn't seem to exist wide variation in permissibility among European Countries.

Comment

There is no variation permissibility of the technology across Europe. Indirect variation permissibility could be linked to different funding system across Europe.

Is health care tourism expected from/to other European countries?

Methods

Medline was searched using as keywords “stent”, “angioplasty” and “mobility”. Also other non scientific search engines were consulted.

Results

No specific articles on this issues were found.

Comment

DES seems not to have consequences on patient mobility among European States, when compared with BMS. This could probably be linked to the very similar penetration of DES across Europe. Another possible reason for mobility is the waiting lists for angioplasty procedure. National waiting lists for angioplasty could push patients to health care tourism.

In Italy an agreement was signed during 2006 between the State and Region (28/03/06) to guarantee adequate services to patients. It defines waiting times for several interventions. According to this agreement, the maximum waiting time for angioplasty intervention is 60 days.

Authorisation & safety

Has the technique proper national/EU authorisation?

Methods

Use of EMEA document (EMEA/CHMP/EWP/56477/2006, London, February 2006)²³ and Council directive 93/42/EEC²⁴, MEDDEV 2.1/3 rev 2 guidelines relating to the application of The Council Directive 90/385/EEC²⁵ on active implantable medical devices.

Results

The introduction of medicinal substance-eluting stents has dramatically impacted the market size and growth rates for coronary stents worldwide. Many new companies are currently entering the field. Guidance is needed with regard to the non-clinical and clinical data required for the evaluation of the medicinal substances contained in medicinal substance-eluting stents. Differences have been noted in the amount of non-clinical and clinical information: in some case producers

strengthen their application dossier by introducing pharmacological data, in other cases application dossiers are supported by wide, multi-centred, randomized controlled clinical studies.

Comments

These medicinal substance-eluting stents are combination products composed of medicinal products and medical devices, where the medicinal product has an ancillary function to the device. They are classified in the Community as medical devices, in accordance with Council Directive 93/42/EEC concerning medical devices and in line with the MEDDEV 2.1/3 rev 2 guidelines relating to the application of: The Council Directive 90/385/EEC on active implantable medical devices and the Council Directive 93/42/EEC on medical devices. The authorisation of such combinations falls ultimately under the remit of the relevant Notified Bodies. According to the medical device legislation, the Notified Body shall consult one of the competent bodies of the Member States or the EMEA with regards to the quality, safety and usefulness of the medicinal substance incorporated as integral part of the device, taking into account the intended purpose of the device.²

Does DES need to be listed in a national/EU register?

Methods

Study and description of the procedure for registration of medical devices, MEDDEV 2.1/3 rev 2 guidelines

Results

A Medical Device is defined in Directive (93/42/EEC) as “any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for the proper application, intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of a disease, an injury or a handicap.
- Investigation, replacement or modification of the anatomy or of a physiological process.
- control of conception

And which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted by such means”.

The 2001 guidelines (see MEDDEV 2.4) classify the medical devices into 3 classes, mainly on the basis of 17 rules that identify safety level and potential risks. The classification on which a MDD falls into constitutes the basic frame for the product to receive the CE marking.

For a number of products it is not clear whether they are medical devices or not. There are a number of examples of products that may or may not be classified into medical devices depending on the Intended Purpose for Use, assigned by the manufacturer to the products. Drug eluting stents are classified in the EU as medical devices falling into MEDDEV class III.

² Each member state specifies some *Competent Body(ies)* (CB), also called "Competent Authority(ies)" to enact the directive within its territory. Each CB can specify one or more *Notified Bodies* (NB), to act as third party assessors of the manufacturer's compliance. A NB may be Notified for accessing the products under all allowed conformity modules under the particular directive or only part of modules.

In April 2002, CYPHER™, a sirolimus-eluting stent of Cordis Inc received CE conformity marking in Europe and in January 2003 the TAXUS medical device, a Paclitaxel-eluting stent of Boston Scientific received CE conformity marking in Europe for treatment of de novo coronary artery lesions in native coronary arteries.

Does DES fulfil product/tissue safety requirements?

Methods

Consultation of the directive 2001/104/EC²⁶, EMEA document²⁴ (EMEA/CHMP/EWP/56477/2006, London, February 2006).

Results

Sirolimus-based DES reduces restenosis risk with respect to Paclitaxel, although a limited follow-up does not reveal significant differences in the reducing risk for thrombosis, myocardial infarction and death. At present there is no evidence of the link between restenosis and mortality. Long-term evidence is required.

The evaluation of medicinal substance-eluting stents introduces additional considerations for preclinical and clinical testing, and for manufacturing. Aspects of manufacturing, mechanical performance & testing regimens, chemistry, animal experimentation, pharmacology and safety and efficacy evaluation call for an integrated assessment. Furthermore, taken into account that the clinical studies are performed in highly selected patient groups but the devices after launching are commonly used beyond the main study selection criteria, recommendations for post-marketing surveillance should also be considered. Regulatory harmonization regarding requested information about safety and usefulness of the medicinal substances contained in drug-eluting stents is needed to achieve optimal care for all patients.

Comments

The EMEA CHMP Efficacy Working Party and the Safety Working Party recommend to draft a guidance document detailing what data are required to be included in the dossier of a medicinal substance eluting stents for an adequate assessment of the safety and usefulness of a medicinal product used as an ancillary medicinal substance in a medical device in the context of a Notified body consultation procedure and of the post-marketing programs to be recommended. Recommendations will also be given on presentation and interpretation of results.

Ownership & liability

Does DES infringe some intellectual property rights?

Methods

Internet search was performed.

Results

In Europe CYPHER™ (J&J Cordis corp.) and TAXUS (Boston Scientific) were registered respectively in 2002 and 2003. On 5 April 2007 a U.S. federal court ruled that the stent made by

Johnson and Johnson unit Cordis Corp. does not infringe a patent held by Boston Scientific Corp. according to court documents. Actually Conor Medsystems completed enrollment of COSTAR II piloted Randomized Drug-Eluting Stent Trial to test the development of an innovative controlled vascular drug delivery technology, COSTAR II (CObalt chromium STent with Antiproliferative for Restenosis). If the results of this clinical trial prove favourable, the company will submit an application for marketing approval to U.S. Food and Drug Administration for its CoStar(TM) stent in early 2007, and it may receive regulatory approval in late 2007 or early 2008. Nevertheless, the company advised potential investors, that among the risk factors that could influence the results of the experimentation's, the chance of infringing property rights should be included.

Does the introduction of DES presume some additional licensing fees to be paid?

Methods

Internet search, manufacturer web-sites

Results

No licensing fees apply to health care organisations that use drug eluting stents.

Companies which intend to produce Drug Eluting Stents, should pay an additional licensing fee, for loading the devices with a drug registered under another company's label. Some examples of additional licensing fees are reported:

- To develop CYPHER, Cordis Corporation. paid an additional fee to SurModics Inc.;
- BIOTRONIK AG and Conor MedSystems signed an agreement with NOVARTIS to develop a next-generation Drug Eluting Stents;
- Singapore-based Biosensors International sold certain assets of its everolimus eluting stent programme to Guidant Corporation (part of Boston Scientific).

Furthermore, DES producers should pay an additional fee to other companies to run clinical trials which compare stents loaded with different drugs.

What are the width, depth and length of the manufacturers guarantee?

Methods

Internet search, manufacturer web-sites, technology brochures and users-guide

Results

Manufacturers provide information on the guarantee in their documentation that is sometimes freely available online. In some cases the guidelines are available only through specific request.

Is the user guide of DES comprehensive enough?

Methods

Internet search, manufacturer web-sites, technology brochures and users-guide

Results

Some users' guides have been downloaded and examined. In our opinion the best guide found is available for free and is structured as follows:

1. device and drug component description
2. indications
3. contraindications
4. warnings
5. precautions
6. drug information
7. overview of clinical studies
8. adverse events
9. clinical studies
10. individualization of treatment
11. patient counselling information
12. how supplied
13. operators instructions
14. in vitro information
15. reuse precaution statement
16. warranty.

The user guide seems to be very comprehensive and satisfactory for patients and clinicians. In particular, the section about clinical evidence appears very clear. Other users' guides are not available immediately on the web. User is expected to fill out a request form. Nevertheless, a company web-site is linked with a site dedicated to stents that provides information for patients.

Regulation of the market

Is DES subject to price control?

Methods

The European Court of Justice Database has been searched by using the keyword "stent". Medline database has also been searched by using keywords "stent" and "price control". In addition, a grey literature research regarding the Italian system has been performed.

Results

European Court of Justice Database research did not identify any useful information on stents. Medline research identified 15 articles but they are not directly linked to this issue. According to the authors, there is not an explicit price control of the stent market. Stent financing methods (i.e. centralized purchasing by Regional Health System, in the Italian region Emilia-Romagna) can be considered indirect systems to control price.

Is DES subject to acquisition regulation?

Methods

"Directive 2004/18/Ec" was consulted to verify if it contains prescriptions that may influence stents acquisition

Results

“Directive 2004/18/Ec” does not contain prescriptions on stents acquisition. This is a general law on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts, without explicit reference to medical devices or stents sector.

Is the marketing of DES to the patients restricted?

Methods

Medline was searched using keywords such as “stent”, “device” and “marketing” (“stent or device and marketing”) in title. Also other non-scientific search engines were consulted.

Italian Ministry of Health website and “Eurolex” were searched, in order to identify national laws on marketing in Italy and in the EU.

Results

Articles from Medline were not pertinent to this issue. Other search engines underlined the role of CE certification to allow the introduction of a new device into the market. No information was found about the possibility to perform marketing activities directly to patients.

The Council Directive 93/42/EEC of 14 June 1993 concerning medical devices defines, in the article 2, that “Member States shall take all necessary steps to ensure that devices may be placed on the market and put into service only if they do not compromise the safety and health of patients, users and, where applicable, other persons when properly installed, maintained and used in accordance with their intended purpose”. In addition article 17 states that “Devices ... must bear the CE marking of conformity when they are placed on the market”. In Italy this directive has been ratified with Law n. 46 of 24-02-97. Italian Ministry of Health website published national laws on advertising of devices. In particular, the Italian Law states that medical devices which need medical assistance must not be advertised (Ministry of Health Law of 23.2.2006, GU 21.4.2006, art 1, part1, letter d)

Comment

Marketing and advertising activities are usually restricted by national laws. In Europe, pre-marketing requirements are based on the CE mark

Legal regulation of novel/experimental techniques

Are new legislative measures needed?

Methods

A search of grey literature on the European level was performed. We searched in EURLEX database and in the websites of EMEA and EUCOMED.

Results

Given the complexity and rapid evolution of this sector, a regular review of Directive 93/42/EEC has been provided for by the regulator. On 22 December 2005, the European Commission published its proposed amendments after extensive stakeholder consultation. The text is now with the European Parliament Environment in first reading.

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APPENDIX: Table template for translating assessment elements

Domain	Topic	Issue	Relevance in the context of DES Yes/No	Research question(s) in the context of DES	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not
Legal aspects	Autonomy of the patient	Is the patient competent to make his/her own health care decisions?	YES		3	3
		Can the patient understand the implications of using/not using the technology?	YES		3	2
		Are there relevant optional technologies that the patient should be allowed to consider?	YES		3	2
		Is it possible to give the patient enough time to consider his/her decision?	YES		2	2
		Is it possible to obtain an advance directive on the use of the technology?	NO because it is not necessary to obtain an advance directive on the use of this specific technology.		2	1
		Has the patient prescribed such a directive?	NO because it is not necessary to obtain an advance directive on the use of this specific technology.		3	1
	Privacy of the patient	Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the patient?	NO because PTCA procedure with Stent insertion (both DES and BMS) doesn't produce additionally information, diagnostically and/or therapeutically irrelevant regard PTCA.		3	3
		Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the relatives of the patient?	NO because PTCA procedure with Stent insertion (both DES and BMS) doesn't produce additionally information, diagnostically and/or therapeutically irrelevant regard PTCA.		3	1
		Is the access to the patient data secured properly?	YES		2	1
		How many people in the chain of care need to get access to the patient information?	YES		1	1
	Equality in health care	Is the technology equally accessible to all needing members in a given society?	YES		3	2
		Is the technology subsidized by the society?	YES		2	1
		Is there a wide variation in the permissibility of the technology across Europe?	No because there is nothing specific on DES permissibility.		3	3

		Is health-care tourism expected from/to other European countries?	YES		2	3
	Authorisation & safety	Has the technique proper national/EU level authorisation?	YES		3	3
		Does the technology need to be listed in a national/EU register?	YES		2	2
		Does the technology fulfil product safety requirements?	YES		3	3
		Does the technology fulfil tissue safety requirements?	YES		3	3
	Ownership & liability	Does the technology infringe some intellectual property right?	YES		2	3
		Does the introduction of the technology presume some additional licensing fees to be paid?	YES		2	2
		What are the width, depth and length of the manufacturers guarantee?	YES		3	3
		Is the user guide of the technology comprehensive enough?	YES		3	3
	Regulation of the market	Is the technology subject to price control?	YES		3	2
		Is the technology subject to acquisition regulation?	NO because DES doesn't determine variations on laws in comparison with BMS.		3	2
		Is the marketing of the technology to the patients restricted?	YES		3	2
	Legal regulation of novel/experimental techniques	Is the technology so novel that no legal rules are directly applicable?	NO (don't applicable to DES technology)		3	1
		How the liability issues are solved according to existing legislation?	NO (don't applicable to DES technology)		3	1
		Are new legislative measures needed?			2	1
		Is the voluntary participation of patients guaranteed properly?	NO (don't applicable to DES technology)		3	1