


EUnetHTA
CORE HTA ON MSCT CORONARY ANGIOGRAPHY
PILOT ASSESSMENT - NOT FOR DECISION-MAKING
WORK PACKAGE 4
DECEMBER 2008
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eunetha
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Core HTA on MSCT Coronary Angiography

was developed by

Work Package 4

The HTA Core Model

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



December 2008

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 Members 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 MSCT Coronary Angiography

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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Editors' Notes

This is the final deliverable of this document, Core HTA on multislice computed tomography (MSCT) coronary angiography. This Core HTA is based on the HTA Core Model for diagnostic technologies, 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 diagnostic HTA Core Model. We wanted to gather experiences from a novel way of preparing of health technology assessment work, rather than prepare a valid assessment on MSCT. 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 is 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. Feedback from other EUnetHTA work packages, collaborators and the public was received in the validation round.

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 EUnetHTA project aims at facilitating HTA information sharing within Europe. In order to achieve this, the development of a standardised structure for the conduction and reporting of HTAs, a HTA Core Model, was considered essential. Work Package (WP) 4 of the EUnetHTA Project developed two applications of the HTA Core Model - one for medical and surgical interventions and the other for diagnostic technologies – which describe the structure, means of rigorously developing, and transparently presenting information in HTA (1, 2).

In this document the feasibility of the HTA Core Model on diagnostic technologies was piloted in an assessment of multislice computed tomography (MSCT) angiography. The pilot Core HTA on MSCT focused on the use of the MSCT angiography in patients with low or moderate risk for coronary artery disease. Patients with the history of acute myocardial infarction or with acute or severe symptoms, as well as screening of asymptomatic patients, were not included in the assessment.

Policy questions related to the use of MSCT coronary angiography can vary markedly between countries. The Core HTA covers a wide range of questions to fulfil the different needs. The HTA Core Model can be seen, among other things, as a checklist for producing an HTA on any single topic. The resulting Core HTA may 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 pick out building blocks for their own national or regional assessments. National, regional or local technology assessments based on a Core HTA may therefore come out differently with different sets of issues included depending on the country and the policy question.

Reports on MSCT that have utilized the Core HTA or a local HTA that is based on the Core HTA may provide different answers to one and the same question, for instance due to the price of stents, salaries of health professionals, or reimbursement systems that may vary notably from country to country. However, regardless of those differences, a thoroughly performed Core HTA should provide a useful starting point for preparing a context-specific report more rapidly than would be possible by starting the whole assessment from scratch or by adapting from a traditional full-text report from another country.

Methodology

The assessment of MSCT coronary angiography was based on the HTA Core Model for diagnostic technologies (2) developed by the participants in EUnetHTA Work Package 4 (WP4). The Model

employs ten domains, nine of them originally established in the EUR-ASSESS project (3) and one added regarding diagnostic accuracy.

The domains

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

There has been discussion about the position of the Accuracy domain. Taking into account the opinions of several investigators in WP4 and the validation feedback, it is possible that the accuracy issues will be incorporated in the Effectiveness domain in the next version of the HTA Core Model for diagnostic technologies.

Selection of topic

An invitation to participate in the web-based survey was sent by email to the participating organisations of WP4 in 17 European countries. From among 14 proposals, a two-step voting process in December 2006- February 2007 identified the multislice computed tomography (MSCT) coronary angiography as a topic of high interest.

The selection of MSCT coronary angiography as the piloting theme was motivated with following reasons:

- As MSCT is a non-invasive technology, there is a risk that it will be inappropriately used.
- MSCT has the potential to reduce the number of invasive coronary angiographies
- Information on the cost-effectiveness of MSCT compared to other non-invasive procedures, e.g. MRI, would be useful.
- There are several safety and patient issues of relevance, e.g. radiation, contrast agents, and beta-blockade.

The work process

The working teams were re-built in April-Sept 2007 from the previous WP4 teams that had developed the first HTA Core Model for medical and surgical interventions, and produced the Core HTA on drug eluting stents. Substantial changes took place in the description of the technology and safety domain teams. Also in the current use and social aspects domains more than half of the investigators were new.

The ten domain teams all had a coordinator and a primary investigator whose responsibility was to elaborate the document in due time. Each domain team worked independently in their own fashion. In most cases, the primary investigator produced a draft text which was commented and amended

by the other investigators in team. Some teams distributed tasks to their members, thus sharing active authorship more evenly.

The investigators in the domain teams started their work with the preparation of the HTA Core Model on diagnostic technologies in October 2007. In January 2008 the generic research questions in the HTA Core Model were created and the teams could start considering specific questions for the MSCT Core HTA. Basic literature database searches were performed in December 2007, using disease-specific (coronary artery disease) and technology-specific (MSCT) search terms. No restrictions of study designs were used. The detailed search strategies are in Appendix 1. The teams were advised to combine their domain specific search terms to the basic search. Additionally, each team searched additional databases and other information sources.

In February 2008 there was a general discussion on the framing or focusing of the MSCT Core HTA. Investigators in various teams encountered the typical problem of diagnostic tests research; the research questions turned out to be highly context-specific. A simple PICO (patient-intervention-comparison-outcome) was not enough to define the scope of the HTA of this diagnostic procedure. The research questions were very different if we were dealing with the value of MSCT in comparison to conventional invasive coronary angiography, or if we were interested in the ability of MSCT to reliably rule out the diagnosis of coronary artery disease in patients, thus reducing the need for invasive angiographies. We decided to consider the latter: the added value of a management pathway with MSCT in ruling out coronary artery disease in patients with low to intermediate risk of having the disease, compared to a pathway without MSCT. We chose this clinically relevant comparison, although we knew that the majority of published research was done with the view of comparing MSCT with invasive coronary angiography in high risk patients. The next chapter and appendix 2 contain a more detailed description of the framing problem.

The first internal (not public) draft of the Core HTA on MSCT was delivered to all investigators in July 2008. In August 2008 the primary investigators of each domain were asked to produce a brief summary, less than 700 characters long, of the main results from their domain. The editors of the MSCT Core HTA then prepared, on the basis of the domain summaries, a common summary for the whole Core HTA. In October 2008 all EUnetHTA and INAHTA members were called to participate in the validation of the MSCT Core HTA document. There were 17 respondents in the comprehensive multi-element validation questionnaire. Final changes to both project deliverables, The HTA Core Model on diagnostic technologies and Core HTA on MSCT, were made according to the validation feedback. The development of the HTA Core Model will continue and consequent versions published.

Framing the topic

In the present clinical diagnostic setting of coronary artery disease (CAD), it is not straightforward to decide how to compare the costs and effectiveness of MSCT coronary angiography. In the literature, MSCT has mainly been compared to invasive coronary angiography (ICA) due to the similarity of information obtained by these two methods (anatomical or structural imaging). However, in the current use as a rule-out test in low or moderate likelihood CAD patients, this comparison does not represent clinical decision making since ICA is seldom justified solely as a rule-out test for CAD. Widely used early diagnostic tests for CAD, on the other hand, measure other aspects of the CAD: stress tests (ergometry, dobutamine echo, SPECT, PET etc) look at ischemia as

a sign of functional performance of the heart, whereas currently the information obtained from MSCT is purely structural.

Selection of the reference test is also dependent on the indications for diagnostic procedures, which have not been well established. The use of different diagnostic methods depends on physician's and patient's preference, health care system, local facilities, reimbursement and insurance systems, etc. rather than on clinical relevance, making this field even more complex. MSCT has even been used as a screening test for CAD in patients without CAD symptoms.

Current use of the MSCT in Europe is becoming more and more established as a diagnostic test for ruling out significant coronary artery disease in patients with low or moderate risk and specific or unspecific symptoms of coronary disease (see appendix 2). For this purpose there is no other diagnostic method that could totally replace it or could be nominated as the control or reference diagnostic test for MSCT at the moment.

Therefore it might be reasonable to compare the whole diagnostic path (including the selection of treatment options) of defined patient populations with a situation where the treatment decisions are made without the information obtained from MSCT. Pre-assumptions for this path are 1) low or moderate likelihood of CAD related to factors such as age, gender, symptoms, risk factors for CAD, 2) the clinician's suspicion of coronary disease and 3) esteemed usefulness of established CAD diagnosis for decision-making concerning the treatment options.

Information obtained from MSCT should always have clinical impact, either in the sense of ruling out CAD and consequent unnecessary medical treatment, or verifying the diagnosis of CAD with optimal treatment protocol and possibility to avoid coronary disease end-points such as acute myocardial infarction, invasive treatment or death. Costs and effectiveness depend on these.

In patients with high risk for CAD, the use of MSCT does not usually provide any clinically relevant additional information. Ruling out CAD in diabetic patient for instance does not change patient's medical therapy. Therefore, the diagnostic path should proceed either to functional imaging (Stress echo, SPECT etc.) in search for ischemia, or directly to ICA and invasive treatment of the CAD, whenever the patient is judged to benefit from interventional treatment. If invasive treatment is out of the question in these patients, the anatomical CAD diagnosis does not provide any useful information for decision making.

On the other hand, a low-risk patient with atypical symptoms might benefit from the MSCT: if significant CAD can be ruled out, there is no need for medical treatment, no treatment costs and no possible side-effects from the medication. If the diagnosis of CAD can be verified by MSCT, the consequent use of optimal medical treatment will decrease the risk for acute myocardial infarction and probability for invasive treatment.

Modelling of different diagnostic paths and treatment options either with or without the use of MSCT might provide useful information for costs and economic evaluation as well as effectiveness domains. It would be a challenge for HTA, but of higher clinical relevance compared to the traditional approach where ICA is used as the control test for MSCT. In this situation, the costs caused by MSCT would be compared either with assumed costs of the unnecessary medical treatment of subjects without CAD, or with the costs of acute myocardial infarction etc. in the population that did not get medical treatment for CAD due to failed diagnosis. In this way we could obtain relevant information for the definition of indications and use of MSCT that might also benefit clinical decision making.

Research questions and exclusion criteria

The following important questions and study exclusion criteria were jointly considered during the assessment process:

What are the questions?

- What is the accuracy of MSCT coronary angiography in the diagnosis of coronary artery disease (CAD) (or exclusion of the disease) in patients with suspected or stable angina pectoris.
- Does MSCT diminish the need for invasive coronary angiography?
- What is the added value of MSCT coronary angiography in selecting proper treatment, e.g. risk factor reduction, medical treatment, invasive treatment?
- What is the added value of MSCT coronary angiography in patient health outcomes and quality of life?
- What are the harms that rise using MSCT coronary angiography?
- What are the legal premises and organisational, ethical, social and economical consequences of the use of MSCT coronary angiography?

What kind of studies will be excluded?

- Diagnosis of acute chest pain, myocardial infarction/acute coronary syndrome.
- Monitoring treatment effect after PTCA, stent or CABG.
- Assessment of coronary arteries in adjunction with other diseases of the myocardium, heart valves or ascending aorta.
- Assessment of coronary anomalies.
- Screening of asymptomatic high-risk or low-risk populations.

Application of the HTA Core Model

Translating issues into research questions

The HTA Core Model is structured into ten domains, and each domain is further divided into more specific topic areas. Each topic is further divided into one or more issues, i.e. generic 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.

First, all domain teams started with their respective assessment element table from the HTA Core Model on diagnostic technologies. The teams went through the generic research questions of each assessment element (i.e. the issues) and considered their relevance for MSCT Core HTA. After selecting the relevant ones, the teams translated the issues into MSCT-specific research questions. For example, in the domain of Safety, under the topic of Technology dependent safety issues, the issue asks: What is the timing of onset of harms: immediate, early or late? For MSCT Core HTA this was translated into a specific question: What are the immediate and long term consequences of the radiation exposure from MSCT coronary angiography? Some issues were translated into several related research questions. Omitted issues (and reasons for omission) were recorded in the Core HTA report, as it may provide useful information.

Finding answers to the research questions

After defining relevant issues and translating them into answerable questions, the teams proceeded in finding answers to the questions. The Methodology sections of the respective domains in the HTA Core Model on diagnostic technologies give guidance on where to find published literature or other relevant information, how to search for it, assess its quality, synthesize, and report the findings of published literature or other information. If other sources or means of assessment were used with a certain research question, the teams were asked to report this in the Methods section of the respective assessment element in the MSCT Core HTA report.

A Systematic review of published primary and secondary literature and other information sources are usually the method of choice in finding evidence for a specific research question. For every assessment element this was not a feasible approach, and even not necessary. For example there is an assessment element in the domain "Health problem and current use of technology" called "What are the potential indications and aims of MSCT in diagnostic cardiology?" where systematic review was not intended. Instead, information was retrieved from earlier HTA reports and consensus statements. Most important is that the authors are transparent and state in the methods section of the assessment element whether they intended to do a thorough search of primary publications with predefined inclusion criteria, or if they were just considering some recent information sources, in order to be convinced about the trustworthiness of the information.

Sometimes there are no published studies that answer the issue. This was the case in the Social aspects domain where no relevant literature on patient experiences of MSCT coronary angiography was found. In this case the solution was that the investigators interviewed patients and professionals in order to gather original data for the assessment.

Assessment elements from previous Core HTAs will be increasingly available when the number of Core HTAs rise. These will be useful sources of information for Core HTA authors in future. Even in MSCT Core HTA, where there was only one prior Core HTA, namely that of drug eluting stents (DES), some domain teams were able to use the results of some assessment elements of the previous Core HTA as such, or updating, or modifying them. This was due to the fact that both reports deal with coronary artery disease. For transparency the original work and authors were referred in the methods section of the corresponding elements in the Core HTA on MSCT.

Assessing the quality of information

The domain teams were asked to assess and report the quality of information retrieved and used in the assessment. They were also asked to report the tool or the specific quality assessment criteria in the methodology section of the domain, or in the Methods section of the single assessment element if the tool differs from that explained in the methodology section. It should be also stated in what way the quality of information will be used (e.g. in the exclusion process, or looking at studies in quality adjusted subgroups). A comment should also be included if no formal quality assessment criteria was used.

Reporting answers to the questions

The issues and answers to them can be presented in a traditional way as text in chapters. Tables and figures are also possible. For the purposes of this report we chose the same standard structure for each domain that was used already in the Core HTA on drug eluting stents. The following main chapters are included:

- **Introduction**

puts the assessment in context within the domain. It provides information on the reasons for assessing MSCT (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.

In the future and online version of the HTA Core Model will support the presentation of the results of Core HTAs that could be stored in an electronic database and accessed for only those elements that are relevant for the user. In the next steps of the EUnetHTA project, we will still pilot with various modes of using the Core Model and presenting the results.

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. In the current version of the Core Model, it has not yet been possible to consider extensively the overlaps between domains and indicate these in the structure.

There were some overlapping issues in the MSCT Core HTA as well and probably also some double work done too. This information will be used to further improve the HTA Core Model to guide its users in the future to careful coordination between domains to avoid the identified overlap.

References

- (1) EUnetHTA WP4. HTA Core Model for medical and surgical interventions. 2008.
http://www.eunetha.net/Work_Packages/WP_4/Activities/
- (2) EUnetHTA WP4. HTA Core Model for diagnostic technologies. 2008.
http://www.eunetha.net/Work_Packages/WP_4/Activities/
- (3) Liberati A, Sheldon TA, Banta HD. EUR-ASSESS Project Subgroup report on Methodology. Methodological guidance for the conduct of health technology assessment. *Int.J.Technol.Assess.Health Care* 1997 Spring;13(2):186-219.

Appendix 1 Basic search strategy

Database: CRD (= HTA, EED, DARE)

Search date: 4.12.2007

Name of search performer: Jaana Isojärvi, information specialist, Finohta

Search strategy:

#1 MeSH Coronary Disease EXPLODE 1 2

#2 (coronary AND (disease* OR arter* OR aneurysm* OR stenosis* OR restenosis* OR thrombosis* OR vasospasm* OR vessel*)) OR "angina pectoris" OR "chest pain" OR atherosclerosis*

#3 #1 OR #2

#4 MeSH Coronary Angiography EXPLODE 1 2 3

#5 MeSH Tomography, X-Ray Computed EXPLODE 1 2 3 4 5 6

#6 #4 AND #5

#7 angiograph* AND tomograph*

#8 #6 OR #7

#9 #3 AND #8

#10 msct OR mdct

#11 (multislice OR "multi-slice" OR "multi slice" OR multirow OR multidetect* OR "multi-detect*" OR "multi detect*" OR multiselect*)

#12 (4 OR 16 OR 32 OR 40 OR 64) AND (slice* OR row*)

#13 #10 OR #11 OR #12

#14 #9 AND #13 □ 24

Database: Ovid MEDLINE(R) <1950 to November Week 2 2007>

Search date: 7.12.2007

Name of search performer: Jaana Isojärvi, information specialist, Finohta

Search strategy:

1 exp Coronary Disease/di, ra [Diagnosis, Radiography] (36545)

2 (coronary adj2 (disease\$ or occlus\$ or vessel\$ or arter\$ or stenosis\$ or restenosis\$ or aneurysm\$ or thrombosis\$ or vasospasm\$ or obstruct\$)).tw. (147726)

3 calcinosis/di, ra or myocardial ischemia/di, ra (13707)

4 1 or 2 or 3 (174520)

5 exp Coronary Angiography/ (32102)

- 6 exp Tomography, X-Ray Computed/ (191788)
- 7 5 and 6 (2083)
- 8 (angiograph\$ and tomograph\$).tw. (12150)
- 9 7 or 8 (13378)
- 10 4 and 9 (3087)
- 11 (msct or mdct).tw. (2055)
- 12 (("8" or "16" or "32" or "40" or "64") adj2 (slice\$ or row\$)).tw. (1262)
- 13 (multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi-detect\$" or "multi detect\$" or multiselect\$ or "multi-select\$" or "multi select\$").tw. (6255)
- 14 11 or 12 or 13 (7422)
- 15 10 and 14 (944)
- 16 animals/ (4261058)
- 17 humans/ (10120566)
- 18 16 not (16 and 17) (3224038)
- 19 15 not 18 (937)
- 20 limit 19 to yr="1990 - 2008" (936)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 03, 2007>

Search date: 5.12.2007

Name of search performer: Jaana Isojärvi, information specialist, Finohta

Search strategy:

- 1 (coronary adj2 (disease\$ or vessel\$ or arter\$ or stenosis\$ or obstruct\$ or restenosis\$ or thrombosis\$ or vasospasm\$ or occlusion\$)).ti,ab. (3498)
- 2 (angina pectoris or calcinosis\$ or myocardial ischemia\$).ti,ab. (499)
- 3 1 or 2 (3795)
- 4 coronary angiography\$.ti,ab. (417)
- 5 (ct or computer tomography\$ or computed tomography\$ or computerized tomography\$).ti,ab. (6058)
- 6 4 and 5 (102)
- 7 (angiograph\$ adj5 tomography\$).ti,ab. (216)
- 8 6 or 7 (284)
- 9 (mdct or msct).ti,ab. (227)
- 10 (multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi detect\$" or multi-detect\$" or multiselect\$ or "multi-select\$" or "multi select\$").ti,ab. (440)
- 11 (("8" or "32" or "16" or "64" or "40") adj2 (slice\$ or row\$)).ti,ab. (137)
- 12 9 or 10 (519)
- 13 3 and 8 and 12 (50)

Appendix 2 Diagnostic pathway

FIGURE 1. DIAGNOSTIC PATHWAY FOR STABLE CORONARY ARTERY DISEASE

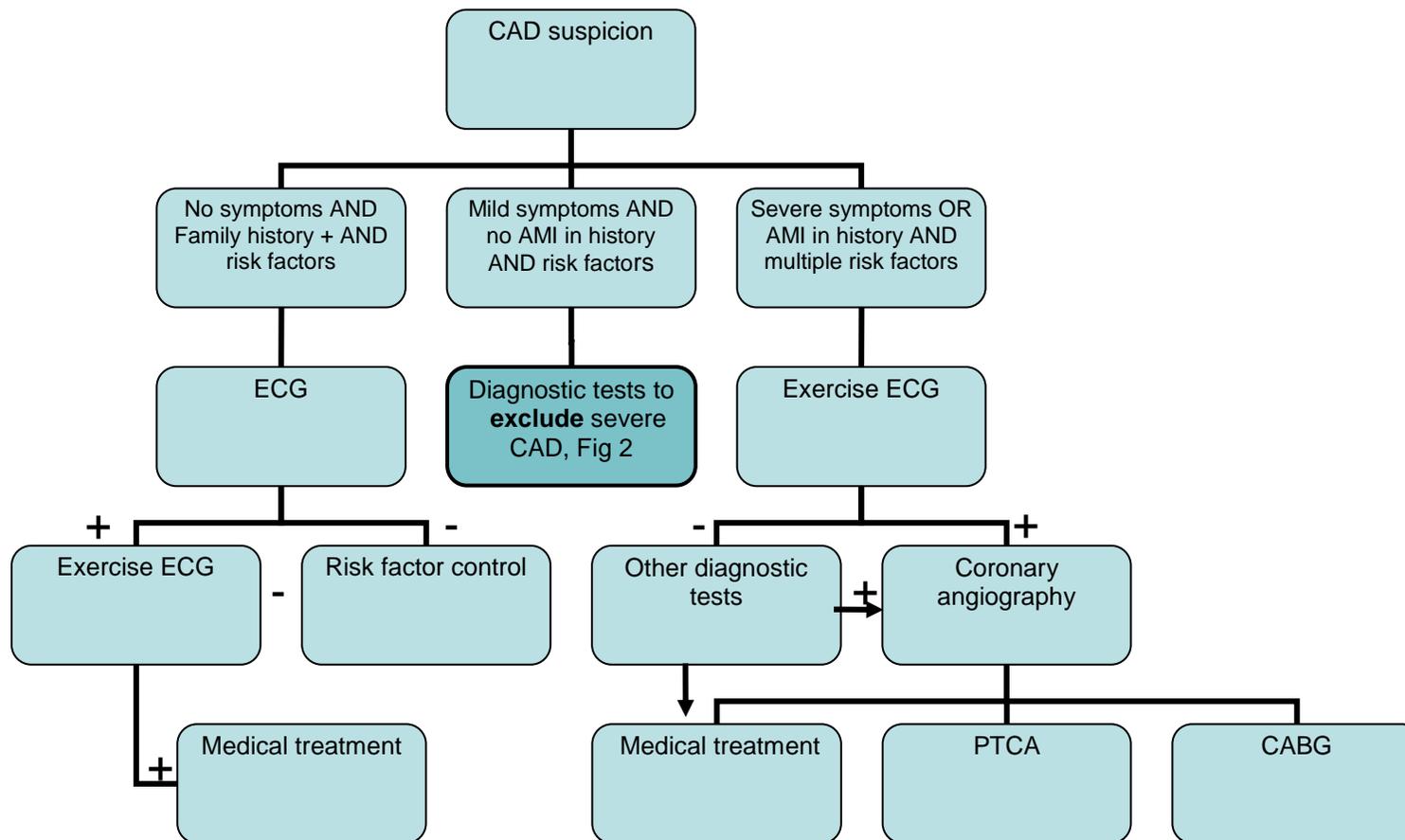
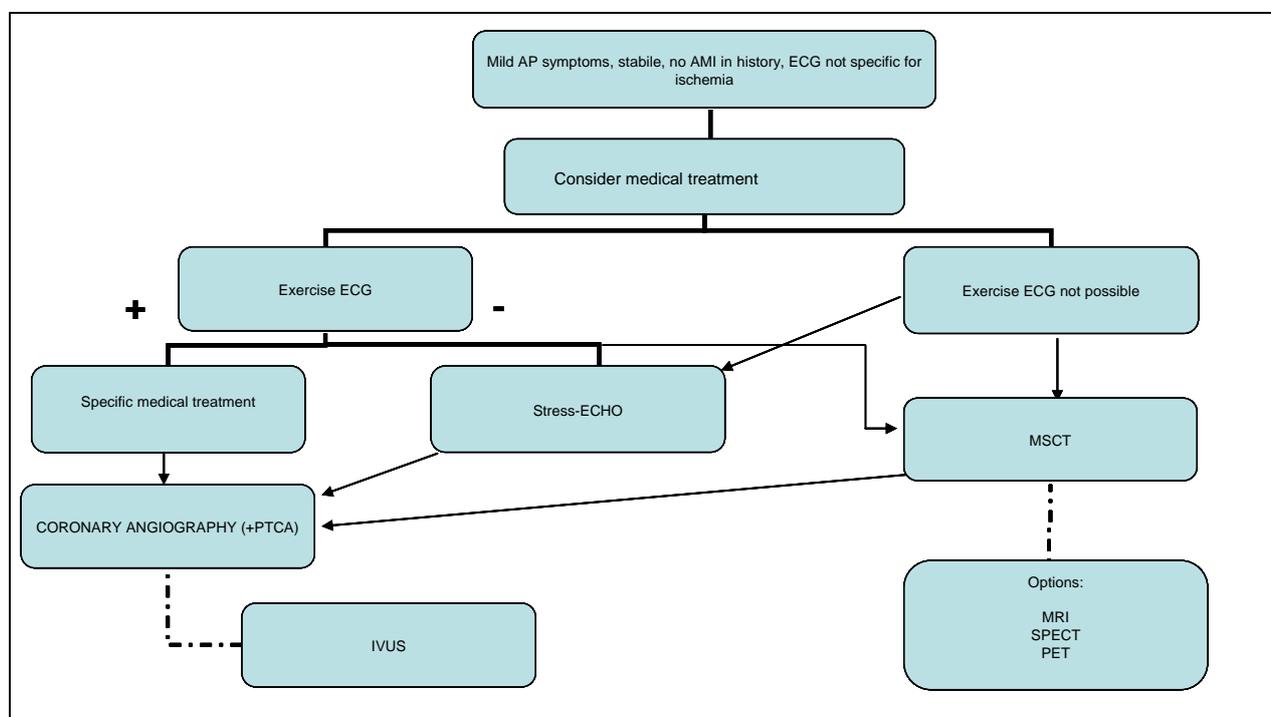


FIGURE 2. DIAGNOSTIC PATHWAY FOR MILD TO MODERATE CORONARY SYMPTOMS IN PATIENTS WITH LOW PROBABILITY FOR SEVERE CORONARY ARTERY DISEASE



Glossary:

MSCT	Multi-slice Computed Tomography
CAD	Coronary Artery Disease
AP	Angina pectoris, chest pain with cardiac origin
PTCA	Percutaneous Transluminal Coronary Angioplasty (usually balloon angioplasty or stenting)
CABG	Coronary Artery Bypass Surgery
AMI	Acute myocardial infarction
ECG	Electrocardiogram
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SPECT	Single photon emission computed tomography
IVU	Intra vascular ultrasound

Summary

Coronary artery disease (CAD) is the single most common cause of death in the Europe. In developed European countries, 17% of all DALYs (Disability Adjusted Life Year) lost are due to cardiovascular diseases. The golden standard for the diagnosis of coronary artery disease (CAD) is invasive coronary angiography (ICA). In past decades non-invasive imaging has been developed to serve as first-line diagnostic tool instead of or alongside ICA. Computed tomography angiography, and especially its advanced multi-slice versions (MSCT), has been suggested as a promising non-invasive imaging modality which could triage patients for ICA. In 2004 only early adopters were using 64-slice CT. Since then it has become increasingly available in many European countries.

MSCT is a rapidly evolving technology; completely new generations, with added image slices or dual X-ray tube sources, with new features are entering market. The use of MSCT in coronary angiography requires close cooperation between radiologists and cardiologists. There are guidelines that define the training requirements and proper user conditions for cardiac computed tomography. There are consensus statements about appropriate indications for MSCT. According to them one of the indications for cardiac imaging is to rule out CAD in patients with suspicion but with low to moderate risk of having the disease.

Radioactivity and the use of iodinated contrast media are the major safety issues in the use of MSCT. Induction of cancer especially in the young and women, and contrast induced nephropathy in patients with impaired renal function are the principal concerns. There are technical means to reduce the radiation dose received, but this is usually with the cost of image quality. The risk of contrast induced nephropathy may be reduced with careful patient assessment prior to MSCT.

The sensitivity of 64-slice CT against ICA for the diagnosis of CAD is excellent, and specificity is good. The values do not seem to be affected by the pre-test likelihood of CAD in a patient group where the risk of having the disease is low to intermediate. Research results support the use of 64-slice MSCT for exclusion of CAD in patients with low or intermediate risk of the disease. The negative predictive value (NPV) of MSCT is excellent in this group, which means that a negative test result reliably excludes CAD and the need for ICA. The positive predictive value (PPV) is therefore only modest to good. The accuracy of MSCT to detect CAD is better than in another non-invasive imaging test, single photon emission computed tomography (SPECT), when ICA is considered as the common reference test.

Assessment of effectiveness for a diagnostic test requires different approach from the basic accuracy assessment and leads to a more complex study design. Very few studies were identified that dealt with the usefulness of 64-slice CT in the diagnostic path of patients with stable chest pain and low to intermediate risk of coronary artery disease (CAD). Based on accuracy data and what is known from large population studies of CAD prevention, 64-slice CT helps to identify and classify the patients between groups of primary and secondary prevention and patients between obstructive and non-obstructive disease. Further studies are needed to find more specific and direct evidence to the questions asked in the elements of EUnetHTA effectiveness domain. These questions are of major interest and they are essential requirements in the core of clinical work: does the effort paid for diagnostic work-up really benefit the patients?

A full economic evaluation of MSCT coronary angiography requires more data on the clinical effectiveness of this diagnostic technique in preventing morbidity and mortality. It is yet impossible to conclude whether MSCT is cost-effective compared to the standard diagnostic protocols in low to intermediate pre-test likelihood patients. Nevertheless, a specific economic evaluation alongside a randomised controlled trial (RCT) is frequently cited to demonstrate the technique's cost-effectiveness. We challenge the conclusion drawn from the one RCT available in this assessment saying that MSCT is cost-effective relative to standard of care. A basic economic evaluation, based on this data showed that taking treatment or patient outcomes into account might reverse the conclusion about the cost-effectiveness of MSCT. However, given the small number of patients in the RCT, firm conclusions about cost-effectiveness cannot be drawn.

From an ethical point of view following points should be taken into consideration. The relation of benefits and harms in all potential clinical applications is still unclear. While typical patients in cardiac MSCT present mild and stable symptoms, they are probably capable of making their own decision about testing. Nevertheless, there may be some important but complex trade-offs between MSCT and other diagnostic technologies (such as stress testing or ICA), the consequences of which may be difficult to comprehend regardless of thorough information.

The investigation of MSCT's impact on management and structure of organization was very complex, because organisational aspects are rarely analysed within clinical studies and HTA reports and hence little evidence is available in the scientific literature. The traditional systematic literature review was not completely suitable to obtain full information on organisational aspects, and it was necessary to complement the search with analysis of other sources. The impact of MSCT-64 on clinical pathways of patients could lead into reduced length of stay and avoidance of unnecessary further investigations for chest pain. Introducing MSCT-64 into practice does not lead into completely novel organisational challenges. Comparative imaging systems have been introduced before. Closer co-operation across the disciplines of cardiology and radiology is probably a new or incremental feature brought by the introduction of cardiac CT.

Social and patient related aspects of MSCT were analysed from the published scientific literature as well as from semi-structured interviews of patients and experts. Major life areas where change may be generated by MSCT are life at home and working life. While the direct social consequences by technology use seem to be minor, larger consequences are to be expected by a diagnosis of CAD. Individuals report only minor physical and psychosocial consequences of MSCT, with conflicting information regarding the experience of pain and uneasiness during the waiting time for the results being the major components. According to the limited data available, communication regarding the conduct of the examination and the meaning of results seem to be satisfactory - as it was expressed in patients and experts interviews as well as in the literature. These preliminary results need confirmation in further research.

The objective of legal domain was to point out questions on basic rights of patients (autonomy, informed consent, privacy and confidentiality) and legal requirements of the new technology (authorisation, guarantee, and regulation of market). It was very difficult to find specific information on MSCT on legal issues, because usually the literature and the laws use the general concept of CT. As a consequence, the MSCT, from this point of view is not a completely new technology, because its use, as far as legal issues are concerned, is similar to traditional CT. The main issues are about legal requirement to guarantee the safety (health protection of individuals against the dangers of ionizing radiation).

Health problem and current use of the technology

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Nieves Sobradillo, Nick Hicks, Leonor Varela Lema, Marcial Velasco Garrido*

Introduction

Coronary artery disease (CAD) is caused by impaired blood flow and deficient oxygen supply to myocardium, mostly induced by atherosclerosis or build up of plaque in the arteries. CAD may be manifested by stable angina pectoris, acute coronary syndromes - including myocardial infarction and unstable angina, or sudden death. CAD is one of the leading causes of death in Europe. The reference standard for the diagnosis of CAD is conventional coronary angiography which enables visualisation of the coronary lumen. Due to its invasiveness, coronary angiography is less suitable for first line diagnostic test. In past decades non-invasive imaging has been developed for this purpose.

Several non-invasive technologies such as stress echo cardiography, myocardial perfusion imaging and single photon emission computed tomography (SPECT) have become available to assess cardiac function. The anatomical assessment of coronary arteries has become possible with the introduction of multi-slice computed tomography (MSCT) coronary angiography. Other anatomical non-invasive modalities, magnetic resonance imaging (MRI) and electron beam computed tomography (EBCT), have not yet gained a role in routine clinical practice (1).

The 64-slice computed tomography (CT) application came to market in 2004. Since then several trials have been performed. The first trials using dual-source 64-slice CT scanners were published in 2007, at which time also 256- and 320-slice devices became available. Because of the rapid development and the penetration of next generation scanners into use, the assessment in this domain focuses on 64 or more slice CT-scanners.

MSCT can be used for risk stratification in evaluating CAD by assessing calcifications in coronary arteries, and coupled with intravenous contrast administration, as diagnostic coronary angiography. The assessment elements in this domain may briefly describe risk assessment, screening and other uses of the technology, but they concentrate on the diagnostic use of MSCT in native coronary arteries (no stents or bypass grafts) in a population with no known heart disease.

Currently MSCT coronary angiography is becoming increasingly established in Europe as a diagnostic test for ruling out significant coronary artery disease in patients with low or moderate risk and specific or non-specific symptoms of CAD. There is no other diagnostic method available that could totally replace it in this role.

As MSCT is a non-invasive technology there is a risk that it will be inappropriately used beyond its original indications. While it is an expensive and rapidly evolving technology with potentially harmful effects (from ionizing radiation), frequent and comprehensive assessments of its role and effectiveness are important.

Methodology

Information for this domain comes from epidemiological research, reviews and registries. We did a basic search for HTA-reports and systematic reviews, and an additional search in Medline. Details of search strategies are described in Appendix 1. Further information was sought from the bibliographies of relevant documents and the Internet.

We did not intend to conduct a systematic review of issues like current indications or diagnostic pathways. Rather, information was retrieved from earlier HTA reports, consensus statements, and introduction sections of guidelines, reviews and original articles.

The disease (i.e. CAD) that the technology is used for is essentially the same as in the other Core HTA (on drug eluting stents) that has been prepared within the EUnetHTA project. Therefore we utilized results of several corresponding assessment elements from the earlier work as such or as a base for more focused text. This is mentioned and original work referred to in the methods section of the elements.

There is no standard, straightforward way to assess the quality of sources and information used in this domain. Due to restrictions in time during this project we did not use any formal quality assessment.

Assessment elements

Target condition

What are the potential indications and aims of MSCT in diagnostic cardiology?

Results

Potential uses of cardiac MSCT angiography include diagnosing CAD and other conditions, screening vessel calcium as a risk factor for CAD, and monitoring patency of stents and bypass grafts.

Diagnosing coronary artery disease

MSCT coronary angiography (MSCT) can be used to visualize narrowing of coronary arteries and to diagnose CAD. In intermediate risk patients, in whom there is diagnostic uncertainty after resting ECG and exercise testing, further assessment is generally required. Patients may be referred for myocardial perfusion scanning, while some go directly to invasive coronary angiography (ICA). MSCT coronary angiography is one option for such further assessment, and offers the possibility of

reducing the number of unnecessary ICAs and the risks associated with them. High risk patients (several risk factors, typical syndromes, and positive ECG and lab findings) are referred directly to ICA.

Several recent reviews and recommendations state that MSCT is best indicated in patients with **intermediate risk** of coronary artery disease (a 10-year risk of cardiovascular disease of 10-20%) (1, 2,3). The American College of Cardiology Foundation (ACCF) gives appropriateness criteria for the use of cardiac computed tomography in patients with the following indications (3):

- Evaluating patients with chest pain and intermediate pre-test probability of coronary artery disease AND uninterpretable electrocardiogram OR unable to exercise.
- Evaluating acute chest pain in patients with intermediate pre-test probability of coronary artery disease AND no ECG-changes and serial enzymes negative.
- Evaluation of chest pain syndrome in patients with uninterpretable or equivocal stress test (exercise, perfusion, or stress echo).

In **low risk** patients using MSCT as triage for further examinations might be useful (1,4). This is a large group of people, who have chest pain, with normal ECG and blood test and few risk factors or other convincing evidence of acute coronary syndrome.

MSCT has been used to rule out CAD in patients with heart failure and patient who are going to valvular surgery (3).

Diagnosing other intra- and extra-cardiac conditions

According to American College of Cardiology Foundation (ACCF) appropriateness criteria for cardiac computed tomography (3), following indications (other than CAD) are deemed appropriate for MSCT coronary angiography:

- Assessment of complex congenital heart disease including anomalies of coronary circulation, great vessels, and cardiac chambers and valves.
- Evaluation of coronary arteries in patients with new onset heart failure to assess etiology.
- Evaluation of suspected aortic dissection or thoracic aortic aneurysm
- Evaluation of suspected pulmonary embolism.

Although coronary anomalies are rare, their possible consequences include myocardial infarction and sudden death. Numerous case reports and several research papers have shown that MSCT analysis of coronary anatomy is a reliable way to detect anomalies (5). In a recent study MSCT has been shown to be useful in the differentiation of the idiopathic from ischemic etiology in dilated cardiomyopathy (6).

Guiding treatment decisions in patients with definite CAD

Patients with a high pre-test probability of CAD (typical symptoms and findings in previous tests e.g. positive rest and stress ECG and enzymes), at least those with severe or persistent symptoms, go directly to invasive coronary angiography (ICA). Treatment options are medical treatment only, angioplasty (vessel dilatation with or without stent) or coronary artery bypass graft (CABG). ICA allows immediate intervention with angioplasty. MSCT may not have a large role in this group, unless it could identify those in whom CABG is required (1).

Calcium screening

Coronary calcium is a surrogate marker for the presence and amount of coronary plaques. Calcifications occur in the context of atherosclerotic lesions. However not every atherosclerotic coronary plaque is calcified, and calcification is neither a sign of stability nor of instability of an individual plaque. In several studies the absence of coronary calcium has ruled out significant coronary stenosis. However, even pronounced coronary calcification is not necessarily associated with hemodynamically relevant luminal narrowing. Numerous prospective trials have demonstrated that coronary calcium in asymptomatic individuals is a strong prognostic parameter for future heart events. Patient management approaches based on calcium score have not been prospectively investigated (5). In the guidelines of American heart Association, repeated imaging assessment of progression of coronary calcification is not recommended (7).

Knowledge of the presence or absence of coronary artery calcification and atherosclerosis may add value in a risk assessment and potential to improve the targeting of cardiovascular preventive activities such as lifestyle modification and lipid lowering therapies (2).

Monitoring coronary artery stents and bypass grafts

In patients with previous revascularisation (angioplasty or bypass grafting) imaging with MSCT is possible but challenging. Imaging of bypass grafts is less affected by motion than the coronary arteries but it may be affected by surgical metal clips. Assessment of the native coronary arteries distal to the anastomosis may be difficult due to the frequent presence of extensive calcification. Studies that have investigated the accuracy of MSCT in detecting stenosis in native arteries in patients with bypass grafts have reported low accuracies, which severely limits the use of MSCT in these patients (5).

Assessment of in-stent re-stenosis is usually not recommended because of metal artefacts caused by the stent. However, in selected patients with larger stent diameter, results with 64-slice CT have been promising (5,7,8).

Screening

MSCT has been proposed as a screening tool in asymptomatic subjects. Currently there is global consensus that it should not be used for this purpose, both because of the radiation burden and lack of accuracy in this population, and because WHO criteria for screening are not met. No evidence was found for the impact of screening on patient management (7,9).

In summary:

In 2006 the American College of Cardiology Foundation produced recommendations on the appropriate uses of cardiac computed tomography (3). The indications include:

- evaluation of chest pain where there is intermediate pre-test probability of CAD and either an uninterpretable ECG or inability exercise; or after an uninterpretable or equivocal stress test;
- evaluation of suspected coronary anomalies in symptomatic CAD;
- acute chest pain with intermediate pre-test probability of CAD, no ECG changes and enzymes negative; and
- evaluation of coronary arteries in patients with new onset heart failure to assess aetiology.

It should be taken into account that the imaging technology has evolved rapidly since the writing of these guidelines.

What are the pathological findings that MSCT coronary angiography is able to detect?

Results

Coronary artery stenosis

Main use of MSCT is in detecting or excluding significant coronary stenosis (>50% diameter reduction) in coronary arteries. Studies usually use invasive coronary angiography (ICA) as the gold standard for measuring stenosis. A research group led by American heart association states that a normal CT coronary angiogram allows the clinician to rule out the presence of haemodynamically relevant coronary artery stenosis with a high degree of reliability (7).

Studies comparing anatomical MSCT assessment to functional imaging (perfusion scan, SPECT) show that only approximately 50% of significant stenoses (>50% narrowing of vessel diameter) on MSCT are functionally relevant; a large proportion of significant lesions in MSCT does not lead in perfusion abnormalities (10).

Vulnerable plaques

Vulnerable plaques are the ones that most likely cause thromboembolism. They are not necessarily big enough to cause significant stenosis and their calcium content is generally lower than in stable atherosclerotic plaques. The use of MSCT to identify and further characterise vulnerable plaques is promising but premature (7). There are a small number of studies that compare MSCT with intra-vascular ultrasound (IVUS). Uncertainties about the treatment of vulnerable plaques may reduce the value of diagnostic information (1).

Vessel calcification

MSCT allows for accurate detection and quantification of coronary artery calcium. The radiation dose for a calcium scan is lower than in MSCT angiography, 1-2 mSv.

Coronary calcium is a surrogate marker for the presence and amount of coronary plaques. With the exception of patients with renal failure, calcifications occur exclusively in the context of atherosclerotic lesions. On the other hand not every atherosclerotic coronary plaque is calcified, and calcification is a sign of neither stability nor instability of an individual plaque. Absence of coronary calcium has ruled out significant coronary stenosis in several studies. However, even pronounced coronary calcification is not necessarily associated with hemodynamically relevant luminal narrowing (5).

Numerous prospective trials have demonstrated that coronary calcium in asymptomatic individuals is a strong prognostic parameter for future heart events. Patient management approaches based on calcium score have not been prospectively investigated (5).

What is the characterisation of coronary artery disease (CAD)?

Methods

We used some material from the corresponding issue in the Core HTA on DES: Which are the diagnoses or patient groups for which DES is or may be indicated? Authors: Bo Freyschuss, Marcial Velasco Garrido, Marjukka Mäkelä.

Results

Coronary artery disease (CAD) is generally caused by impaired blood flow and deficient oxygen supply to myocardium, mostly induced by atherosclerosis or build up of plaque in the arteries. CAD may be manifested by stable angina pectoris, acute coronary syndromes - including myocardial infarction and unstable angina, or sudden death.

Stable angina pectoris is caused by the partial blockage of the artery by a plaque. Blood flow to the heart is still sufficient, however in physical or emotional stress or activity blood flow may be restricted resulting in temporary chest pain. It is traditionally accepted that the vessel narrowing has to be at least 50% in the internal diameter (or >75% reduction in cross sectional area) in order to cause ischemia and angina pectoris.

Acute coronary syndromes cover a heterogeneous spectrum of ischemic heart diseases, extending from acute myocardial infarction, through minimal myocardial injury to unstable angina. In acute myocardial infarction there is, by definition, loss of myocardial tissue. It is the result of a complete blockage of the artery by a ruptured plaque, not necessarily involving flow limiting stenosis (10). Loss of myocardial tissue due to myocardial infarction can lead to heart failure and arrhythmias leading to sudden death.

Unstable angina is a syndrome of cardiac ischemia, manifesting itself as prolonged chest pain, in which no myocardial necrosis can be documented. It 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).

What are the symptoms of coronary artery disease (CAD)

Methods

We used the corresponding assessment element from the Core HTA on drug eluting stents (DES) as base text and made some changes and amendments. Issue name in DES: What are the most common or serious symptoms and consequences of the conditions that may be treated with DES? Authors: Bo Freyschuss, Marcial Velasco Garrido, Marjukka Mäkelä.

Results

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

Stable angina

Typical stable angina

Typical angina has three characteristics:

1. discomfort in the chest, jaw, shoulder, back or arms, that is
2. provoked by exertion or emotional stress, and
3. relieved by rest or nitro-glycerine.

Angina is stable when the symptoms remain unchanged, i.e. there is no change in the usual pattern of pain occurrence. Unstable angina is discussed under acute coronary syndromes (10). Stable angina is often graded using the scale from the Canadian Cardiovascular Society (CCS) (11).

CCS Angina Classification by Canadian Cardiovascular Society

Class	Description
Class I	Ordinary activity such as walking or climbing does not precipitate angina. Angina occurs with strenuous work.
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

Atypical angina

Atypical angina has only two of the three characteristics of typical angina. Very often these patients have significant CAD (12).

Atypical chest pain

Atypical or non-anginal chest pain show only one or none of the characteristic symptoms of typical angina (13).

Acute coronary syndromes

Acute coronary syndromes cover a heterogeneous spectrum of ischemic heart diseases, extending from acute myocardial infarction, through minimal myocardial injury to unstable angina. Patients with acute coronary syndrome may have chest discomfort that has all the qualities of typical angina except that the episodes are more severe and prolonged, may occur at rest, or may be precipitated by less exertion than in the past (14).

Myocardial infarction

Chest pain is a major symptom of acute myocardial infarction, mostly occurring at rest and usually lasting at least 20 minutes (15).

Unstable angina

In unstable angina chest pain becomes more easily provoked than usual or it occurs with increased frequency, severity or duration (10)

Which are the known risk factors for coronary artery disease (CAD)?

Results

The main risk factors for CAD development are tobacco use, high blood pressure, raised blood cholesterol, and diabetes mellitus (10).

What is the natural course of coronary artery disease (CAD)?

Results

In patients with atypical chest pain, the prevalence of CAD is estimated to be between 0.8 and 28.1%, depending on age and gender. In patients with typical angina the prevalence of CAD is much higher, from 25.8 to 94.3%, depending on age and gender (12). High risk CAD, defined as disease of the left main vessel or three vessels, is rare in men under 70 years and almost nonexistent in women of any age, who present atypical chest pain (16).

Estimates of annual mortality of patients with stable angina in recent clinical trials range from 0.9% to 1.7%, with higher mortality in populations with more severe symptoms (17). Patients with documented CAD may have excellent prognosis. During a five year follow-up of 2000 patients with stable angina and median age of 65 years, it was found that 1.4/100 patient-years died (18).

Patient with stable angina have been classified into risk categories according to their 5 year risk using a composite of death, myocardial infarction or disabling stroke. In the highest decile the risk of composite outcome was 35% and in the lowest 4%. Clinical variables that contributed most to the risk were age, left ventricular ejection fraction, and smoking (19).

What is the incidence of coronary artery disease?

Methods

We used the corresponding assessment element from the Core HTA on DES (paragraphs marked with *...*), and added material. Issue name: What is the incidence of CAD? Authors: Bo Freyschuss, Marcial Velasco Garrido, Marjukka Mäkelä.

Results

At present there is no routinely updated source of Europe-wide CAD morbidity data (20). The WHO MONICA (monitoring trends and determinants in cardiovascular disease) examined the

incidence of major coronary events in 16 European countries in 1990's (21). The project showed that the incidence of coronary events was higher in Northern, Central and Eastern Europe than in Southern and Western Europe. The geographical pattern in coronary event rates was similar to the pattern in death rates. The results of the MONICA project showed also that incidence of coronary events was decreasing rapidly in Northern and Western Europe but was not decreasing as fast in the rest of Europe, and even increased in some research populations (20).

According to the latest 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. 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).

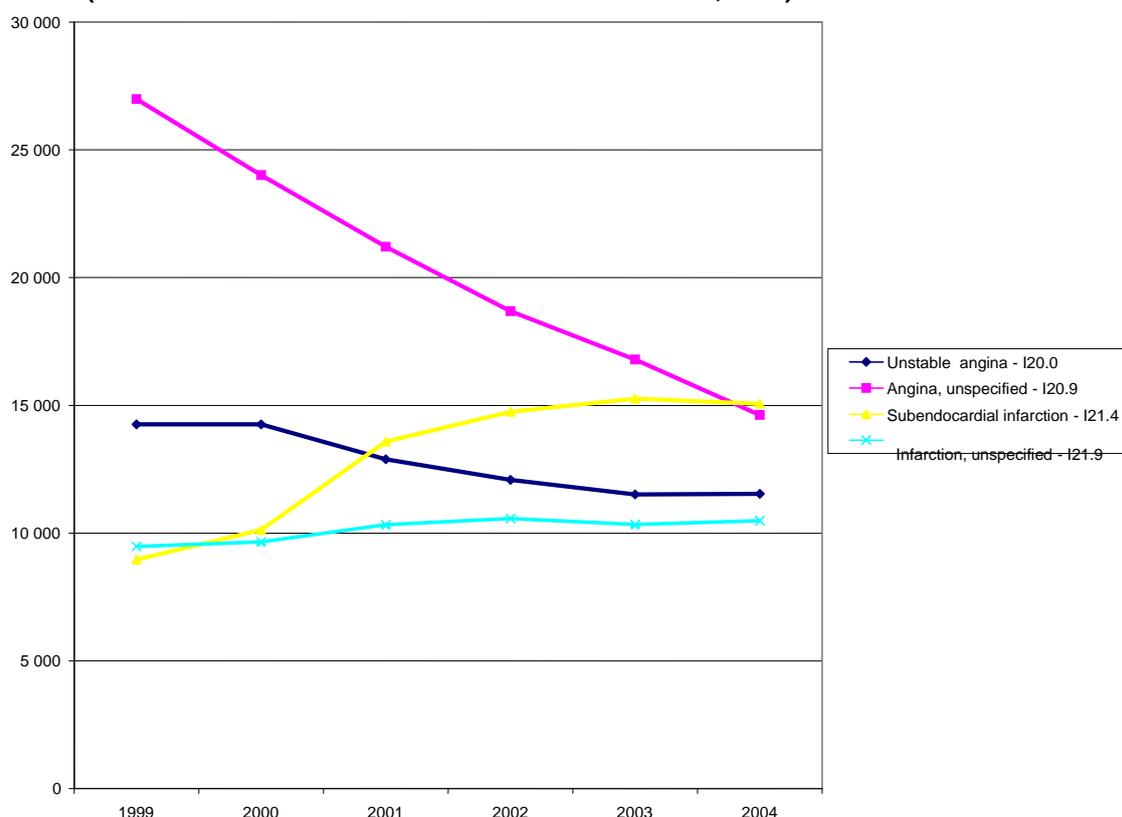
The MONICA project also investigated patterns in case fatality defined as dying within 28 days of a coronary event. Case fatality from CAD was higher in many populations in Central and Eastern Europe. Case fatality was not decreasing there as fast as in other parts of Europe*.

Coronary event rates, case fatality and their annual changes in the European MONICA populations can be found at the European cardiovascular disease statistics, table 2.1 (20).

**Sweden*

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 myocardial infarction 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 12 000 for instable angina yearly. About 5 000 bypass operations (CABG) and 18 000 revascularizations (PCI) are performed yearly. Coronary heart disease accounts for about 18 000 deaths each year in Sweden, which constitutes 22% of all deaths in men and 18% in women (22)*.

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



What is the incidence of cases presenting with angina symptoms but with low to moderate probability of CAD?

Results

In patients with atypical chest pain, the prevalence of CAD is estimated to be between 0.8 and 28.1%, depending on age and gender. In patients with typical angina the prevalence of CAD is much higher, from 25.8 to 94.3%, depending on age and gender (12). High risk CAD, defined as left main or three vessel disease, was rare in men under 70 years and almost nonexistent in women of any age, who presented atypical chest pain (16).

What is the mortality of coronary artery disease (CAD) and how many years of (healthy) life are lost due to early death or disability in Europe?

Methods

We used the corresponding assessment element from the Core HTA on drug eluting stents (paragraphs marked with *...*), and added it substantially. Issue name: What is the burden of coronary artery disease? Authors: Bo Freyschuss, Marcial Velasco Garrido, Marjukka Mäkelä.

Results

Mortality

Coronary artery disease (CAD) is the single most common cause of death in the Europe, accounting for 1.92 million deaths in Europe each year. 22% of women and 21% of men die from the disease. The same holds for countries that belong to European Union (EU). There are 741 000 deaths per year, and 15% of women and 16% men die from CHD in EU. Number of deaths in each European country can be found in the European cardiovascular disease statistics, table 1.1 (20).

CAD is the single most common cause of death before the age of 75 in Europe, accounting for over 900 000 deaths every year. In men 20 % of the deaths are from CAD, and in women 19%. The same holds for EU countries. There are 250 000 deaths per year. In men 15% of the deaths are from CAD, in women 10%. Number of deaths in each European country can be found in the European cardiovascular disease statistics, table 1.2 (20).

CAD is the single most common cause of death before the age of 65 in Europe, accounting for just under 401 000 deaths per year. In men 17% of the deaths are from CAD, in women 12%. The same holds for EU countries. There are just over 104 000 deaths per year. In men 13% of the deaths are from CAD, in women 6%. Number of deaths in each European country can be found in the European cardiovascular disease statistics, table 1.3 (20).

Death rates from CAD are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe. Western European countries generally have higher rates than southern European countries. Age standardized death rates from CAD (deaths per 100 000) in individual European countries can be found in the European cardiovascular disease statistics, table 1.4 (20). Latest figures are from the year 2005.

Death rates have been falling rapidly in most Northern and Western European countries and rising rapidly in some Central and Eastern European countries over the past 30 years (20).

Years of life lost due to an early death

The WHO Global Burden of Disease Study found that in 1990 on average 16% of years of life lost were due to CAD in Established Market Economies (mostly Northern, Southern and Western countries). This was the single most important cause of years of life lost in these countries (23). In Central and Eastern European countries 18% of years of life lost were due to CAD (20).

Years of healthy years lost due to disability

In 2002 the WHO Burden of Disease project (23) estimated the morbidity caused by different diseases. The main measure of the burden of the disease was DALY (Disability Adjusted Life Year), an aggregate of years of life lost due to premature death and years of healthy life lost due to disability.

In developed European countries, 17% of all DALYs lost are due to cardiovascular diseases. In the EU, over 12 million DALYs (19% of total) and in Europe 34 million (23% of total) are lost each year to cardiovascular disease. There are no figures given for coronary artery disease (20).

The prevalence/incidence of early retirement due to CAD 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.

Finland

In Finland (population 5.3 million) there are annually 44 000 incidents of acute coronary artery syndrome. Out of them 23 000 are myocardial infarctions and 21 000 unstable angina pectoris. Out of the 23 000 myocardial infarction cases, 5 000 die before they reach hospital. Altogether, there are annually 13 000 deaths due to myocardial infarction. These data are collected from Finnish hospital discharge register and causes of death register in 1995 (23).

Sweden

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

UK

CAD is the leading cause of mortality in the UK, with 92,289 deaths recorded in England and Wales in 2004. Data for England suggests a morbidity prevalence of 7.4% in men and 4.5% in women (2).

Utilisation

How much is MSCT coronary angiographies used in European countries?

Methods

Apart from information retrieved from published HTAs, investigators of the team were asked to find out whether there are national registers in their countries that could provide data for his issue:

Results

Spain

In Spain there is not a known register of the use of computed tomography cardiac imaging or invasive coronary angiographies (ICA).

Finland

In 2005 there were 10 recorded cases of imaging coronary arteries with computed tomography (24). More recent register data is not available.

What kind of international, national or regional variation is there in the use of MSCT coronary angiography?

Methods

Investigators of the team were asked to find out whether there are national registers in their countries that could provide data for this issue:

Results

In Spain, MSCT coronary angiography is included in the "basket of benefits". It is used more in the private sector than in the public sector. MSCTs have not a specific way of registration, so there is not a registry entry with the name MSCT.

In Australia MSCT coronary angiography is predominantly used in the private sector with limited use in public hospitals. Many radiologists operate within both the public and private health systems (25).

Current Management of the Condition

How is coronary artery disease (CAD) currently diagnosed?

Results

Diagnosis of CAD can often be made by history taking alone, based on the pain characteristics, age, gender, and patients' cardiovascular risk profile (13). Physical examination can further increase the probability of CAD if signs of peripheral atherosclerosis or heart failure are found.

Electrocardiogram (ECG) at rest and/or during exercise is usually performed. Laboratory testing can, in patients with non-acute chest pain, exclude anaemia or hyperthyroidism as a cause of angina, or establish other causes of chest pain (pleuritis, pneumonia etc.). In acute conditions, cardiac enzymes are measured from a blood sample. In patients where the resting ECG is abnormal because of left bundle branch block, cardiac pacing, left ventricular hypertrophy or drug effects, stress-ECG is of no help. In these patients, myocardial perfusion scintigraphy (SPECT) and in those who have contraindication to SPECT (e.g. asthma), dobutamine stress echocardiography may be used to further evaluate chest pain. These non-invasive tests are considered also for patients who are unable to exercise due to orthopaedic, pneumologic or other reasons (10). According to the diagnostic pathway proposed by ACC/AHA, invasive coronary angiography is only indicated when symptoms,

clinical findings or results from previous tests suggest high risk of CAD (13). The potential role of multislice computed tomography (MSCT) angiography lies before invasive coronary angiography (ICA) in the diagnostic pathway. It has been advocated as a technology that might prevent ICA in patients who turn out not to have obstructive CAD.

Is there evidence for inappropriate use of MSCT coronary angiography in the diagnostic pathway of CAD?

Results

We found no information on this.

What is the role of MSCT in the management of coronary artery disease (CAD) according to evidence based guidelines?

Methods

Source	Search terms	Date of inquiry	Investigator	Selected
Evidence Based Medicine Guidelines (EBMG) http://ebmg.wiley.com/ebmg/ Finnish version	sepelvaltimotauti	26.8.2008	IP	(25)
SIGN http://www.sign.ac.uk/	Guidelines>by topic>CHD and stroke	26.8.2008	IP	(26)
NICE guidelines http://www.nice.org.uk/Guidance/CG/Published	browsed all 78 published guidelines	26.8.2008	IP	found no relevant
The evidence-based Finnish Current Care guidelines (in finnish) http://www.kaypahoito.fi/	browsed all 6 guidelines under subtitle "cardiology"	26.8.2008	IP	(27,28)
National Guidelines Clearinghouse http://www.guideline.gov/	"coronary" yielded 310 hits guidelines, 16 of them were published 2005 or later. If full text of the guideline was not available elsewhere information on MSCT was sought in the NGC summaries. Find-function using the words "tomography" or "ct" was used to search the documents.	27.8.2008	IP	(25,26,29-36)

GIN http://www.g-i-n.net	coronary, heart, cardiac	26.8. 2008	IP	found no relevant
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Results

Ten evidence-based guidelines on management of coronary artery disease (CAD), published in 2005 or later, were identified. Seven of them did not mention MSCT. In three guidelines the statements about the use of MSCT are cautious but emphasize that it is a developing technology that may have potential. See more detailed expressions in the table below.

Guideline	Published	Role of MSCT in the diagnostic pathway
Coronary heart disease (CHD): symptoms, diagnosis and treatment. In: EBM Guidelines. Evidence-Based Medicine (25)	2007	No mention
Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology (29)	2007	At the current state of development, cardiac computed tomography (CT) cannot be recommended as the coronary imaging modality in non-ST-elevation acute coronary syndrome, because of suboptimal diagnostic accuracy. Fast technical evolution may result in improved diagnostic accuracy in the near future and lead to reconsideration of the use of this tool in the decision-making process.
Diagnosis and treatment of chest pain and acute coronary syndrome (ACS). Institute for Clinical Systems Improvement (ICSI) (30)	2006	CT angiogram is generally the quickest and most readily available diagnostic test in diagnosis of aortic dissection in clinically stable and asymptomatic patients.
ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction (31)	2007	<p>The detection of subclinical atherosclerosis by noninvasive imaging represents a new, evolving approach for refining individual risk in asymptomatic individuals beyond traditional risk factor assessment alone. A recent AHA scientific statement indicates that it may be reasonable to measure atherosclerosis burden using electron-beam or multidetector computed tomography (CT) in clinically selected intermediate-CAD-risk individuals (e.g., those with a 10% to 20% Framingham 10-year risk estimate) to refine clinical risk prediction and to select patients for aggressive target values for lipid-lowering therapies (Class IIb, Level of Evidence: B).</p> <p>Two imaging modalities, CMR and multidetector computed tomography for coronary calcification and CCTA, are increasingly becoming clinically validated and applied and hold promise as alternative or supplementary imaging modalities for assessing patients who present with chest pain syndromes.</p> <p>Multislice cardiac computed tomography, which combines coronary calcium scoring with noninvasive coronary angiography (current resolution 0.5mm), has undergone favorable initial evaluation for assessment of the low- to intermediate-risk chest pain patient. The current status and appropriate application of CMR and cardiac CT are addressed in recent ACC/AHA documents</p>
Stable coronary artery disease. Institute for Clinical Systems Improvement (ICSI) (32).	2007	no mention
2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (33)	2008	no mention
Management of stable angina. A national clinical guideline. Scottish Intercollegiate Guidelines Network (26)	2007	no mention
Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. Task Force on Diabetes and Cardiovascular Diseases. European Society of Cardiology (ESC) (34)	2007	no mention
Acute coronary syndromes. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN) (35).	2007	no mention
Guidelines for the management of acute coronary syndromes 2006.	2006	no mention

Acute Coronary Syndrome
Guidelines Working Group (36)

Which are the other evidence based diagnostic procedures for coronary artery disease (CAD)?

Methods

This research question was deemed relevant by the investigators team, but for time constraints we did not study it.

Regulatory status

Which approval status has MSCT coronary angiography in EU or internationally?

Methods

Source	Search terms	Date of inquiry	Investigator
Google	"msct regulatory status" "eu regulatory status msct"	13.7.2008	NS, LVL
FDA	"msct regulatory"	13.7.2008	NS, LVL

Results

The European Directive 97/43/Euratom provides information about Computed Tomography (CT) in general; but we could not find any specific data related to MSCT coronary angiography.

What is the reimbursement status of MSCT cardiac angiography?

Results

Reimbursement of cardiac CT is currently heterogeneous between countries and often even between health insurance funders within a country. In most countries there is no specific reimbursement for cardiac CT procedures (5). The question regarding reimbursement is not relevant in some settings, particularly if the patient does not pay for the investigation himself. For example in Finland the cost is covered by the hospital that performs the investigation (applies to public hospitals only).

Spain

In Spain, MSCT coronary angiography is included in the benefit basket. Spanish benefit basket is not standard within the European Union (38).

Other

Who manufactures MSCTs?

Results

The manufacturers of the technology are GE (General Electric), Philips, Siemens and Toshiba (www.msct.eu/MSCT_INFO/Links.htm, accessed 13.7.2008). The technical performance of their respective 64-scanners has been assessed recently by the ECRI institute (39).

Discussion

Coronary artery disease (CAD) is the single most common cause of death in the Europe. In developed European countries, 17% of all DALYs (Disability Adjusted Life Year) lost are due to cardiovascular diseases. The golden standard for the diagnosis of coronary artery disease (CAD) is invasive coronary angiography (ICA). In past decades non-invasive imaging has been developed to serve as first-line diagnostic tool instead of or alongside ICA. In 2004 only early adopters were using the technology. Since then it has become increasingly available in many European countries.

MSCT coronary angiography (MSCT) is a non-invasive technology that can be used to visualize stenosis of the coronary arteries and thus diagnose CAD. Several recent reviews and recommendations state that MSCT is best indicated in patients with intermediate risk of coronary artery disease. It has been suggested that using MSCT as triage for low-risk patients could reduce unnecessary further examinations and better target optimal preventive medication.

Currently there is global consensus that MSCT should not be used for screening of CAD, both because of the radiation burden and lack of diagnostic accuracy in this population, but also because the WHO criteria for screening are not met. MSCT has been used also for assessing coronary calcium, which is a surrogate marker for the presence and amount of coronary plaques. According to current consensus repeated imaging assessment of progression of coronary calcification is not recommended. Assessment of in-stent restenosis with MSCT is difficult because of metal artefacts caused by the stent.

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- (39) ECRI Institute. 64-slice computed tomography systems. Health Devices 2007;36(12):377-402.

Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT or Comment (if regarded as a not relevant issue in this context)
A0001	Health Problem and Current Use of the Technology	Target Condition	For which disease/health problem/potential health problem will the diagnostic intervention used?*	yes	What are the potential indications (target condition and its pre-test probability) and aims (diagnosing, screening, monitoring, assessing prognosis) of MSCT in diagnostic cardiology? What are the pathologic findings that MSCT coronary angiography is able to detect?
A0002	Health Problem and Current Use of the Technology	Target Condition	What, if any, is the precise definition/ characterization of the target disease? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?*	yes	What is the characterisation of CAD?
A0003	Health Problem and Current Use of the Technology	Target Condition	What are the symptoms of the disease?	yes	What are the symptoms of CAD?
A0004	Health Problem and Current Use of the Technology	Target Condition	What are the consequences of the condition?	no	Consequences will be covered in the issue no A0008 about the burden of the disease
A0005	Health Problem and Current Use of the Technology	Target Condition	Which are the known risk factors for acquiring the condition?*	yes	Which are the known risk factors for CAD?
A0006	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?*	yes	What is the natural course of coronary artery disease (CAD)?
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 (describe according to sex, age)?	yes	What is the incidence of CAD? What is the incidence of cases presenting with angina symptoms but with low to moderate probability of CAD?
A0008	Health Problem and Current Use of the Technology	Target Condition	What is the burden of disease (mortality, disability, life years lost)?	yes	What are CAD mortality and years of (healthy) life lost due to early death or disability in Europe?
A0020	Health Problem and Current Use of the Technology	Target Condition	What aspects of the burden of disease are targeted by the technology, i.e. are expected to be reduced by the technology?	no	We found it difficult to see the relevance of this issue to MSCT(Does MSCT target differently the different aspects of the burden of disease : symptoms, morbidity, mortality, quality of life, costs
A0009	Health Problem and Current Use of the Technology	Utilisation	How much is the technology being used?	yes	How much is MSCT coronary angiographies used in European countries?
A0010	Health Problem and Current Use of the Technology	Utilisation	Describe the variations in use across countries/regions/settings, if any?	yes	What kind of international, national or regional variation is there in the use of MSCT coronary angiography?
A0011	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the disease/health condition currently being diagnosed?	yes	Is there evidence for inappropriate use of diagnostic tests in the diagnostic pathway of CAD?
A0012	Health Problem and Current Use of the Technology	Current Management of the Condition	According to published algorithms/guidelines (if any), how should the condition be diagnosed?	yes	What is the current evidence based diagnostic pathway for CAD ?
A0014	Health Problem and Current Use of the Technology	Current Management of the condition	What are the other evidence-based alternative diagnostic procedures, if any?	yes	What are the other evidence based diagnostic procedures for CAD?
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)?	no	Will be answered in Description-domain
A0016	Health Problem and Current Use of the Technology	Regulatory Status	Which approval status has the technology in other countries, or international authorities?	yes	Which approval status has MSCT in EU or internationally?
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? How is the coverage of the technology across countries? (e.g. full-coverage, co-payments, coverage under special circumstances/conditional coverage?)	yes	What is the reimbursement status of MSCT cardiac angiography?

EUnetHTA WP4 - Core HTA on MSCT Coronary Angiography
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

A0019	Health Problem and Current Use of the Technology	Other	Who manufactures the technology?	yes	Who manufactures MSCTs?
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Appendix 1

Database: CRD (= HTA, EED, DARE)
Date of search: 4.12.2007, yield 24 references
Search strategy:

#1 MeSH Coronary Disease EXPLODE 1 2
#2 (coronary AND (disease* OR arter* OR aneurysm* OR stenosis* OR restenosis* OR thrombosis*
OR vasospasm* OR vessel*)) OR "angina pectoris" OR "chest pain" OR atherosclerosis*
#3 #1 OR #2
#4 MeSH Coronary Angiography EXPLODE 1 2 3
#5 MeSH Tomography, X-Ray Computed EXPLODE 1 2 3 4 5 6
#6 #4 AND #5
#7 angiograph* AND tomograph*
#8 #6 OR #7
#9 #3 AND #8
#10 msct OR mdct
#11 (multislice OR "multi-slice" OR "multi slice" OR multirow OR multidetect* OR "multi-
detect*" OR "multi detect*" OR multiselect*)
#12 (4 OR 16 OR 32 OR 40 OR 64) AND (slice* OR row*)
#13 #10 OR #11 OR #12
#14 #9 AND 13

Additional search in Medline

pattern\$.tw.
volume
case load" or caseload.tw.
workload/
utilization
delivery of health care/
volume\$.tw.
Physician's Practice Patterns/.

Description and technical characteristics of technology

*Iris Pasternack, Sigurður Helgason, Sami Kajander, Lorenzo Leogrande,
Paolo Oppedisano, Heikki Ukkonen*

Introduction

Multislice computed tomography (MSCT) coronary angiography is a relatively new non-invasive imaging modality with many potential indications. When policy questions about the applicability of the new technology are translated into research questions, we need to understand the technical and other features of the technology and its current status in a fast developing field. Newer MSCT devices with improved software have been shown to be more accurate and sometimes safer than the older generations. The role of MSCT coronary angiography is an anatomic, rather than functional, imaging method. This is a very important difference when we consider the role of MSCT in the management pathway of patients with suspected coronary artery disease.

In order to assess the applicability of MSCT, there are assessment elements that answer the questions about premises, equipment, and staff requirements needed for the use of MSCT. As it is a technology that uses ionizing radiation, specific staff training and performance requirements exist. Balanced risk communication to patients and the general public is also of great importance.

Methodology

We did not intend to conduct a systematic review of issues within this domain. Information was retrieved from earlier HTA reports, consensus statements, and introduction sections of guidelines, reviews and original articles.

We used the corresponding assessment element from the Core HTA of drug eluting stents as such or as base text for several elements. This is mentioned and original work referred to in the methods section of the elements.

We did a basic search for HTA-reports and systematic reviews and an additional search in Medline. Search strategies are in Appendix 1. Further information was sought on the internet and by snowballing references from relevant documents. For technical information useful information was sought from administrative and manufacturers' web sites.

Methods for the topic "Investments and tools required to use the technology"

Information was retrieved through a short literature search (1-9) and several interviews with radiologist, cardiologist and technical staff in a University Hospital (UCSC Policlinico Gemelli). Additional information sources in the Investments and tools -topic include:

- Manufacturers web sites
- Company brochures and data sheets

- Regional Law n. 4/2003: “Requisiti minimi organizzativi strutturali, tecnologici e organizzativi delle strutture sanitarie e socio sanitarie”
- Decreto Legislativo 26 maggio 2000, n. 187:
- Attuazione della direttiva 97/43/ EURATOM in materia di protezione sanitaria delle persone contro i pericoli delle radiazioni ionizzanti connesse ad esposizioni mediche.
- Dicom Conformat statment
- HL7 Standard Protocol
- IHE Standard Protocol
- US Technical Information Service <http://www.ntis.gov/>

Methods for the Topic "Training and information needed for utilizing the technology"

Information was retrieved from:

- References to HTAs, systematic reviews, guidelines, meta-analyses and reports from selected medical insurance organisations.
- Interview with clinical specialist in medical imaging (radiology & nuclear medicine)
- Manufacturers web sites:
 - General Electric (www.gemedicalsystems.co.uk)
 - Siemens (<http://www.usa.siemens.com/en/index.htm>)
 - Philips(<http://www.medical.philips.com/main/products/ct/applications/clinical/cardiovascular.html>)
- Company brochures, patient information and data sheets
- European Communities (Medical Ionising Radiation Protection) Regulations, 2002.
http://www.iir.ie/files/fileman/si_478_of_2002.pdf

Text words used to search were:

- Training / competenc\$ / variation / variability / kappa / learning curve /accreditation / standard\$
- Technical / inspection /maintain\$ / audit
- Patient information or leaflet / consent / patient concerns

Assessment elements

Features of the technology

What is the technological basis of cardiac MSCT?

Results

Computed tomography (CT) is a radiological imaging technique that generates a three-dimensional volume or a set of pictures of an object from a large series of two-dimensional X-ray images. Cardiac motion makes conventional CT examination of the heart unsuitable. Additionally, imaging of small objects like coronary arteries, require high spatial resolution. Multislice CT (MSCT) with ECG gating has partly overcome these limitations (1).

Currently 64-detector row scanners are the industry standard. These systems acquire a tissue volume using up to 64 detectors in a single tube rotation of just 330 - 500 ms. After data acquisition, the images are reconstructed for further analysis. Tube current is usually 400-950mAs and voltage 100 – 120 kV. On average, it causes radiation exposure comparable to 160 PA chest films or 3-4 times the average yearly effective dose of natural background radiation (2.5 mSv) (2). However, there is great variation of dose depending on the techniques used.

Image quality is determined for the most part by temporal and spatial resolution. Temporal resolution (shutter speed) means time required to acquire data for one image. It is determined by the rotation time, number of X-ray beams, and the reconstruction protocol used. It needs to be high because of the constant motion of the heart and coronary arteries. Spatial resolution means the number of pixels of information that make up a digital image. It is determined by the minimal slice thickness. Invasive coronary angiography is the 'gold standard' for the anatomical diagnosis of coronary artery disease due to its high temporal and spatial resolution (2).

64-slice or detector CT angiography uses electrocardiogram (ECG) gating or triggering techniques to capture data at points in the cardiac cycle when motion is minimal, usually in the mid to late diastolic phase. ECG is used either to prospectively trigger imaging or retrospectively reconstruct data from continuous acquisition. Use of ECG dependent dose modulation can decrease radiation dose by 30-50% and use of prospective triggering by 60-80%. Time to acquire data for one image, and time for the patient to hold breath, is 5-10 seconds in the new 64-slice devices (2). The newest scanners with 256 and 320 slices allow imaging of the coronary arteries during one or two heartbeats (1).

Beta-blockers (or calcium channel blockers in patients with contraindications to beta-blockade) have been used to reduce heart rate, and lengthen the diastole to improve image quality. Iodinated contrast agent is administered intravenously. To ensure adequate contrast enhancement, a bolus tracking technique is usually used to synchronize its arrival in the coronary arteries (2).

Imaging procedure

Patient preparation includes informing the patient about the procedure, verifying sinus rhythm, and administration of beta-blockers and nitrates when needed. After patient preparation several exploratory scans are performed to determine accurate start and end positions. About 60-100 ml of highly iodinated contrast media is usually given with a flow rate of 4-5 ml/s. In some circumstances, especially in obese patients, using a high flow rate may be useful (3). Then, the ECG gated contrast enhanced scan is performed.

Cardiac CT is usually based on continuous spiral scanning of the heart within a single breath hold in 5-10 seconds. Simultaneous ECG permits retrospective reconstruction of images at any desired phase of the cardiac cycle. Sequential imaging (so called "step-and-shoot" -mode) is used in some instances. Synchronisation of data acquisition and contrast enhancement can be achieved by calculating veno-atrial transit time of test bolus of contrast agent before scanning or tracking the arrival of the bolus by real-time monitoring. After the data is acquired, the cardiac phase with least motion is identified and used to reconstruct a dataset of the entire heart. For lower heart rates, the best time instant is usually in the mid- to end-diastolic phase. For higher heart rates end systole may yield better results (3). These data sets usually consist of 200-300 thin (0.5-0.75 mm) slices in transaxial orientation. Reconstructions are transferred to a workstation for further analysis. The presence of coronary artery stenosis is typically evaluated by assessing the axial images in

combination with processed images, including 3D volume rendered and curved multiplanar reconstructions or maximum intensity projections (4).

What advantages does MSCT have over other modalities in cardiac imaging?

MSCT versus functional imaging

MSCT coronary angiography provides anatomic visualization of stenoses and does not provide information of the functional relevance of the lesion. Only approximately half of the significant stenosis prove to cause ischemia in a SPECT or PET examination (3,4). Additionally, many patients with a normal perfusion scan show considerable atherosclerosis on MSCT scan. There appears to be a discrepancy between anatomic and functional testing. They seem to produce complementary information, one on the atherosclerosis and the other on hemodynamically significant lesions. Further testing of patients with borderline stenosis or equivocal findings on MSCT with functional imaging could verify ischemia and lead to referral to invasive coronary angiography (ICA). Non-ischemic patients with borderline stenosis would be saved from ICA.

Ruling out coronary artery disease (CAD) in low to intermediate risk patients with chest pain implies that it is not complete absence of CAD which is required, but rather absence of sufficient stenosis to cause angina. In defining 'sufficient' stenosis the following issues arise: a stenosis causing angina is dependent not only on the percentage narrowing of the lumen, but also length of the stenosis, the difference of pressure across it, and the amount of exercise or demands set for the heart.

MSCT versus invasive coronary angiography (ICA)

Invasive coronary angiography (ICA) offers spatial resolution of 0.1mm. In 64-slice CT the spatial resolution is 0.4mm or poorer. To differentiate a 10 from a 20% coronary stenosis, a resolution of 0.3mm is required. MSCT offers thus a semi-quantitative estimate of coronary stenosis. Only vessels with diameter of 1.5mm or more can be reliably assessed. Studies with 64-slice CT indicate that quantitative estimates of stenosis severity by MSCT correlate only modestly with ICA (1).

High risk plaques are lipid-rich unstable plaques which may show little or no stenosis (2). They are the most likely sources of coronary thrombosis. Several studies have identified differences in plaque composition between patients with acute coronary syndrome and stable CAD. There is some evidence that CT could assess the composition of plaques and identify high risk plaques better than ICA (2).

Invasive coronary angiography (ICA) takes approximately an hour to perform but may require several hours of preparation beforehand and a recovery period afterwards. Therefore an overnight stay in hospital may be required. ICA carries a risk of heart attack or stroke. Due to the ineffectiveness of the pre-ICA diagnostic testing, between 25 % and 50% of diagnostic ICAs present a normal or minimal atherosclerosis. In England 67% of ICAs did not involve percutaneous coronary intervention in 2005. In 2003 in Spain 34% of ICAs led to therapeutic intervention (5).

MSCT versus stress electrocardiograph (ECG)

In Berman's study intermediate risk patients (those who on risk scoring might have 10-20% risk of a cardiac event in the next ten years) CT coronary angiography was a more sensitive test than exercise testing for CAD. It was better in selecting patients for aggressive medical management and further testing (6).

MSCT versus magnetic resonance angiography (MRA)

Magnetic resonance angiography (MRA) is still in research and development for the evaluation of coronary arteries. It is non-invasive and uses no radiation. It has inferior spatial resolution and accuracy for CAD. Around 20% or more of clinically significant stenoses could be missed using MRA (7).

MSCT versus electron beam computed tomography (EBCT)

EBCT is also in the research and development phase. It is faster than MSCT but more expensive and the scanners are not widely available and not suitable for general imaging purposes. EBCT is non-invasive and involves some radiation exposure but at a lower level than for MSCT. It is inferior to MSCT in terms of power and slice thickness (7).

Who send/select patients to MSCT coronary angiography? Who perform the studies? Who interpret the studies?

Methods

The research questions under this issue were considered relevant, but due to time constraints, we did not answer them in this assessment.

What is the optimal patient population for cardiac MSCT?

Results

American College of Cardiology Foundation has produced recommendations on appropriate uses of cardiac computed tomography (8). The appropriate indications include:

- evaluation of chest pain where there is intermediate pre-test probability of coronary artery disease (CAD) and either an uninterpretable ECG or inability exercise; or after an uninterpretable or equivocal stress test;
- evaluation of suspected coronary anomalies in symptomatic CAD;
- acute chest pain with intermediate pre-test probability of CAD, no ECG changes and enzymes negative; and
- evaluation of coronary arteries in patients with new onset heart failure to assess aetiology.

In what kind of institutions, hospitals or clinics should MSCT coronary angiography be used?

Methods

This research questions was considered relevant, but due to time constraints, we did not answer it in the assessment.

When was MSCT coronary angiography introduced and what is its position currently?

Results

The first (since early 1990s) CT technology that allowed ECG gated cardiac CT imaging was electron beam CT (EBCT). EBCT provides very high temporal resolution (100 ms per image), but has substantial limitations in spatial resolution and image noise (3). Previously, magnetic resonance imaging (MRI) and electron beam CT (EBCT) were considered as non-invasive cardiac imaging modalities of choice, due to their high temporal resolution. Neither has been used in routine clinical practice due to limited availability (2).

The introduction of multidetector computed tomography in the late 1990's led to significant improvement of resolution in CT imaging. Small and rapidly moving structures could be visualised with good image quality. This permitted expansion to new imaging indications. Already the initial four-slice scanners demonstrated the potential of MSCT to visualize coronary arteries. This was a major driving force behind an ongoing, rapid evolution of scanner technology along with improvements in software and post processing tools (3).

Four-slice machines appeared in 1998, 16-slice in 2001, and 64-slice at the end of 2004. Initially, four slices of five mm thickness required a 35 second breath hold from the patient. Improvements in hardware and software led to more advanced MSCT technology that produces more images in less time. Improved spatial resolution in 64-slice scanners allows better assessment of smaller coronary arteries such as the distal left anterior descending (LAD) and left circumflex arteries (LCX). Assessment of calcified or stented vessels is improved, where older machines overestimated the degree of stenosis (2). The number of uninterpretable segments has reduced substantially in newer machines: in 64-slice scanners only 4% of segments remain uninterpretable compared to 30% of uninterpretable segments in 4-slice scans that had to be excluded from analysis (4). This improvement in image quality is paralleled by an increase in the radiation dose (1).

Currently 64-slice CT is considered as the industry standard for cardiac CT imaging (3). Recent meta-analysis demonstrated a significant improvement in the accuracy for the detection of coronary artery stenosis for 64-slice CT compared to the previous scanner generations (9). However, it is important to realize that patient selection may still heavily influence the results. Patients with higher heart rates or arrhythmias were generally excluded because of lowered image quality. The same applies to patients with severe CAD with extensive calcifications.

The dominating manufacturers of the technology are GE (General Electric), Philips, Siemens and Toshiba (www.msct.eu/MSCT_INFO/Links.htm, accessed 13.7.2008). The technical performance of their respective 64-scanners has been assessed recently by the ECRI institute (10)

In 2007, 256- and 320-slice MSCT systems became available (1). They have large coverage along patient's longitudinal axis. They allow imaging of coronary arteries during one or two heartbeats and thus make coronary CT angiography less susceptible to arrhythmias or heart rate variability. This significantly lowers the scan time and reduces the amount of contrast needed (4). Although the spatial resolution is comparable to the older generations, the newer devices obtain more evaluable scans.

Since motion artefacts, due to limitations in the temporal resolution, remained a problem even in 64-scanners, dual source CT (DSCT) has been introduced. DSCT integrates two X-ray tubes into one scan system, increasing the temporal resolution to 83 ms. This results in improved image quality and less dependency on heart rate control (4). High diagnostic accuracy can be obtained even in patients with high heart rate. Preliminary studies using DSCT showed that up to 98% of all coronary segments could be visualized without motion artefacts, even without beta-blockers, or in people with uneven rhythm or extensive calcifications (3). Reports on radiation dose exposure when using DSCT are conflicting. Contrary to normal 64 MSCT, it seems likely that this technique is best with patients who have relatively high heart rates.

A major improvement has been a reduction of the radiation dose by the development of progressive ECG gating. With a "step and shoot" protocol, images are taken typically in end-diastole. Because of intermittent data acquisition, the radiation dose can be substantially lowered down to approximately 1.1-3.0mSv (11,12).

Although 64-slice CT is a reliable tool to rule out functionally relevant CAD in a population with intermediate pre-test risk of disease, an abnormal CT angiogram does not necessarily predict ischemia (3). Since coronary CT angiography and perfusion imaging provide different and complementary information, their sequential use or hybrid imaging may provide useful incremental information. In a feasibility study, hybrid PET/CT was evaluated and was accurate (sensitivity 90%, specificity 98%) in detecting hemodynamically relevant coronary lesions (13). In another study hybrid SPECT/MSCT had much better accuracy in detecting functionally relevant lesions than MSCT alone (14).

Are major technological advantages expected with MSCT?

Methods

This issue was considered relevant but due to time constraints, and because this is partly answered in the issue B0003 "Is the MSCT technology mature?", we left this unanswered.

Will current technology be outdated or phased out in near future?

Methods

This issue was considered relevant but due to time constraints, and because this is partly answered in the issue B0003 "Is the MSCT technology mature?", we left this unanswered.

Is there an established reference method for the assessment of coronary artery luminal stenosis?

Is there an established reference method for the assessment of coronary artery atherosclerosis (coronary artery disease)?

Is there an established reference method for the assessment of the cardiac function (myocardial perfusion and cardiac wall motion)?

Is there an established method to evaluate the clinical consequences of the CT findings?

Methods

The research questions under this issue were considered relevant, but due to time constraints, and because these are addressed at least partly in the accuracy domain, we did not answer them in this assessment.

Are there specific technological features of cardiac MSCT that are different from other MSCT applications?

Results

Imaging of the heart is technically challenging due to continuous motion during the cardiac cycle. Image quality depends on the patient's ability to hold his breath. Image is acquired in a single breath-hold to improve image quality. Currently this has been reduced to below ten seconds (2).

Thinner slices have improved the resolution of three dimensional datasets and the quality of reformatted images. This is at the cost of increased image noise, which can significantly limit the use of MSCT in obese patients with a body mass index of greater than 30 (2).

Heart rate significantly influences motion artefacts. Despite the use of ECG gating techniques motion artefacts remain a major technical problem with heart rates above 70 beats per minute (2). Only patients with sinus rhythm should be studied; imaging should not be performed in patients with severe arrhythmias (4). Low (<60 beats per minute) and regular (+/- 2 beats per minute) heart rates predict good image quality (3). For this reason beta blockers are frequently used.

In MSCT angiography iodinated contrast agent is administered intravenously unlike conventional invasive coronary angiography in which contrast is administered directly into the coronary arterial tree. To ensure adequate contrast enhancement, a bolus tracking technique is usually used to synchronize its arrival in the coronary arteries. Verified and severe hypersensitivity to iodinated contrast agents is an absolute contraindication of the study. Relative contraindications include renal insufficiency, multiple myeloma and phaeochromocytoma (2).

So called "blooming" artefacts occur in the presence of highly attenuating objects in coronary vessels, such as calcium and stents. These artefacts make objects look larger on CT image than their

actual size, leading to an overestimation of luminal narrowing. The problem is less severe but still present in 64-slice devices. Because the presence of calcium in coronary artery walls increase with age, this can compromise the ability to perform technically adequate MSCTs in the elderly (6). The quantification of coronary calcium prior to imaging may thus play a role in identifying optimal candidates for MSCT imaging. Some centres have adopted routine calcium scoring and a limit of 400 IU in Agatston score, above which MSCT is not performed (1).

The diagnostic performance of MSCT in detecting one or more coronary stenoses can be expressed on per-segment or per-patient level. Earlier studies preferred reporting per-segment level results. This may be misleading, because the prevalence of coronary artery disease based on per-segment analysis is much lower since most of the coronary segments will not be narrowed. Patient-level analysis is considered more clinically relevant (15).

Investments and tools required to use the technology

What material investments are needed to use MSCT coronary angiography?

Results

The use of MSCT scanner for cardiovascular applications requires considerable investments in adequate spacing, hardware and software. All biomedical technology described in this paragraph is required in order to ensure a safe and appropriate use of MSCT in hospital setting.

An electrocardiogram (ECG) machine is required (usually integrated in MSCT scanner) to perform a specific imaging reconstruction and to implement a retrospective ECG-gated technique. It is necessary to have access to ventilatory support, monitoring system and an emergency trolley complete with cardiac defibrillator for resuscitation. A Power Injector (preferable two-way) is required to perform MSCT accurately.

In coronary angiography MSCT it is necessary to utilize a post processing workstation compatible with specific software, appropriate acquisition modality and imaging processing. High performance centralised storage systems are often required to manage diagnostic and radiological output (function: storage, retrieve, send, print) in larger institutions. Information system integrated with RIS-PACS (Radiologic Information System – Picture Archiving and Communication System) that allow a safe and accurate management of data and for back-up of data/images is usually necessary. For power breakdowns it is very important to have a system that allows for continuing and finishing current examination.

What kind of special premises are needed to use MSCT coronary angiography?

Results

Countries have different structural and safety requirements for installing radiological instruments. General requirements for radiological units (16) have to be checked against the instructions from local regulatory body.

General requirements:

- There should be adequate space for proper positioning of the patient, interpretation of the CT examination, patient observation after testing and preparation of the reports.
- Space permitted for storage of examination data and supplies must be sufficient for the volume of the unit.
- CT room has to be properly built and insulated against radiation (usually with lead). Load limit of the floor should be taken into account
- Standard and auxiliary power plant, vacuum, oxygen and medical gas plants and air conditioning system are required
- Direct visualization of the patient should be available through a leaded glass window.
- Patient privacy must be assured with the use of appropriate curtains and doors.
- A sink and antiseptic soap must be readily available and used for hand washing.

What equipment and supplies are needed to use MSCT coronary angiography?

Results

Heart rate is monitored; only patients in sinus rhythm and who are able to hold their breath should be scanned. Most centres administer beta-blockers to patients with heart rates above 60-65 beats per minute, either with intravenous or oral beta blockers. Many centres also administer sublingual nitrates which dilate the coronary arteries thereby enhancing image quality (4).

60-140 ml iodinated contrast agent is needed, depending on scanner type, patient size, heart rate, and body mass index. The contrast agent should be of high iodine concentration, followed by 40-50 ml saline for optimal arterial enhancement.

Otherwise the use of MSCT requires equipment and supplies that are frequently utilised in health care units i.e. syringes, needles, and bandages.

What kind of data and records are needed to monitor the use of MSCT coronary angiography?

Results

Health care organizations create their records of patient and staff data and care process with HL7 communication protocol (17). Links to national standards are available at <http://virtual.vtt.fi/virtual/hl7/index.htm>. Diagnostic imaging records are created according to Dicom Protocol. A record for radiation doses provided to patients is needed. RIS – PACS system allows the optimization of workflow procedure.

What kind of registers is needed to monitor the use of MSCT coronary angiography?

Methods

This issue was considered relevant but due to time constraints we left this unanswered.

Training and information needed for utilizing the technology

What kind of qualifications, training and quality assurance are needed for the use and maintenance of MSCT?

Results

International Atomic Energy Agency (IAEA) has published basic safety standards in diagnostic radiology (18). National or regional regulatory bodies authorize practices in the form of registration or licence. They provide guidelines for maintenance and periodic quality control. Regulatory authorities may require that the authorization be renewed periodically. Periods of renewal are based on safety criteria. In the view of IAEA-TECDOC-1067 a reasonable period for radiology is five years (19).

Personal qualifications and training

Cardiac MSCT requires competence on many levels. Data acquisition needs to be carefully performed, including necessary pre-medication. Appropriate measures are needed to keep radiation exposure as low as possible. Image reconstruction and post-processing require knowledge in CT physics, radiology, and cardiac physiology. Image interpretation must be based on knowledge in CT angiography, cardiac anatomy, normal and variant patterns of coronary circulation and CAD assessment in general. Training in radiology or cardiology alone will not provide sufficient background to perform and evaluate cardiac MSCT (3).

There is no scientific data on the required amount of training to achieve a certain level of diagnostic confidence and safety in cardiac CT (3). The published recommendation described here are consensus-based statements.

National regulations may require a personal accreditation as formal recognition of competence. Accreditation is usually provided by the relevant professional bodies. Some countries require a formal personal authorization. General requirements are described in the IAEA Report no 39, page 4-6 (18). Some national regulatory agencies are listed in Appendix 2.

Personal accreditation, continuous training and safety programmes regarding the use of MSCT for cardiovascular applications are important both for the safety point of view (optimal radiation safety, avoiding adverse effects of drugs and contrast agents), and for optimal outcome of testing (adequacy of image quality and proper interpretation of results with as few false negative and false positive results as possible). The difficulties in this rapidly changing field are the complexity of the imaging devices and anatomy, continually changing imaging technology, and the rapidly advancing uses with many new indications

A licensed unit should establish a policy that encourages and provides continuing professional development programme, with the aim of improving staff skills, maintaining familiarity with current practices and fostering safety culture. Such training and development can be set up through informal meetings of the radiology department, seminars, accredited continuing education programmes or other means.

Professional education and training to obtain the necessary qualifications need to have been completed before commencement of duties and continued subsequently as part of professional development and as required by the regulatory body. Furthermore, the instruction of personnel is required whenever significant changes occur in duties, regulations, the terms of licence or radiation safety procedures. Licensees need to maintain records with respect to the initial and periodic training of personnel (18).

The training needs, assurance of competence and maintenance of certification of those using the MSCT applies primarily to radiologist although other experts (cardiologists) or specialized personnel (technologists, nurses, physicist) may be involved. Considerable subspecialty training may be required in certain areas. The appendix 2 of the IAEA safety standards report (18) contains requirements for training of medical practitioners, radiographers/radiological technologists, medical physicists, radiation protection officers (RPOs), nurses and maintenance staff.

Most cardiology and radiology training programmes do not incorporate mandatory sections of cardiac CT at a volume that would suffice to provide competent diagnostic service. There are some specialty fellowship programmes in cardiac CT available. Guidelines addressing what level of training is required for the performance of cardiac imaging with computed tomography have been developed by a joint committee of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) (20). The guideline helps in the assessment of physicians' expertise in the ability to apply and interpret cardiovascular computed tomography (CCT) in hospital or outpatient settings. The minimum education, training, experience, and cognitive skills necessary for the evaluation and interpretation of MSCT are specified. These guidelines that were published in 2005, with a minor update in 2007, are used by organisations like the Intersocietal Commission for the Accreditation of Computed Tomography Laboratories (ICACTL, www.intersocietal.org) for their standards.

Minimum requirements for competency in cardiac CT have been defined for three levels. Level 1 defines a basic knowledge of cardiac CT, which is sufficient for practice in general adult cardiology or general radiology, but not for independent interpretation of patient data sets. Level 2 defines the minimum experience required in order to independently perform and interpret CT coronary angiography. Level 3 training would qualify an individual to direct an independent cardiac CT programme.

In summary the committee recommends the following:

- The minimum level of training required to be able to independently perform and interpret coronary CT angiography consists of at least 150 mentored CT scan examinations interpreted and at least 50 mentored examinations performed.
- The minimum level required to be able to continue to independently perform and interpret coronary CT angiography requires at least 50 examination conducted and interpreted per year.
- Candidates for competence in coronary CT angiography should have completed a formal residency in cardiology, nuclear medicine or radiology.
- A CT laboratory performing coronary CTA should have a continuous quality control program co-ordinated by a level 3-trained physician. At this time, no definitive statements about the quality of scanners has been made, although on the basis of the current literature, coronary CTA imaging on multidetector CT units should be performed on systems with ≥ 16 detectors.

Similar standards have been set forward by the American College of Radiology in their Practice Guidelines (21) and the recently revised CT Accreditation Program (22). In their statement the qualifications of a radiologist who supervises and interprets cardiac CT examinations should include supervision and interpretation of 75 cardiac CT cases within 36 months, excluding cases performed exclusively for calcium scoring.

Managerial commitment to safety culture and quality assurance

Licensed radiology units are usually required to implement quality assurance programs that provide adequate assurance that the specified requirements relating to protection and safety are satisfied. Items for radiation protection and safety programmes are described in Appendix 1 in the IAEA's report no 39 (18).

Hospital senior management should be committed to an effective protection and safety policy and demonstrate support for those persons whose responsibility radiation protection is. The commitment can be demonstrated by a written policy that assigns the importance to protection and safety. This statement should be made known to the hospital personnel and should be followed by establishing a radiation protection programme (18).

Managers should appoint sufficient number of medical and paramedical professionals with personal accreditation for imaging tasks to ensure that all activities relevant to protection and safety are carried out in accordance with regulations. The number of persons should be kept under review, especially when workload increases or new techniques and new equipment are incorporated. Inspection of the facilities and records by the regulatory body are possible (18).

How does training and quality assurance affect management of MSCT angiography?

Results

It is difficult to determine to what extent training and experience translate into better patient outcomes. Different radiation doses are used with different imaging protocols. Careful attention to technique, including the employment of dose-reduction strategies, can minimize the radiation dose patients receive (23-25).

Experience and level of training of those interpreting the results affects the accuracy and number of false negative and false positive readings. A high level of training and extensive experience increases accuracy but there is significant variation in individual performance even after training. This has been shown for computerised tomography of the colon (virtual colonoscopy) (26) but it is unclear how this applies to cardiac MSCT.

Inter-rater agreement is generally slightly lower than intra-rater agreement (kappa-values from 0.558- to 0,76 compared with 0,79 to 0,81) and slightly lower with patient-based compared to segment based analysis. How this is affected by level of training or experience is unclear (27).

What kind of training or information about MSCT angiography is needed for the patients and their families and general public?

Results

Informing potential users, the general public, key decision- and policy-makers is increasingly important in the light of extensive use, variation in practice (referral for MSCT) and public interest and demand for MSCT. Patients advised to have MSCT should receive verbal and written information on the risks and benefits of the procedure. Such information should be balanced, unbiased and of high quality and preferably from recognised official sources (radiological associations/societies and government agencies) that adhere to the Health On the Net (HON) code principles (<http://www.hon.ch/>).

Suggested high quality portals for health related information:

- Healthinsite <http://www.healthinsite.gov.au/> (Australia)
- Health On the Net Foundation www.hon.ch/ (Switzerland)
- NHS Direct Online <http://www.nhsdirect.nhs.uk> (UK)
- MEDLINEplus <http://medlineplus.gov> (USA)
- EQUIP <http://www.equip.nhs.uk/> (UK).

MSCT is safer than invasive coronary angiography (ICA) as it is less invasive and does not have the risks associated with arterial catheterisation. Negative consequences, in addition to the risks of the procedure (radiation and contrast exposure), include the downstream effects of false negative (delayed or missed diagnosis and potentially beneficial treatment), false positive (inappropriate diagnosis and labelling and even unnecessary and potentially harmful interventions) and inconclusive results (anxiety, further tests). The risks of ionizing radiation are perhaps best put into perspective by explaining the magnitude in relation to other common radiology investigation (comparable to 160 PA chest films or 3-4 times the average yearly effective dose of natural background radiation) (2). Claustrophobia is a problem for some patients and as with any procedure that involves radiation pregnancy is a contraindication. Allergy to contrast agents and beta-blockers should also be excluded. The limitation of MSCT on certain indications might need explaining in patients who previously had a cardiac intervention (in particular small stents) where evidence of effectiveness is insufficient and also the potentially harmful or beneficial incidental extra cardiac findings on MSCT.

Discussion

The use of 64-slice CT coronary angiography seems to be increasing and its indications become clearer. It is usually not mentioned in clinical management guidelines of coronary artery disease, but there are consensus statements about appropriate indications and conditions of use. The technology is rapidly evolving and completely new generations, with added image slices or dual X-ray tube sources, with new features are entering market. Radiation is the major safety issue, which has not been resolved in a satisfactory manner.

The aim of this document, the Core HTA on MSCT coronary angiography, was to test the first draft of the diagnostic Core Model by EUnetHTA project. The testing revealed some weaknesses in the

content of the assessment elements. Therefore we decided to combine the issues B0012 and B0019 and handle the qualifications, training and quality assurance thing in a single issue, because we felt it was difficult to handle them separately. Instead we added an element, numbered B0020, that considers the effect of training and quality assurance on the management of the technology. We also combined the patient training and information issues B0014 and B0015 into one issue (B0014).

The time-lines were strict and we ended up with a situation with not enough resources of substance expertise. Therefore some issues remained unanswered and some answers are not as complete as they should have been if it were a "real" Core HTA. A more systematic approach and a formal quality assessment would have been needed in some instances.

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Assessment elements table

	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT or Comment (if regarded as a not relevant issue in this context)
B0001	Description and technical characteristics of technology	Features of the technology	What is this technology?	yes	What is the technological basis of cardiac MSCT?
B0002	Description and technical characteristics of technology	Features of the technology	Why is this technology used?	yes	What advantages does MSCT have over other modalities in cardiac imaging?
B0004	Description and technical characteristics of technology	Features of the technology	Who are the users of this technology?	yes	Who send /select the patients to MSCT coronary angiography? Who perform the studies? Who interpret the studies?
B0016	Description and technical characteristics of technology	Features of the technology	Who are the persons this technology will be used on?	yes	What is the optimal patient population for cardiac MSCT?
B0005	Description and technical characteristics of technology	Features of the technology	Place and context for utilising the technology?	yes	In what kind of institutions, hospital or clinics should MSCT coronary angiography be used?
B0003	Description and technical characteristics of technology	Features of the technology	Phase of the technology: When was it developed or introduced in health care?	yes	When was MSCT coronary angiography introduced and what is its position currently?
B0017	Description and technical characteristics of technology	Features of the technology	Is the technology rapidly changing / improving?	yes	Are major technological advantages expected? Will current technology be outdated or phased out in near future?
B0018	Description and technical characteristics of technology	Features of the technology	Are the reference values or cut-off points clearly established?	yes	Is there an established reference method for the assessment of coronary artery luminal stenosis? Is there an established reference method for the assessment of coronary artery atherosclerosis (coronary artery disease)? Is there an established reference method for the assessment of the cardiac

					function (myocardial perfusion and cardiac wall motion)? Is there an established method to evaluate the clinical consequences of the CT findings?
B0006	Description and technical characteristics of technology	Features of the technology	Are there any special features relevant to this technology?	yes	Are there specific technological features of cardiac MSCT that are different from other MSCT applications?
B0007	Description and technical characteristics of technology	Investments and tools required to use the technology	What material investments are needed to use the technology?	yes	What material investments are needed to use MSCT coronary angiography?
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?	yes	What kind of special premises are needed to use MSCT coronary angiography?
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?	yes	What equipment and supplies are needed to use MSCT coronary angiography?
B0010	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use of the technology?	yes	What kind of data and records are needed to monitor the use of MSCT coronary angiography?
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 kind of registers is needed to monitor the use of MSCT coronary angiography?
B0012	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What kind of qualifications, training and quality assurance are needed for the use and maintenance of the technology?	yes	What kind of qualifications, training and quality assurance are needed for the use and maintenance of the MSCT?
B0020	Description and technical characteristics of technology	Training and information needed for utilizing the technology	How does training and quality assurance affect the management of the technology?	yes	How does training and quality assurance affect management of MSCT angiography?
B0014	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What kind of training or information about the technology is needed for the patients, their families and general public?	yes	What kind of training or information about the MSCT angiography is needed for the patients, their families and general public?

Appendix 1

Basic search 15.12.2007

#1 MeSH Coronary Disease EXPLODE 1 2

#2 (coronary AND (disease* OR arter* OR aneurysm* OR stenosis* OR restenosis* OR thrombosis* OR vasospasm* OR vessel*)) OR "angina pectoris" OR "chest pain" OR atherosclerosis*

#3 #1 OR #2

#4 MeSH Coronary Angiography EXPLODE 1 2 3

#5 MeSH Tomography, X-Ray Computed EXPLODE 1 2 3 4 5 6

#6 #4 AND #5

#7 angiograph* AND tomograph*

#8 #6 OR #7

#9 #3 AND #8

#10 msct OR mdct

#11 (multislice OR "multi-slice" OR "multi slice" OR multirow OR multidetect* OR "multi-detect*" OR "multi detect*" OR multiselect*)

#12 (4 OR 16 OR 32 OR 40 OR 64) AND (slice* OR row*)

#13 #10 OR #11 OR #12

#14 #9 AND 13

Additional search in Medline in March 2008

equipment/

device\$.tw.

(technique\$ or method\$).tw.

diagnostic tests, routine/

diagnos\$ test\$.tw.

diagnostic techniques/

Mass Screening/

Safety

Iris Pasternack, Nick Hicks, Cecile Camberlin, Irina Cleemput, Hans van Brabandt, Sami Kajander, Ritva Bly, Leonor Varela Lema, Alberto Ruano-Ravina,

Introduction

MSCT coronary angiography is a technology that may have the potential to replace a proportion of invasive coronary angiographies (ICA) in patients with suspected coronary artery disease. MSCT is non-invasive but uses more ionizing radiation than ICA and a balanced assessment of the benefits and risks of utilisation of the current and recent generations of MSCTscanners to other diagnostic modalities is necessary.

Safety concerns related to cardiac MSCT can be divided into three groups: those that arise from the use of ionizing radiation, the use of iodinated contrast media, and the use of premedication needed to provide adequate image quality. The overall risk of harms of a technology is a summation of the risk contribution of each component of the procedure. When weighing the overall risk of any medical procedure, it is important to consider how this compares to the overall risk of alternative procedures. In the case of MSCT coronary angiography clinical indications for cardiac CT must always take radiation exposure into account. All possible measures should be taken to keep the dose as low as possible. The statistical risk of cancer induction due to radiation exposure is difficult to assess at an individual level, and the harms may only manifest themselves years later. By contrast certain harms may appear immediately such as a decline in renal function or an allergic reaction due to contrast media.

Methodology

We did a basic search for HTA-reports and systematic reviews and an additional search in Medline. Search strategies are described in Appendix 1. We used the two new HTAs on MSCT coronary angiography published in spring 2008 (1,2). Further information was sought in internet and snowballing references from relevant documents and using the 'related articles' feature in PubMed.

We did not intend to do a systematic review for each research question. Instead, information from published HTAs and systematic reviews formed the basis, and recent publications were checked.

There was no formal quality assessment of the included publications.

Assessment elements

Technology dependent safety risks

What are the safety risks of MSCT coronary angiography?

Results

Direct harms related to cardiac MDCT studies can be divided into three groups: those that arise from the use of ionizing radiation, those that are due to the use of iodinated contrast media, and those that may occur because of the use of premedication needed to provide adequate image quality. In each group, the amount of harms expected or known to occur is related to different subpopulations subjected to the study. Morbidity figures range from 1-2% and mortality is estimated to be 0,1 %, but it can increase to 1 % in patients with unstable angina pectoris(3).

Ionizing radiation

If performed with faultless equipment according to manufacturer's instructions, the radiation doses due to diagnostic use of multislice CT is well below the threshold for the induction of deterministic effects (such as skin burns, epilation and the induction of eye cataracts). Genetic risk from CT studies is nowadays considered to be negligible as well. The principal concern at patient doses is the induction of cancer in the exposed individual.

The effective radiation dose of a contrast enhanced cardiac CT scan is 5-20 mSv (4). In studies included in a systematic review published in 2007 (5) the estimated mean effective radiation dose per patient was 15 mSv for males and 20 mSv for females. With modulated protocols the corresponding figures were 7 and 14 mSv. This is much higher than the radiation dose of an invasive coronary angiography (ICA) which is about 2-7 mSv.

This radiation exposure is comparable to 160 posterior-anterior chest films or three to four times the average yearly effective dose of natural background radiation (2.5 mSv) (2).

Iodinated contrast media

MSCT necessitates intravenous administration of contrast medium. This can lead to allergic reactions and to renal failure. In most cases renal impairment reverses within a week. Meanwhile it is essential to avoid further nephrotoxic agents and carefully control fluid and electrolyte balance. In more severe cases temporary dialysis may be necessary (1).

Typically, 100 to 130 ml of non-ionic contrast media containing 300 to 350 mg of iodine per millilitre is injected for MSCT angiography. Extravasation (average of 18 ml) occurs in 0,3% to 0,6% of patients when power injector is used in a peripheral vascular line (6).

Allergic reactions

Contrast material is generally well tolerated although approximately 1% of patients who receive low-osmolar non-ionic contrast material will develop anaphylaxis symptoms. Most anaphylactic reactions are mild and non-allergic. The risk for serious or severe reactions—anaphylaxis grade 3—

has been estimated to be from 0.02% to 0.04% with non-ionic contrast material. In more than 90% of cases, the direct release of histamine and other mediators is responsible for the anaphylaxis symptoms after application of contrast material. However, genuine IgE-mediated allergic anaphylaxis is rare but may arise.

Contrast induced nephropathy

Contrast-induced nephropathy (CIN) is a serious complication of the use of iodinated contrast media. It is the third most important cause of hospital-acquired renal failure and is associated with increased morbidity and mortality.

CIN involves an acute decline in renal function that occurs 24 to 48 hours after intravascular injection of contrast medium (CM). The commonest definition in use is an increase in serum creatinine (SCr) of >25% of baseline value occurring following the intravascular administration of CM without an alternative explanation. Serum creatinine usually peaks 2-3 days following CM use and returns to the baseline within 14 days. Some patients, however, progress to acute renal failure (ARF) requiring dialysis (7).

Prospective studies of the incidence of CIN have produced a wide range of values, due to the differences in the definition of the renal failure and differences in patient comorbidity. Patients without risk factors had an average 3 % risk for contrast induced nephropathy (8). However, in a consecutive series of 1800 patient undergoing invasive cardiac procedures, the incidence of CIN was 14,5% (1). Contrast registry data of patients undergoing diagnostic investigations requiring contrast media suggest an incidence of 0.4% for subsequent dialysis (9).

The occurrence of CIN has been closely identified with eight pre-existing risk factors: hypotension, intra-aortic balloon pump use, congestive heart failure, age over 75 years, anaemia, diabetes, contrast medium volume and impaired renal function (10-17).

Careful patient selection can identify those patients for whom contrast media may present an increased risk or be contraindicated. For some of these patients preventive pre-treatment strategies may reduce the risk of CIN following administration of contrast media. The physician should also be available to treat adverse reactions to contrast media (9,18-21).

Premedication

Most patients who are prepared for MSCT, will receive a beta-blocker if their heart rate is above a certain threshold, typically 60 or 65 b.p.m. Potential adverse effects of beta-blockade are hypotension, extreme bradycardia and bronchospasm. Careful clinical monitoring of blood pressure and heart rate during and after the procedure is usually required (1).

The need for pre-test administration of beta-blocking agents is less compelling in dual-source 64-slice CT, although this advantage may disappear when prospective ECG-gating is used (1).

The use of sublingual or peroral nitrate substances is recommended in many cardiac MSCT protocols as a means to enhance image quality. Necessary precautions must be taken into account while using this premedication.

Comment

Currently, majority of users are moving towards the use of newer dose saving protocols. E.g prospective gating provides significant radiation saving without significant effects on image quality. The newest devices will have a dose of <1-3 mSv/patient in routine work, which is actually considerably less than that of an invasive angiography.

References:

Maruyama T, Takada M, Hasuike T, Yoshikawa A, Namimatsu E, Yoshizumi T. Radiation dose reduction and coronary assessability of prospective electrocardiogram-gated computed tomography coronary angiography: comparison with retrospective electrocardiogram-gated helical scan. *J Am Coll Cardiol*. 2008 Oct 28;52(18):1450-5.

Kajander S, Ukkonen H, Sipilä H, Teräs M, Knuuti J. Low radiation dose imaging of myocardial perfusion and coronary angiography with a hybrid PET/CT scanner. *Clin Physiol Funct Imaging*. 2008 Nov 6. [Epub ahead of print]

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Javadi M, Mahesh M, McBride G, Voicu C, Epley W, Merrill J, Bengel FM. Lowering radiation dose for integrated assessment of coronary morphology and physiology: first experience with step-and-shoot CT angiography in a rubidium 82 PET-CT protocol. *J Nucl Cardiol*. 2008 Nov-Dec;15(6):783-90. Epub 2008 Sep 12.

What are the immediate and long term consequences of the radiation exposure from MSCT coronary angiography?

Results

Harms due to cardiac CT may be acute or delayed. They are caused by a variety of factors both independent and related. If performed with faultless equipment according to manufacturer's instructions, the radiation doses due to diagnostic use of multislice CT is well below the threshold for the induction of deterministic effects (such as skin burns, epilation and the induction of eye cataracts). Immediate risk for genetic changes from CT studies is nowadays considered to be negligible. The principal concern at patient doses is the induction of cancer in the exposed individual. No major body that investigates radiation risks recommends the use of threshold values of radiation in evaluating risks of cancer induction (22-24).

For any individual aged 55 years or older, lifetime risk of developing cancer after a single MSCT cardiac exam is low and generally considered to be below 1.0 %. In the study of Coles (25) it is estimated that the risk of inducing a fatal cancer is 0,07 % for MSCT and 0,02 % for invasive coronary angiography (ICA).

The lifetime excessive risk of breast and lung cancer for girls and young women after a single MSCT study is much higher. Recent estimate for the relative risk of breast carcinoma incidence is 1.004 – 1.042 from a single scan. Relative risk for lung cancer incidence, in comparison, is 1.005 – 1.076 from a single scan. Other organs directly in the field of view (heart and oesophagus in the addition to the above) exhibit the highest absorbed doses. These risks, as well as risks related to ionizing radiation in general, are greatest in younger patient populations.

In a simulation study, equivalent doses to individual organs from MSCT were determined, and life time cancer risk from these doses calculated using the approach of the BEIR II (National

Academies' Biological Effects of Ionizing radiation) 7th report (26). Life-time cancer risk estimates for standard MSCT varied from 1 in 143 for a 20-year-old woman to 1 in 3261 for an 80-year-old man. Use of simulated ECG controlled current modulation decreased these risk estimates to 1 in 219 and 1 in 5017, respectively. The highest organ lifetime attributable risks were for lung cancer and, in younger women, breast cancer.

Comment

Currently, majority of users are moving towards the use of newer dose saving protocols. E.g prospective gating provides significant radiation saving without significant effects on image quality. The newest devices will have a dose of <1-3 mSv/patient in routine work, which is actually considerably less than that of an invasive angiography.

References:

Maruyama T, Takada M, Hasuike T, Yoshikawa A, Namimatsu E, Yoshizumi T. Radiation dose reduction and coronary assessability of prospective electrocardiogram-gated computed tomography coronary angiography: comparison with retrospective electrocardiogram-gated helical scan. *J Am Coll Cardiol*. 2008 Oct 28;52(18):1450-5.

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What is the dose relatedness of harms of ionizing radiation in MSCT coronary angiography?

Results

High doses of radiation clearly link to immediate as well as delayed harms, whereas the effects of long term exposure to low levels of radiation, as used in MSCT, remain highly controversial. Although there is no clear evidence of harm various advisory bodies use the conservative zero threshold assumption: only no radiation is without excess risk. To estimate the immeasurable risk from low-level radiation requires mathematical models. Currently, a linear relationship between dose and risk is used in models (6).

As CT doses are much higher than those from conventional radiography, and as cardiac CT doses are among the highest of CT, use of the ALARA principle (“as low as reasonably achievable”) is particularly important.

What kind of psychological harms does coronary MSCT potentially have?

Methods

This issue was considered relevant for this Core HTA. Due to time constraints, and because this issue will be at least partly answered in the social domain, we left this unanswered.

Which are the means to reduce the radiation dose of MSCT coronary angiography?

Results

Using as low radiation dose as possible in cardiac patients is particularly important since the patients may undergo many radiographic investigations including fluoroscopically guided cardiac interventions that may require a high radiation dose. Use of ALARA (“as low as reasonably achievable”) principle is therefore recommended. The supervising physician should be familiar with the technical parameters that affect radiation dosage: mAs, kVs and scan pitch. Automated X-ray-dose shaping algorithms and X-ray tube pulsing should be applied in order to minimise the radiation exposure while allowing diagnostic image quality.

Reduction in radiation dose can be achieved by obvious methods, such as keeping the length of the scan volume as short and tube current as low as possible (4). This is achieved through smaller z-axis scan coverage and extensive use of dose-modulating techniques, such as ECG-gated and attenuation based tube current modulation, use of reduced tube voltage in small patients, use of prospective ECG triggering (instead of retrospective gating), use of sequential (instead of spiral) imaging and combinations of these (27,28).

Reducing tube voltage to 100 kV instead of commonly used 120 kV should be considered in patients with normal or low body mass (4). However this is often at the cost of image quality.

Because the X-ray beam attenuation is less in the shorter postero-anterior direction than in the longer lateral direction, the radiation dose may be reduced when the X-ray tube is either anterior or posterior of the patient (6).

ECG-correlated tube current modulation, in which full tube current is limited to a short time period in diastole, can reduce the radiation dose by 30-50% (2,4). This is particularly effective in low heart rates.

The x-ray tube may be prospectively triggered to generate X-rays only during ventricular diastole, when cardiac motion artefacts are less likely. This so called "Step-and-shoot mode" could reduce the ionizing radiation exposure down to 2,5 mSv in non-obese patients (BMI<30) with heart rate less than 70 beat per minute (1,29-32). Prospective image construction enables significant reduction of radiation dose with the cost of diagnostic capability.

Comment

Currently, majority of users are moving towards the use of newer dose saving protocols. E.g prospective gating provides significant radiation saving without significant effects on image quality. The newest devices will have a dose of <1-3 mSv/patient in routine work, which is actually considerably less than that of an invasive angiography.

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By what means may the risk of harms from iodinated contrast medium be reduced?

Results

MSCT necessitates intravenous administration of contrast medium. This can give rise to allergic reactions and renal failure. In most cases renal impairment is transient and reverses within a week. Meanwhile it is essential to avoid further nephrotoxic agents and carefully control fluid and electrolyte balance. In more severe cases temporary dialysis may be necessary.

A number of approaches have been used to reduce the risk of contrast induced nephropathy (CIN) although not all are supported by a strong evidence base (19). The issues may be considered as patient dependent factors and patient independent factors (9).

Approaches include:

- reducing the quantity of iodine medium infused
- using low-osmolar or iso-osmolar contrast media
- optimising the contrast media injection regime
- optimising the dose to the physical characteristics of the individual patient
- increasing patient hydration by oral or intravenous means before undertaking the procedure
- using renoprotective drugs like N-acetylcysteine
- stopping nephrotoxic drugs

Undertaking an individual patient assessment in order to identify those with specific risk characteristics allows identification of those at highest risk of experiencing CIN (7,9).

Are there differences in the safety profile of different MSCT devices or generations?

Results

In the original studies included in a review by Hamon 2007, the effective radiation dose in 16-slice CT scans ranged from 5.4 to 16.3 mSv, and from 10-21.4 mSv for 64-slice CT scans (33). Radiation exposure with 320-slice CTs has been reported to be around 7 mSv (1).

In dual source 64-slice CT, the radiation exposure does not seem to be different than in standard 64-slice CT (1).

The need for pre-test administration of beta-blocking agents is less compelling in dual-source 64-slice CT, although this advantage may disappear when prospective ECG-gating is used (1).

With prospective ECG-gating (the "Step-and-shoot mode") the X-ray beam is turned on only during late diastole, and ionizing radiation can thus be reduced. Because of intermittent data acquisition

radiation dose can be substantially lowered to approximately 1.1-3.0mSv (34). There are no studies that compare MSCT with prospective ECG-gating with invasive coronary angiography (ICA).

Emerging hybrid techniques that combine MSCT with myocardial perfusion scanning will inevitably lead to an increase in radiation exposure (32).

Comment

Currently, majority of users are moving towards the use of newer dose saving protocols. E.g prospective gating provides significant radiation saving without significant effects on image quality. The newest devices will have a dose of <1-3 mSv/patient in routine work, which is actually considerably less than that of an invasive angiography.

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What is the safety of MSCT coronary angiography in comparison to alternative diagnostic technologies?

Results

MSCT versus invasive coronary angiography (ICA)

Overall mortality MSCT vs ICA

ICA is invasive and often performed with the intention to treat. Less invasive procedures are purely diagnostic but they may help to select patients for ICA. Contrast medium induced harms, such as allergic reactions and contrast nephropathy, are similar in MSCT than in ICA, while the doses of contrast medium are similar. MSCT appears to be safer despite its higher radiation dose (25).

Overall mortality risk for ICA is 0.13%: radiogenic risk 0.02% and non-radiogenic risk 0.11% (25). In United States ICA has an adverse event rate of approximately two per cent including vascular complications (1,6%), arrhythmia (0.3%), stroke (0.1%), myocardial infarction (0.05%) and death (0.12%) (35). Most of the severe harms are a consequence of cardiac catheterization and would therefore be avoided with the use of MSCT.

Overall mortality risk for MSCT is 0.07% (25). Morbidity figures in MSCT range from 1-2% and mortality is estimated to be 0,1 %, but it can increase to 1 % in patients with unstable angina pectoris (3).

Radiation MSCT vs ICA

MSCT requires higher doses of ionising radiation than ICA when conventional spiral technique and retrospective image reconstruction is used. Previous studies state that MSCT exposes the patient to 2-3 times more radiation than invasive angiography (36). Although the risk associated with the dose of this size is minimal, it may raise concerns about repeated doses, or in children or women of child-bearing age (35).

The effective radiation dose of a contrast enhanced cardiac CT scan is 5-20 mSv (4). In studies included in a systematic review published in 2007 (5) the estimated mean effective radiation dose per patient was 15 mSv for males and 20 mSv for females. With modulated protocols the corresponding figures were 7 and 14 mSv. This is much higher than the radiation dose of an invasive coronary angiography (ICA) which is about 2-7 mSv.

MSCT versus myocardial perfusion scintigraphy (MPS)

MPS involves exposure to ionizing radiation. Its estimated dose is approximately 8 mSv if both rest and stress studies are performed (37).

MSCT versus magnetic resonance imaging (MRI)

MRI is non-invasive and uses no radiation.

MSCT versus electron beam computed tomography (EBCT)

EBCT is non-invasive and uses lower radiation. EBCT yielded effective doses of 1.5 and 2.0 mSv for male and female patients. In same study MSCT delivered effective doses of 6.7-10.9 for male and 8.1-13.0 for female (38).

Comment

Currently, majority of users are moving towards the use of newer dose saving protocols. E.g prospective gating provides significant radiation saving without significant effects on image quality. The newest devices will have a dose of <1-3 mSv/patient in routine work, which is actually considerably less than that of an invasive angiography.

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Accuracy problems and incidental findings

What is the incidence and consequences of incidental extracardiac findings?

Results

Several extracardiac incidental findings have been described in patients that undergo MSCT coronary angiography. Incidental findings may lead to further and sometimes inappropriate testing and therapeutic acts (1). Follow-up has been considered mandatory in 5 to 56 % of patients with incidental findings (39).

Current software programs are reasonably sensitive for pulmonary nodules, but they have limited to poor specificity, and a high rate of false positive findings (1).

What are the safety consequences for patients receiving false positive test result in MSCT?

Results

Low specificity of MSCT coronary angiography in detecting significant stenosis originates from motion artefact and intramural coronary calcifications. The resulting high number of false positive test results, especially in low risk population, is a major limitation to the clinical usefulness of the technique (1).

False positive test result may cause anxiety and lead to further unnecessary and potentially harmful diagnostic and therapeutic interventions. An inconclusive test result in MSCT coronary angiography will qualify as false positive, because it inevitably leads to invasive coronary angiography (1).

Detection of an obstructive lesion by MSCT may be anatomically significant but clinically irrelevant if the patient's symptoms have no relation to the coronary stenosis thus detected. Studies comparing anatomical MSCT assessment to functional imaging (perfusion scan, SPECT) show that only approximately 50% of significant stenoses (>50% narrowing of vessel diameter) on MSCT are functionally relevant; a large proportion of significant lesions in MSCT does not lead in perfusion abnormalities (40).

Performance of 64-slice CT coronary angiography is not yet defined in clinical practice, because no significant trials have been performed in real world conditions and measuring patient relevant outcomes (1)

What are the safety consequences for patients receiving false negative test result in MSCT?

Results

A false negative test result in MSCT coronary angiography gives the individual false reassurance, which may lead to ignoring signs of early disease which would cause a delay in diagnosis and treatment (41).

Presence of luminal narrowing less than 50% may not lead to symptoms but does not exclude future severe events. Low grade stenosis may be prone to plaque rupture and may lead to serious clinical events (1).

What are the psychological harms for families of patients with false positive test result in MSCT?

Methods

This issue was considered relevant for this Core HTA. Due to time constraints, and because this issue will be at least partly answered in social domain, we left this unanswered.

Use- or user-dependent safety risks

How does the level of training or experience of the staff affect the safety of the MSCT coronary angiography?

Methods

This issue was considered relevant for this Core HTA. Due to time constraints, we left this unanswered.

What can be done to reduce user dependent risks in MSCT coronary angiography?

Methods

This issue was considered relevant for this Core HTA. Due to time constraints, we left this unanswered.

Patient dependent safety risks

What are the susceptible patient groups in MSCT coronary angiography?

Results

Young and women

In cardiac MSCT, radiation is targeted at chest, therefore subjecting females to high organ doses of the breast. Recent estimate for the relative risk of breast carcinoma incidence is 1.004 – 1.042 for a single examination. Relative risk for lung cancer incidence, in comparison, is 1.005 – 1.076 from a single study. Other organs, directly in the field of view (heart and oesophagus, in the addition to the above), exhibit highest absorbed doses. These risks, as well as risks related to ionizing radiation in general, are greatest in younger patient populations.

For any individual aged 55 years or older, lifetime risk of developing cancer after a single MSCT cardiac exam is low and generally considered to be below 1.0%. The lifetime excessive risk of

breast and lung cancer for girls and young women after a single MSCT study is much higher, recently estimated at 1.7% - 5.5 % after a single scan (42, 43, 44).

To conclude, young patients, especially young women and girls, are particularly prone to the induction of cancer due to radiation from CT. Therefore, these subpopulations should be imaged with cardiac MSCT only with caution and in special situations.

Previous anaphylaxis to contrast media

Contrast material is generally well-tolerated although approximately 1% of patients who receive low-osmolar non-ionic contrast material will develop anaphylaxis symptoms. Genuine IgE-mediated allergic anaphylaxis is rare but may arise. Therefore, for patients with undiagnosed previous anaphylaxis to contrast material (i.e., allergologic testing not performed), imaging procedures that do not require the administration of iodinated contrast material should be considered (13).

Impaired renal function

The occurrence of contrast-induced nephropathy (CIN) has been directly related to the number of eight pre-existing risk factors: hypotension, intra-aortic balloon pump use, congestive heart failure, age over 75 years, anaemia, diabetes, contrast medium volume and impaired renal function. Impaired renal function, in turn, is more likely to occur in patients with proteinuria, previous kidney surgery, hypertension, gout, diabetes and recent intake of nephrotoxic drugs. Although measures such as evaluation of the renal function and hydration before and after the study decrease the risks for CIN, all studies involving the use of iodinated contrast must be carefully considered within these patient groups. (10-12,18).

What can be done to improve the safety of the management of susceptible patient groups in MSCT coronary angiography?

Results

Although many risks are deterministic in nature, in a number of instances, the patient subpopulation at particular risk may be identified before the examination. Individual patient assessment at time of referral for investigation enables identifying those with those at highest risk of experiencing e.g. contrast induced nephropathy (CIN) (7). Thus appropriate measures can be considered either to perform the examination with least possible harm, or to use an alternative diagnostic method or test.

A survey in 2005 of knowledge and attitudes of 509 European radiologists to contrast induced nephropathy (CIN) showed that many did not have a systematic approach to the identification of patients and underestimated the importance of certain risk factors and the incidence of CIN (45).

Occupational safety

What is the occupational radiation exposure in staff performing MSCT coronary angiography?

Methods

Source	Search terms	Date of inquiry	Investigator	Selected
Medline (PubMed)	"occupational" AND "exposure" AND "radiation". Limits: published in the last 5 years, humans.	3.9.2008	IP	(48,49)
STUK - Radiation and Nuclear Safety Authority, Finland web pages http://www.stuk.fi/en_GB/		3.9.2008	IP	(43,44)
International Commission on Radiological Protection (ICRP) http://www.icrp.org/		3.9.2008	IP	(50)

Results

Clinical staff involved in fluoroscopically guided interventional procedures, like invasive coronary angiography, receive significant doses of ionizing radiation; 45 mSv annual dose above lead aprons and 1.6 mSv under lead aprons. There are differences in the radiation doses received by radiologists and cardiologists, which may reflect the differences in the way they perform the procedures (48). A systematic review presented the published range of effective doses to operators: for diagnostic ICAs 0.02-38.0 µSv per examination, and 0.17-31.2 µSv for percutaneous coronary interventions. The doses vary by 2 to 3 orders of magnitude, and it was related to the patient dose. However, there was much greater variation in operator than in patient doses. This could be due to the varied use of personal and movable protective devices. This might imply that radiation dose to the operator might be reduced by improving radiation protection practices (49).

What are the staff safety requirements in MSCT coronary angiography?

Results

Principles of radiation protection

The aim of radiation protection is to ensure that radiation is used safely. The principles of radiation protection are based on the recommendations of the International Commission on Radiological Protection (ICRP) (50). The ICRP recommendations are widely accepted internationally and have also been taken into account in national radiation acts (46).

Acceptable radiation use must fulfil the following basic principles:

- Principle of justification
 - o The benefits of using radiation must outweigh the drawbacks.
- Principle of optimisation (ALARA principle, As Low As Reasonably Achievable)
 - o Radiation exposure caused by the use of radiation must be kept as low as reasonably achievable.
- Principle of limitation
 - o Radiation exposure must not exceed dose limits.

Only persons whose presence is essential for the examination or for the safety of the patient may be present in the examination room during an X-ray examination. The persons should be appropriately protected using suitable protective devices, and no part of them may be exposed to primary radiation. Unnecessary presence in the vicinity of the patient and of the X-ray tube should be avoided during an X-ray examination.

A systematic review presented the published range of effective doses to operators for diagnostic invasive coronary angiographies (ICA) and noticed that the doses vary by 2 to 3 orders of magnitude, and relate to the patient dose. However, there was much greater variation in operator than in patient doses. This could be due to the varied use of personal and movable protective devices. This might imply that radiation dose to the operator might be reduced by improving radiation protection practices (49).

Radiation shielding that forms part of the appliance or portable radiation shielding should be used when working in the immediate vicinity of the radiation beam in the course of examinations causing high levels of exposure to radiation. Use of safety goggles and a thyroid protective device or radiation shields for the head and upper body are also recommended. Monitoring of the radiation exposure of workers and medical surveillance shall be arranged in accordance with national guidelines. Work of pregnant women in duties causing exposure to radiation is usually governed by specific sections of national guidelines and decrees (47).

Monitoring of radiation exposure in the European Union

Individual monitoring is necessary when an employee regularly or repeatedly stays in the premises where diagnostic radiological procedures are performed or monitored. Dose monitoring also concerns employees who install, fix or maintain radiation equipment. Continual monitoring is not required when X-ray equipment is operated from a shielded control room.

Exposure to radiation is monitored using personal dosimeters. Radiation doses are recorded in the statutory dose register. The dose register is maintained by national regulatory body which also ensures that dose control is organised appropriately. When abroad or outside dosimetric service, the employee records the level of exposure, duration of work, and possible medical surveillance results in the individual radiological monitoring document. Upon returning, he returns the document to local national regulatory body, which enters the data in the dose register. On the basis of data recorded in the dose register, it is possible to determine the total exposure of every radiation worker and ensure that prescribed maximum values, so-called dose limits, are not exceeded.

Radiation work is classified as either A or B. Class A includes all employees who receive over 6 mSv effective dose per year. Employees in class A must use dosimeter and doses must be determined by an approved dosimetric service. Employees in class B should be monitored the same way if exposure exceeds 1mSv per year.

An employee who is going to carry out class A radiation work in another European Union member state will require a radiation passbook. A radiation passbook consists of an individual radiological monitoring document and a medical certificate. The individual radiological monitoring document contains information about the holder's previous exposure to radiation and is issued by a national regulatory body. A medical certificate which details the employee's suitability for radiation work is issued by a doctor who is responsible for medical surveillance of people who do class A radiation work (46).

Medical surveillance

There are national modifications of the principles presented by International Commission on Radiological Protection (ICRP) (50) regarding medical surveillance of radiation workers. Here we present the Finnish custom:

A national safety guide by Finnish radiation and nuclear safety authority exists that describes the medical surveillance necessary for an employee involved with radiation work (46). The Finnish Radiation Act (592/1991, revised 1142/1998) requires that employees classified as Class A radiation worker must have a registered physician responsible for medical surveillance. The competence requirements of the surveying physician are determined in the Radiation Decree (1512/1991, revised 1598/1998). Physicians apply for a certificate from the safety authority, when following requirements are met:

- The physician has specialised in occupational health care or has completed the advanced course offered by the Finnish Institute of Occupational Health.
- He has completed the ‘use of radiation and its effects’ course offered by the Finnish Institute of Occupational Health or equivalent.

Environmental safety

Is there evidence of environmental harms when using MSCT?

What kind of environment protection is needed when using MSCT?

Methods

This question was deemed relevant but due to time constraints we left it unanswered.

Discussion

Radioactivity and the use of iodinated contrast media are the major safety issues in the use of MSCT. Induction of cancer especially in the young and women, and contrast induced nephropathy in patients with impaired renal function are the principal concerns. There are technical means to reduce the radiation dose received, but this is usually with the cost of image quality. The risk of contrast induced nephropathy may be reduced with careful patient assessment prior to MSCT.

We had difficulties in using the assessment elements listed in the July 2008 version of the HTA Core Model for diagnostic technologies. Therefore we made a lot of changes in the element hierarchy, renamed issues, deleted and created new assessment elements. The next version of the Safety domain of the diagnostic HTA Core Model will thus change substantially.

We wanted to categorize the safety issues as either technology-dependent, user-dependent, or patient-dependent, and named the topics accordingly. Under the new topic "Use- or user-dependent safety risks" we created two new issues C0041 and C0042 about the safety problems that occur when using (applying/interpreting/maintaining) the technology and the means of reducing their incidence.

We renamed some assessment elements: The assessment element C0027 "What kind of patient protection is needed?" was given a name "Which are the means to reduce the risk of harms?" In C0022 we changed the name "Does this technology have more harms than alternative technology?" into "What is the safety of the technology in comparison to alternative diagnostic technologies?" We changed also the element C0026 "Where does the harms originate and are there differences in devices or generations?" into the form "How does the safety profile of the technology vary between different devices or generations of devices?" We also left out the element C0032 about learning curve because we thought these issues will be covered in the element C0041 "What are the special features in using (applying/interpreting/maintaining) the technology that may increase the risk of patient safety?"

Under the topic "Patient dependent safety risks" we combined and renamed the issues C0028 and C0029 about susceptible patient groups and optimal patient population into an issue C0028 "Are there patient related (individual or disease specific) factors that modify the safety of the diagnostic technology?" and added another new issue C0043 called "Which are the means to reduce the patient dependent safety risks?"

The Topic called "Consequences of false positive and false negative test results" was changed into "Accuracy problems and incidental findings". Under that topic we created a single new assessment element C0040 named "Consequences of false positive, false negative and incidental findings".

We created a new assessment element C0039 "What kind of psychological harms can the technology cause to the patient?" although we recognize that this is an issue which probably will be answered in the Social domain. At the same time we left out the element C0034 "Are there harms that are especially important for patients, their quality of life?" because these were largely overlapping.

We left out the elements C0001 and C0005 about the need for licence or authorization and restricted use, and the elements C0030 and C0031 about staff quality requirements, because these issues are covered in the Health problem and current use domain, as well as the Description and technical characteristics domain.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT or Comment (if regarded as a not relevant issue in this context)
C0008	Safety	Technology dependent safety risks	What is the spectrum of technology dependent harms: their incidence, severity and duration?	yes	What are the safety risks of MSCT coronary angiography?
C0010	Safety	Technology dependent safety risks	What is the timing of onset of harms: immediate, early or late?	yes	What are the immediate and long term consequences of the radiation exposure from MSCT coronary angiography?
C0033	Safety	Technology dependent safety risks	What is the dose relatedness of the harms?	yes	What is the dose relatedness of harms of ionizing radiation in MSCT coronary angiography?
C0039	Safety	Technology dependent safety risks	What kind of psychological harms can the technology cause to the patient?	yes	What kind of psychological harms does coronary MSCT potentially have?
C0027	Safety	Technology dependent safety risks	Which are the means to reduce the risk of harms?	yes	Which are the means to reduce the radiation dose of MSCT coronary angiography? By what means may the risk of harms from iodinated contrast medium be reduced?
C0026	Safety	Technology dependent safety risks	How does the safety profile of the technology vary between different devices or generations of devices?	yes	Are there differences in the safety profile of different MSCT devices or generations?
C0022	Safety	Technology dependent safety risks	What is the safety of the technology in comparison to alternative diagnostic technologies?	yes	What is the safety of MSCT coronary angiography in comparison to alternative diagnostic technologies?
C0040	Safety	Accuracy problems and incidental findings	Consequences of false positive, false negative and incidental findings	yes	What is the incidence and consequences of incidental extracardiac findings? What are the safety consequences for patients receiving false positive test result? What are the safety consequences for patients receiving false negative test result? What are the psychological harms for families of patients with false positive test result?
C0041	Safety	Use or user dependent safety risks	What are the special features in using (applying/interpreting/maintaining) the technology that may increase the risk of patient safety?	yes	How does the level of training or experience of the staff affect the safety of the MSCT coronary angiography?
C0042	Safety	Use or user dependent safety risks	Which are the means to reduce the user dependent safety risks?	yes	What can be done to reduce user dependent risks in MSCT coronary angiography?
C0028	Safety	Patient dependent safety risks	Are there patient related (individual or disease specific) factors that modify the safety of the diagnostic technology?	yes	What are the susceptible patient groups in MSCT coronary angiography?
C0043	Safety	Patient dependent safety risks	Which are the means to reduce the patient dependent safety risks?	yes	What can be done to improve the safety of the management of susceptible patient groups in MSCT coronary angiography?
C0035	Safety	Occupational safety	Is there evidence of occupational harms?	yes	What is the occupational radiation exposure in staff performing MSCT coronary angiography?
C0036	Safety	Occupational safety	What kind of employee protection is needed?	yes	What are the staff safety requirements in MSCT coronary angiography?
C0037	Safety	Environmental safety	Is there evidence of environmental harms?	yes	What kind of environmental protection is needed when using MSCT coronary angiography?
C0038	Safety	Environmental safety	What kind of environment protection is needed?	no	

Appendix 1

Database: CRD (= HTA, EED, DARE)

Date of search: 4.12.2007, yield 24 references

Search strategy:

#1 MeSH Coronary Disease EXPLODE 1 2

#2 (coronary AND (disease* OR arter* OR aneurysm* OR stenosis* OR restenosis* OR thrombosis* OR vasospasm* OR vessel*)) OR "angina pectoris" OR "chest pain" OR atherosclerosis*

#3 #1 OR #2

#4 MeSH Coronary Angiography EXPLODE 1 2 3

#5 MeSH Tomography, X-Ray Computed EXPLODE 1 2 3 4 5 6

#6 #4 AND #5

#7 angiograph* AND tomograph*

#8 #6 OR #7

#9 #3 AND #8

#10 msct OR mdct

#11 (multislice OR "multi-slice" OR "multi slice" OR multirow OR multidetect* OR "multi-detect*" OR "multi detect*" OR multiselect*)

#12 (4 OR 16 OR 32 OR 40 OR 64) AND (slice* OR row*)

#13 #10 OR #11 OR #12

#14 #9 AND 13

Accuracy

Tuija Ikonen, Sigurdur Helgason, Heikki Ukkonen, Iris Pasternack, Marjukka Mäkelä

Introduction

Based on current practice, one major indication for the use of multislice computed tomography (MSCT) is its use as a diagnostic test for ruling out significant coronary artery disease (CAD) in patients with specific or unspecific symptoms and low or intermediate risk for CAD. There is no other diagnostic method up to date for this purpose in the diagnostic pathway that could totally replace it or could as such be nominated as the reference test for accuracy assessment.

In the literature, the majority of studies of accuracy of MSCT have been designed to compare it with invasive coronary angiography (ICA) due to the similarity of information obtained by these two methods (anatomical or structural imaging of the vessel patency). A typical research setting is to assess the presence of significant (usually over 50 %) coronary stenosis by MSCT from patients who have been scheduled to undergo ICA due to known or suspected CAD, not infrequently in high risk patients. Consequently, the proportion of positive findings is high, varying between 60 % and 80 % (1). High frequency of positive findings refers to appropriate use of ICA, a method associated with a low but not insignificant rate of complications (2).

In its use as a rule-out test for CAD in low or intermediate risk patients, the comparison of MSCT with ICA is not without controversies with the clinical decision making, since ICA is seldom justified solely as a rule-out test for CAD in these patients. Other less invasive diagnostic tests for CAD, on the other hand, measure other aspects of the coronary disease: stress tests (ergometry, dobutamine or stress ECHO, SPECT, PET etc) look at ischemia as a sign of functional performance of the myocardium, whereas currently the information obtained from MSCT is purely morphological. In addition to clinical relevance, the choice of different diagnostic methods depends on physician's and patient's preferences, the health care system, local facilities, reimbursement and insurance systems, making the definition of optimal study setting even more complex.

Selection of the reference test and the cut-off level for a positive test depends on the indications of testing. The definition of significant stenosis as $\geq 50\%$ narrowing of a coronary artery segment on ICA has been established to select patients for consideration of myocardial revascularisation, though it does not necessarily correlate with the degree of myocardial ischemia (3). A higher percentage of lumen obstruction might provide a more specific measure for ischemia. For other indications, such as confirming or ruling out coronary atherosclerosis or plaques, even lesser degrees of atherosclerosis and stenoses might be relevant (4).

In this Core HTA of 64-slice CT, we have chosen to use ICA as a reference standard for the assessment of accuracy, being fully aware of its limitations mentioned above. Our aim is to describe the process of acquiring information and to test the set of assessment elements in the context of 64-slice CT rather than to produce an exhaustive review of the topic. Therefore some answers to the research questions might be incomplete.

Methodology

Literature review

For the review of the literature on MSCT angiography, we searched Medline (936 references), Premedline (50 references) and CRD (= HTA, EED, DARE). The searches were performed between the December 5th and 7th, 2007. Search strategies for each database are presented in Appendix 1. A complementary search was performed from Premedline (84 references) and a specific search for accuracy on the 21st of May, 2008 (Appendix 1).

The search strategy resulted in over 1000 references across all databases. The specific search for accuracy gained 104 references. Two researchers independently selected relevant titles and abstracts. For references selected by only one researcher a consensus was sought by discussion and opinion of a third researcher. HTAs on 64-slice MSCT were accepted as background documents. Letters and editorials were excluded, and studies published only as abstracts were not used for this analysis.

The inclusion criteria for original studies to be accepted for full text retrieval were:

- Suspected coronary artery disease (CAD) with typical or atypical non-acute chest pain in patients with low or intermediate risk for CAD.
- Assessment of the quality/severity/location of the CAD-lesions in patients with stable chronic CAD
- MSCT using 64-slice technology, or a subgroup analysis of 64-slice technology included in the study.

Exclusion criteria were:

- Monitoring treatment effect after PTCA, stent or CABG
- Diagnosis of acute chest pain, myocardial infarction/acute coronary syndrome
- Assessment of the culprit lesion or a specific anatomical location in patients with known CAD
- Assessment of coronary arteries in adjunction with other diseases of the myocardium, heart valves or ascending aorta
- Assessment of coronary anomalies
- Screening of asymptomatic high-risk or low-risk population
- Assessment of high risk population with known CAD or patients with high pre-test probability for CAD only
- Techniques lower than 64 slices.

Initially, 8 HTA reports or reviews with meta-analyses and 60 abstracts were selected for full-text retrieval. A recent HTA report from the NIHR Programme of NCCHTA was selected as a basic background document (5). Of the selected full text articles 12 studies were included in the Mowatt's

HTA. While working on this assessment, another HTA was published on the 7th of July 2008 (4). In addition, 9 full text articles matched with the inclusion and exclusion criteria for accuracy assessment (6-14), and 3 for effectiveness assessment (15,16,17). For specific answers in the accuracy domain, another 3 studies were considered useful (3,18,19). Scanning the full text articles led to exclusion of 33 papers.

Quality assessment of diagnostic accuracy studies

Two assessors (SH and TSI) performed quality assessment on the selected HTA (5) by using a quality assessment tool (SIGN - Methodology: Critical appraisal: Notes and checklists.

Methodology Checklist 1: Systematic Reviews and Meta-analyses

<http://www.sign.ac.uk/guidelines/fulltext/50/checklist1.rtf> and

<http://www.sign.ac.uk/guidelines/fulltext/50/notes1.html>). See Appendix 2.

The QUADAS tool (Appendix 3) was used in a modified form (39). Eleven questions (1, 3, 4, 7, 8, 10 and 11, 12, 14, 17 and 19 of the original QUADAS tool) were used. One reviewer (SH) assessed the quality of all included studies answering these eleven questions with either 'Yes' (+), 'No' (-) or 'Unclear' (?). Due to time limitation a second review was not performed but will be added in the final version of this document. The results of the quality assessment are presented in Appendix 4.

Assessment elements

Accuracy measures

What is the accuracy of 64-slice CT against invasive coronary angiography (ICA) as reference standard?

Methods

The analysis in Mowatt's HTA (5) is presented as background data and is quoted in this report for overall assessment of accuracy for patient-level and segment-level results. From the studies published after studies included in Mowatt's HTA, 8 studies with 50 % stenosis as the cut-off level for CAD were included in the data extraction on a data sheet for accuracy including sensitivity and specificity, likelihood ratios and pre-test probabilities (6-10,12,13,20). In addition, one study is referred, where the cut-off level for CAD was 70 % (14). Of these 8 studies five are used in the HTA of van Brabant 2008 (7-11). In this analysis we will present data for patient-level and segment-level assessment of MSCT. Some studies also presented results from per-vessel analysis (6,8,10-13). See also Appendices 4 and 5.

Results

Background HTA (Mowatt)

In Mowatt's HTA there were two studies (21,22) that looked at the use of MSCT specifically in the low or intermediate risk population without previous CAD diagnosis, which was the first inclusion criteria in this assessment. In a third study the patient population consisted of suspected CAD because of left branch bundle block (LBBB) (23). In other six studies there were heterogeneous

patient populations with the proportion of known CAD varying between 9 % and 57 %, typically including patients with a previous percutaneous intervention (PCI) (24-28)(29). In two studies (30,31) there were patients with unstable angina pectoris (UAP) included (6 % of the patient in the other study and 36 % in the other). Other studies out of the scope of our analysis, but analysed in Mowatt's HTA, were studies on acute coronary syndrome (ACS) (32), patients referred for valve surgery patients assessed for coronary artery bypass graft (CABG) (33), or after CABG (22) , and the use of MSCT together with calcium screening. Suspected ACS, with or without known CAD, was reported only in abstracts (17,34).

Patient-level analysis

Segmental analysis is useful when assessing the accuracy of the test against reference, whereas patient level data are more useful in determining management and effectiveness. In Mowatt's HTA eighteen studies (13 full text and five abstracts) enrolling 1313 people, with 1286 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient level analysis. The median post-test prevalence of CAD was 58 % (range 23 to 96 %). Figure 1 presents the over-all patient-level analysis for sensitivity, specificity, SROC-curve and pooled estimates when 50 % stenosis is used as a cut-off level for significant CAD (5). Overall there was no substantial statistical heterogeneity in terms of sensitivity ($I^2 = 0.1$ %) or specificity ($I^2 = 31.7$ %). In Mowatt's analysis, 11 (2 %) of 718 patients had unevaluable CT scans (median across studies 0 %, range 0 to 6 %), most often because of heavy vessel calcification.

Segment-level analysis

Figure 2 presents the over-all segment-level analysis of sensitivity and specificity with respective measures. In Mowatt's HTA, there were seventeen studies (14 full text and three abstracts) enrolling 1102 people, with 1078 included in the analysis, that provided sufficient information to allow their inclusion in the pooled estimates for segment-level analysis ($n=14,199$). There was substantial statistical heterogeneity across the studies in terms of both sensitivity ($I^2=80.1\%$) and specificity ($I^2=95.1\%$). The heterogeneity in terms of specificity was most noticeable in a study including participants who had previously undergone CABG surgery (22). One reason suggested by the authors for the low specificity and consequently a high level of false positive results, was the prevalence of severe calcifications which led to an overestimation of the extent of stenosis (5). Around 8 % (997) of 12,476 segment scans could not be evaluated (median across studies 9%, range 0 to 18%). The reasons for poor image quality were caused by irregular heart rhythm, sinus tachycardia > 90/min, calcification, vessel motion, inadequate breath hold, low contrast opacification and anomaly (35).

Accuracy for patients with suspected CAD

In Mowatt's HTA the accuracy measures for patients with suspected and known CAD were assessed separately. They are presented in Table 1. In patient-level analysis, better sensitivity, positive predictive value (PPV) and negative predictive value (NPV), but worse specificity, were reported for those with known CAD. The lowest NPV (93%) was reported by Nikolaou and colleagues in a sub-group analysis of 39 patients with suspected CAD, but no explanation of the reasons for the false negative results in this group was provided. For segment-level analysis, better sensitivity was reported for those with suspected CAD, better PPV for those with known CAD, while specificity and NPV were similar for both groups (5).

Figure 1 Patient-level analysis: sensitivity, specificity, SROC curve and pooled estimates (5).

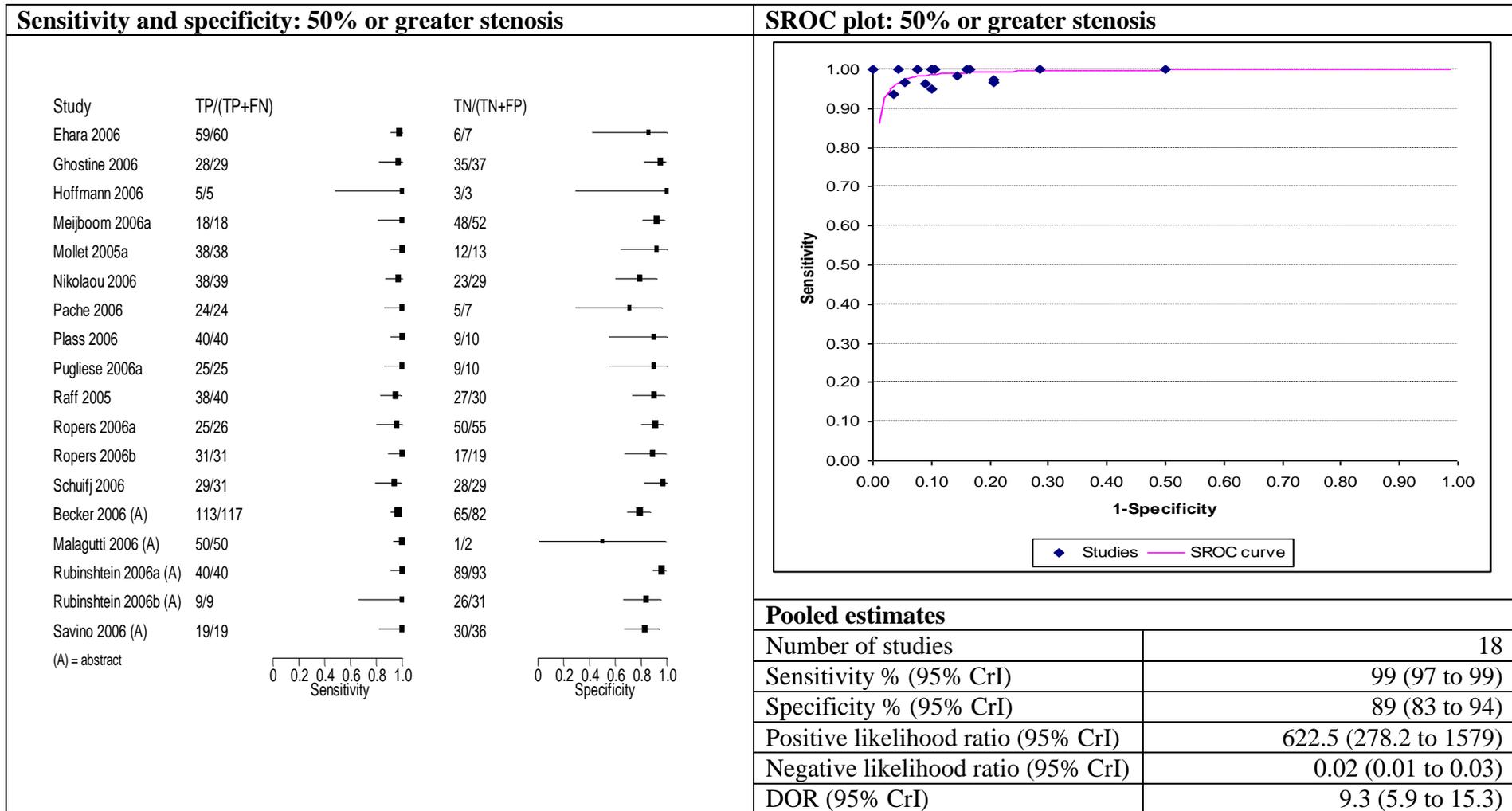


Figure 2 Segment-level analysis: sensitivity, specificity, SROC curve and pooled estimates (5).

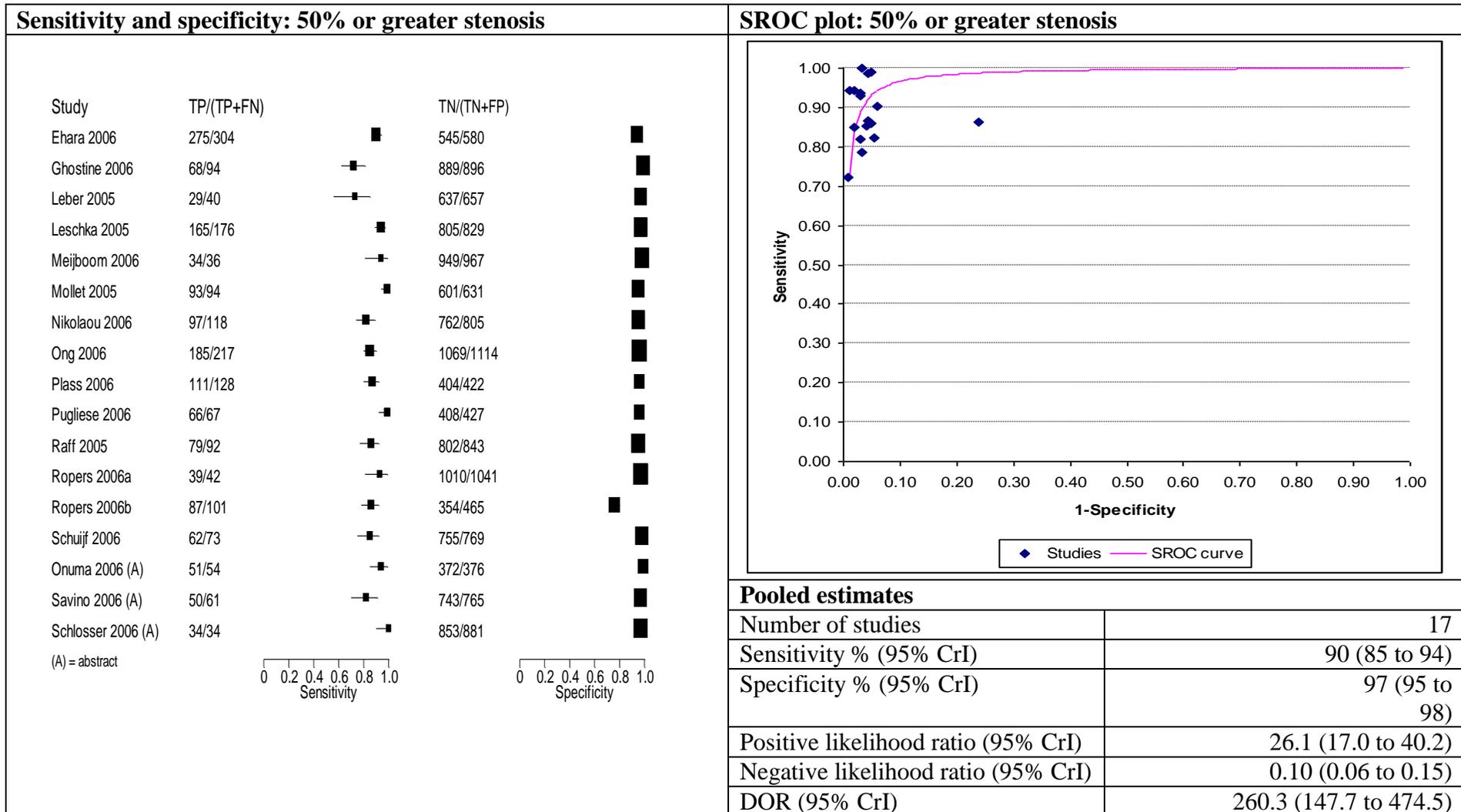


Table 1 Studies reporting data separately for those with suspected and known CAD (5).

	No of studies	Median % (range) sensitivity	Median % (range) specificity	Median % (range) PPV	Median % (range) NPV
Suspected CAD					
Patients (n=283)	4	96 (95-100)	87 (82-91)	86 (76-93)	96 (93-100)
Segments (n=>5606)	6	92 (82-100)	97 (95-99)	68 (55-95)	99 (98-100)
Known CAD					
Patients (n=64)	2	100 (both)	83 (75-90)	91 (85-96)	100 (both)
Segments (n=2623)	3	85 (79-99)	96 (96-97)	78 (72-80)	98 (97-100)

Accuracy studies of patients with high risk or without specification of the risk category

Two studies were identified that were published after Mowatt's HTA and which included symptomatic patients with suspected CAD (12,14) with a high or not specified pre-test probability of CAD.

In the Oncel's study significant (over 50 % stenosis) CAD was present in 77 % of patients. In this prospective analysis of 80 patients sensitivity, specificity, PPV, and NPV of positive CAD diagnosis (patient level analysis) were 100 % against ICA. The respective values for per-segment analysis were 96 %, 98 %, 91 %, and 99 %. The κ -index for the agreement between segments on MSCT and ICA was 0.923 (12).

In the other study by Muhlenbruch that assessed high-risk population, the cut-off level for a significant stenosis was 70 %, wherefore the results are not comparable with other studies quoted in this report. Sensitivity, specificity, PPV and NPV reported on patient-level and segment-level were 97.8 %, 50 %, 93.6 %, 75 % and 86.7 %, 95.2 %, 75.2 % and 97.7 %, respectively.

Accuracy studies for assessment of symptomatic patients with low or intermediate pre-test likelihood for CAD

Patient-level analysis

Accuracy measures for patients with low or intermediate pre-test probability for CAD could be obtained from four studies (6,8,9,10). Altogether 364 patients were analysed per patient level. Out of these 364 patients there were 121 patients with low risk for CAD (55 patients in Herzog's study and a subgroup of 66 patients in Mejboom's study) and 171 with intermediate risk (88 in Leber's study and a subgroup of 83 patients in Mejboom's study). For the 72 patients of Cademartiri's study the risk definition was low or intermediate.

Accuracy data for patient-level analysis are presented in Table 2. For the population with a mean of 28.5 % of patients having at least one significant (over 50 %) stenosis on MSCT, high sensitivity and negative predictive value were obtained in all studies, whereas specificity varied between 84 % and 98.1 % and positive predictive value between 74 % and 95.2 %. Overall the lowest accuracy measures were obtained by Leber. In his study a dual-source CT was used to generate faster reconstruction of the images and no pulse lowering premedication was used.

In two studies the correlation with ICA was analysed on patient-level (10). The κ -values for intermediate and low risk groups were 0.81 and 0.82, respectively in Mejboom's study, and 0.88 for the low-risk patients analyzed by Herzog.

Likelihood ratios were given in one study (10). For patient-level analysis the positive LR was 6.38 in the intermediate and 13.50 in the low risk group, and negative LR was 0.00 for both groups.

Table 2 Patient-level accuracy in studies of low to intermediate risk for CAD

	N of patients analysed / total n of patients	Risk category	Patients (%) with stenosis \geq 50 % on ICA	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cademartiri 2007	72 / 72	low to intermediate	28 %	100	98.1	95.2	100
Herzog 2007	55 / 151 consecutive	low	35 %	100	83.3	76.0	100
Leber 2007	88 / 90	intermediate	24 %	95	90	74	99
Mejboom 2007	(105) 83 66	(high) intermediate low	(78 %) 39 % 18 %	(98) 100 100	(74) 84 93	(93) 80 75	(89) 100 100
Total	364						

In addition to the four studies of patient-level analysis that also included segment-level analyses, two studies were identified with segment-level analysis of the low or intermediate risk patients (7,13). Hausleiter et al reported per segment analysis of a subgroup assessed with 64-slice MSCT from 114 patients with intermediate pre-test probability and Schlosser reported an analysis of 915 segments from 61 patients. Altogether 7499 segments were analysed in these six studies. Image quality was considered good or excellent in 92.4 - 98.5 % of segments in the three studies that assessed image quality. Results from these six studies and the segment based analysis from the study of Oncel (12) are in the table 3. The observed incidence of significant stenosis in ICA was 77 %.

In the patients with low or intermediate pre-test likelihood for CAD, accuracy measures for per segment analysis were inferior to per patient analysis. Sensitivity varied between 81.9 % and 100 %, and NPV was nearly 100 % (98.5-100 %). Specificity was 96 % and PPV was low 62 %. All these figures are in the range of the results from patients with known or suspected CAD analysed in Mowatt's HTA.

Per segment correlation with ICA was analysed in four studies. The κ -values varied from 0.58 to 0.98 (6,8,10,12) . In one study the proportion of segments with overestimation and underestimation were reported as 38.8 % and 17.2 %, respectively (8).

Likelihood ratios were given in one study (10). For segment-based analysis the positive LR was 18.74 in the intermediate and 52.50 in the low risk group, and negative LR was 0.14 and 0.27, respectively.

Table 3. Segment-level analysis of accuracy

Study id	N of patients analysed / total n of patients	N of segments analysed (/ total n of segments) / % of good quality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correlation with CA	N of segments and minimum segment diameter analysed
Cademartiri 2007	72 / 72	1098 / 98,5 %	100	98,6	71,1	100	κ 0,98	17 segments, regardless of diameter
Hausleiter 2007	114 / 243 64 subgr	1266 / 92,4 %	92	92	54	99	not assessed	2 mm diameter of CA
Herzog 2006	55 / 151 consecutive	825 / 92,4 %	81,9	97,1	69,4	98,5	0,65 MSCT underest 39% overest 17%	<1,5 mm regarded as evaluation compromised
Leber 2007	88/90	1216 (/ 1232)	90	98	81	99	not assessed	AHA segment model
Mejboom 2007	105 (high) 83 66	1468 1219 960	90 87 73	90 95 99	56 46 59	98 99 99	0,64 0,58 0,65 κ *per segm	17 segment AHA model, all included
Oncel 2007	80	1200 / 91 %	96	98	91	99	0,923 κ *per segm	15 segment AHA model, all included
Schlosser 2007	61 / 63	915 / 99 %	100	96,8	54,8	100	not assessed	15 segment AHA model, all included

A subgroup analysis of accuracy for male and female patients

One study without pre-test risk definition reported accuracy figures separately for female and male patients (11). Among 402 included symptomatic patients there were 123 women and 279 men with CAD prevalence of 51 % and 68 %, respectively. Of the study population 12 % of patients had unstable angina pectoris (UAP) and 13 % non-ST-segment elevation acute myocardial infarction (AMI). Accuracy was lower in females. Sensitivity, specificity, PPV and NPV for patient level analysis were 100 %, 75 %, 81 %, and 100 % for women, and the respective values for men were 99 %, 90 %, 95 %, and 98 %. For segment level analysis the figures for women and men were 82 %, 94 %, 53 %, 98 % and 93 %, 92 %, 59 %, 99 %, respectively. Positive and negative likelihood ratios on patient level for females and males were 7.24 vs. 6.25 and 0 vs. 0.01, respectively. The respective figures on segment level were 13.87 vs. 12.02 and 0.20 vs. 0.07. Background data for studies referred in this element are presented in Appendix 5.

Comment

This element concentrates on the analysis for per-patient and per-segment level. Per-vessel level analysis was not regarded to be in the focus of this study. Publication bias was not assessed. The studies quoted might include repeated patients in consecutive publications from same centres.

How does 64-slice CT compare to other optional diagnostic technologies (SPECT, stress ergometry, stress ECHO, IVUS, 4-slice or 16-slice MSCT) in terms of accuracy measures?

Methods

Studies comparing MSCT to other diagnostic methods were retrieved from the initial literature search, without considering the PICO of the overall Core HTA or homogeneity of the population in terms of low or intermediate risk. In addition to the studies included in Mowatt's analysis (25,36,37,38) three relevant studies were identified (3,18,19).

Results

Sixty-four-slice CT angiography has the potential to replace some perfusion scanning tests. According to Mowatt et al, the sensitivity of single photon emission computed tomography (SPECT) against invasive coronary angiography (ICA) for detecting a significant stenosis was either 81%, 87% or 88%, depending on the type of analysis undertaken, while specificity was 64%, 65% or 69% from two reviews and in a study re-analysing the results of one of the reviews (37,38). The pooled estimates for MSCT accuracy against ICA in a patient-level analysis are for comparison: sensitivity 99% and specificity 89% (5).

Schuijf et al compared 64-slice MSCT and Stress-rest myocardial perfusion imaging (MPI, technetium 99m) in a subset of 86 of 114 patients with an intermediate likelihood of coronary artery disease (CAD) and without previous CAD diagnosis. In addition, 28 patients were evaluated by 16-slice MSCT. 58 patients were further analysed by ICA. Sensitivity of MSCT and SPECT in detecting a significant stenosis against ICA as reference standard were 100 % and 81% respectively, and specificities were 59 % vs 48 %. There was no difference in the ability to obtain correct diagnosis between 16- and 64-slice CT, 90 % vs. 89 %, respectively (3).

Intravascular ultrasound (IVUS) was compared with 64-slice MSCT in two studies. The study of Leber et al., also included in Mowatt's report, compares all three methods, 64-slice MSCT, ICA, and IVUS in a subset of 18 out of 59 patients. 46 of the 55 lesions (84 %) were identified correctly by 64-slice MSCT compared to IVUS as reference standard. Both plaque areas and vessel obstruction were higher when measured by IVUS compared to CT (25).

In the study of Caussin et al., 40 patients with 54 intermediate lesions of coronary arteries defined as 30 % - 70 % luminal narrowing on MSCT were analysed by IVUS (40 MHz). 23 % of the included patients had had a previous percutaneous coronary intervention (PCI) and 56 % presented with myocardial infarction (MI) or unstable angina pectoris (UAP). Four patients were excluded from the analysis because of inadequate image quality. The correlation of minimal lumen area between the two methods was $r = 0.88$ (Pearson's correlations coefficient). Sensitivity, specificity, accuracy, and Cohen's κ coefficient for inter-observer variability were 87 %, 72 %, 80 %, 0.6,

respectively (18). The authors concluded that there was a good correlation and that MSCT was able to determine the lesion severity in patients with intermediate lesions.

When 64-slice technology has been compared with earlier generations of MSCT e.g. 4-slice or 16-slice scans, the performance of newer generations have shown progressive improvement (19). In detecting CAD of native vessels, the improvement between 16-slice and 64-slice scanners is not as obvious as between 4-slice and 16-slice scanners.

Comment

The methods compared in this element measure coronary artery stenosis from different aspects, from functional and anatomical, wherefore the results are not straightforward comparable with each other.

How likely does invasive coronary angiography (ICA) classify the morphological coronary artery disease (CAD) lesions correctly compared to intravascular ultrasound (IVUS) or pathology?

Methods

Studies comparing invasive coronary angiography (ICA) to other morphological diagnostic methods were retrieved from the initial literature search, without considering the PICO of the overall Core HTA or homogeneity of the population in terms of low or intermediate risk. In addition to the studies included in Mowatt's HTA one study was identified (18).

Results

In the analysis of Mowatt et al. (5) a subset of 18 patients in one study (25) were assessed with MSCT, ICA and intravascular ultrasound (IVUS). There were 19 coronary segments that were graded stenotic by MSCT but had no detected stenosis on ICA. Out of these 19 segments five were graded as stenotic by IVUS.

Caussin et al assessed accuracy of 64-slice CT and ICA compared to IVUS. The sensitivity, specificity, and accuracy for ICA detecting mean luminal area compared to IVUS were 79 %, 68 %, and 77 %, respectively (18). All figures were lower than the respective values for 64-slice CT.

Comment

There are more studies that compare ICA with IVUS. We did not cover this area systematically.

How does invasive coronary angiography (ICA) perform in detecting functionally relevant coronary artery disease (CAD) lesions compared to physiological test (e.g. stress tests or radionuclide imaging)?

Methods

Studies comparing invasive coronary angiography (ICA) to physiological stress tests were retrieved from the initial literature search, without considering the PICO of the overall Core HTA or homogeneity of the population in terms of low or intermediate risk. In addition to the studies included in Mowatt's analysis one study was identified (3,5).

Results

In Mowatt's HTA the reference standard was considered likely to correctly classify CAD in all studies (5).

In the study of Schuijf et al., there is a relatively high disagreement between positive and negative myocardial perfusion imaging (MPI) studies and significant stenosis on ICA. Of the 32 patients with an abnormal SPECT finding, only 16 had a stenosis of 50 % or over. On the other hand, of the 26 patients with a normal SPECT finding, 11 were diagnosed to have CAD on ICA (3).

Comment

There are situations where ICA might not be the ideal gold standard. Comparison between the three methods as in Schuijf et al 2006 might be worth a separate analysis.

Context related requirements for accuracy

What are the requirements for accuracy (sensitivity, specificity, PPV, NPV) for ruling in or ruling out CAD in patients with low or intermediate likelihood of CAD?

Results

There are no specific studies to answer this element. A baseline assumption might be to set a requirement to accuracy measures to be comparable or better than existing imaging modalities, such as isotope stress tests, dobutamine stress test or MRI.

Comment

Answering this element might require an extensive literature review.

What is the optimal threshold value of significant coronary artery disease (CAD) in patients with low or intermediate likelihood of CAD?

Results

The cut-off level used to describe significant CAD is typically 50 %. In one study of this analysis 70 % stenosis was used to define significant CAD (14). The figures are based on the degrees of stenosis at which lesions are thought to be of potential functional significance and where revascularisation may be indicated (5). Since the cut-off level depends on two outcomes, relief of anginal symptoms and reduction in mortality in patients with a severe prognosis such as left main stem disease, the relevance of 50 % cut-off level in patients with low or intermediate risk for CAD has not been widely evaluated. In the study of Shuijf 50 % stenosis on MSCT and invasive coronary angiography (ICA) is associated with a positive SPECT result in 50 % of patients (3).

Comment

Threshold value of 50 % has been traditionally used in different studies comparing ICA. Wide use of this threshold value supports its further use for a reference value, especially when different methods are compared.

Does 64-slice CT have the potential to reliably rule in or rule out significant ($\geq 50\%$) stenosis as a sign of coronary artery disease (CAD)?

Results

According to the accuracy figures, the high sensitivity in the pooled estimates and high negative value (NPV) across studies, it seems like 64-slice CT is able to reliably rule out significant CAD in patients with low or intermediate likelihood for CAD. According to Mowatt et al 64-slice CT is only very marginally worse than invasive coronary angiography (ICA) in terms of detecting true positives. However it is somewhat worse in its rate of false positives. Consequently, diagnostic strategies involving 64-slice CT angiography will result in a number of false positives. In Mowatt's analysis it was considered likely that diagnostic strategies involving 64-slice CT will still require ICA as the final gold standard among MSCT test positives in order to eliminate the incorrect treatment of MSCT false positives (5).

In the low and intermediate risk group, especially with unspecific symptoms, functional imaging (SPECT, ECHO-stress tests) might be more appropriate next step in the diagnostic strategy than ICA. See also effectiveness domain.

Reliability and transferability of reported accuracy

How does the analysis per segment / per vessel / per patient impact the accuracy of 64-slice CT?

Results

In the Mowatt's HTA pooled estimates of 64-slice CT angiography were highly sensitive (99%, 95% CI 97 to 99%) for patient-based detection of significant coronary artery disease (CAD) (defined as $> 50\%$ or $\geq 50\%$ stenosis). Across studies the negative predictive value (NPV) was very high (median 100%, range 86 to 100%). In segment-level analysis compared with patient-based detection, sensitivity was lower (90% versus 99%) and specificity higher (97% versus 89%), while across studies the median NPV was similar (99% versus 100%) (5).

How does learning curve and the experience and volume of diagnostic unit affect the accuracy of 64-slice CT?

Results

Not assessed in the studies included.

What is known about the intra- and inter-observer variation in 64-slice CT test interpretation for per segment / per vessel / per patient analysis?

Results

In Mowatt's HTA ten full text studies reported the results of kappa analysis for inter-observer variation in assessing 64-slice CT scans (Table 4). The median kappa score across these studies was 0.74 (range 0.53 to 0.95). In conclusion, there was good overall inter-observer agreement for 64-slice CT for assessing coronary artery disease (CAD) in native vessels but poor for stents (5).

Table 4. 64-slice CT inter-observer variation in detecting significant stenosis by Mowatt 2008.

<i>Study</i>	<i>Unit of analysis</i>	<i>Kappa</i>
Ehara 2006a	Segment	0.95
Hoffmann 2006	Patient	0.82
Johnson 2007	Patient	0.81
Leschka 2005	Unclear whether patient or segment	0.95
Meijboom 2006	Segment	0.71
Mollet 2005	Unclear whether patient or segment	0.73
Nikolaou 2006	Patient	0.81
Plass 2006	Unclear whether patient or segment	0.93
Pugliese 2006a	Unclear whether patient or segment	0.73
Rist 2006	Stent	0.53

In the studies of low or intermediate risk for CAD, Leber describes the interobserver variation as 5.2 % for the quantification of stenosis within three categories of < 50%, from 50 % to 75 % and > 75 % (9). In Meijboom's study the interobserver and intraobserver variability for segment-based analysis were 0.70 and 0.72, respectively (11).

Discussion

In the per-patient analysis sensitivity of 64-slice CT is excellent, specificity is good and these figures do not seem to be affected by the pre-test likelihood of coronary artery disease (CAD) in low to intermediate risk group when compared to the analysis of Mowatt where the population studied included patients from all risk categories.

Results support the current use of 64-slice MSCT for exclusion of CAD in low and intermediate risk group: the negative predictive value (NPV) is excellent. In classifying the patients for CAD the positive predictive value (PPV) per-patient level analysis is varying between studies, being modest to good. From these studies the results are inconclusive regarding correlation between PPV and pre-test risk. The diagnostic assessment of accuracy is preferably performed on per-segment analysis. For low and intermediate risk group the NPV is excellent in all studies and PPV is mainly modest.

One source of bias is the possible cumulative publication of the material. Included studies are from a limited number of centres. Each publication has been included as independent study, but it does not exclude the possibility that same patients might have been included in the analysis repeatedly.

Some important issues remain unanswered. From the clinical point of view it would be of major interest to know the risk threshold for using MSCT as a rule out test for CAD. None of the included studies looked at this specific question. This might be an aim of further studies.

Answers to the elements were obtained from an HTA and consequent studies selected for accuracy assessment. Some issues would require a separate literature search to be answered explicitly. Due to the scope of this analysis and the character of being a test HTA, further effort was not considered necessary. Since EUnetHTA format is flexible and enables further amendments, some issues might be completed later.

Combining Accuracy and Effectiveness domains has been suggested by some validation reviewers. However, the decision to combine the domains is beyond the scope of this assessment.

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Assessment elements table

Element Identification Code (ID)	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT or Comment (if regarded as a not relevant issue in this context)
J0001	Accuracy	Accuracy measures	What is the accuracy of the test against reference standard?	Yes	What is the accuracy of 64-slice CT in terms of sensitivity and specificity, likelihood ratios, pre-test probabilities, SDORs, AUC or Q* against CA as reference standard?
J0002	Accuracy	Accuracy measures	How does the technology compare to other optional diagnostic technologies or other development stages of the same technology in terms of accuracy measures?	Yes	How does 64-slice CT compare to other optional diagnostic technologies (SPECT, stress ergometry, stress ECHO, IVUS, 4-slice or 16-slice MSCT) in terms of accuracy measures?
J0003	Accuracy	Accuracy measures	What is the reference standard and how likely does it classify the target condition correctly?	Yes	How likely does CA classify the morphological CAD lesions correctly compared to IVUS or pathology? How does CA perform in detecting ischemia inducing CAD lesions compared to physiological test (e.g. stress tests or radionuclide imaging)?
J0004	Accuracy	Context related requirements for accuracy	What are the requirements for accuracy in the context the technology will be used?	Yes	What are the requirements for accuracy (sensitivity, specificity, PPV, NPV) for ruling in or ruling out CAD in patients with low or intermediate likelihood of CAD?
J0005	Accuracy	Context related requirements for accuracy	What is the optimal threshold value in this context?	Yes	What is the optimal threshold value of significant CAD in patients with low or intermediate likelihood of CAD?
J0006	Accuracy	Context related requirements for accuracy	Does the technology have the potential to reliably rule in or rule out the target condition?	Yes	Does 64-slice CT have the potential to reliably rule in or rule out significant ($\geq 50\%$) stenosis as a sign of CAD?
J0007	Accuracy	Reliability and transferability of reported accuracy	How does test accuracy vary in different settings?	Yes	How does the use of 64-slice CT in patients with low or intermediate risk for CAD affect the accuracy of 64-slice CT? How does the analysis per segment / per vessel / per patient impact the accuracy of 64-slice CT?
J0009	Accuracy	Reliability and transferability of reported accuracy	How does learning curve and volume of tests affect accuracy?	Yes	How do learning curve and the experience and volume of diagnostic unit affect the accuracy of 64-slice CT?
J0008	Accuracy	Reliability and transferability of reported accuracy	What is known about the intra- and inter-observer variation in test interpretation?	Yes	What is known about the intra- and inter-observer variation in 64-slice CT test interpretation for per segment / per vessel / per patient analysis?

Appendix 1 Search Strategies

Multislice CT, Basic search for EUnetHTA

Database: Ovid MEDLINE(R) <1950 to November Week 2 2007>

Search date: 7.12.2007

Search strategy:

-
- 1 exp Coronary Disease/di, ra [Diagnosis, Radiography]
 - 2 (coronary adj2 (disease\$ or occlus\$ or vessel\$ or arter\$ or stenosis\$ or restenosis\$ or aneurysm\$ or thrombosis\$ or vasospasm\$ or obstruct\$)).tw.
 - 3 calcinosis/di, ra or myocardial ischemia/di, ra
 - 4 1 or 2 or 3
 - 5 exp Coronary Angiography/
 - 6 exp Tomography, X-Ray Computed/
 - 7 5 and 6
 - 8 (angiograph\$ and tomograph\$).tw.
 - 9 7 or 8
 - 10 4 and 9
 - 11 (msct or mdct).tw.
 - 12 (("8" or "16" or "32" or "40" or "64") adj2 (slice\$ or row\$)).tw.
 - 13 (multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi-detect\$" or "multi detect\$" or multisect\$ or "multi-sect\$" or "multi sect\$").tw.
 - 14 11 or 12 or 13
 - 15 10 and 14
 - 16 animals/
 - 17 humans/
 - 18 16 not (16 and 17)
 - 19 15 not 18
 - 20 limit 19 to yr="1990 - 2008"

Multislice CT, Accuracy

Database: Ovid MEDLINE(R) <1950 to May Week 2 2008>

Search date: 23.5.2008

Search strategy:

-
- 1 exp Coronary Disease/di, ra [Diagnosis, Radiography]
 - 2 (coronary adj2 (disease\$ or occlus\$ or vessel\$ or arter\$ or stenosis\$ or restenosis\$ or aneurysm\$ or thrombosis\$ or vasospasm\$ or obstruct\$)).tw.
 - 3 calcinosis/di, ra or myocardial ischemia/di, ra
 - 4 1 or 2 or 3
 - 5 exp Coronary Angiography/
 - 6 exp Tomography, X-Ray Computed/
 - 7 5 and 6
 - 8 (angiograph\$ and tomograph\$).tw.
 - 9 7 or 8
 - 10 4 and 9
 - 11 (("64" or sixty-four or sixtyfour) adj2 (slice\$ or row\$)).tw.

- 12 (msct or mdct or multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi-detect\$" or "multi detect\$" or multisect\$ or "multi-sect\$" or "multi sect\$").tw.
- 13 11 or 12
- 14 10 and 11
- 15 animals/
- 16 humans/
- 17 15 not (15 and 16)
- 18 14 not 17
- 19 18 not (news or letter or comment or editorial).pt.
- 20 exp "Sensitivity and Specificity"/
- 21 sensitivity.tw.
- 22 specificity.tw.
- 23 ((pre-test or pretest) adj probability).tw.
- 24 ((post-test or posttest) adj probability).tw.
- 25 predictive value\$.tw.
- 26 likelihood ratio\$.tw.
- 27 diagnostic accuracy.tw.
- 28 diagnostic performance.tw.
- 29 false positive\$.tw.
- 30 false negative\$.tw.
- 31 inter-observer variation\$.tw.
- 32 intra-observer variation\$.tw.
- 33 learning curve\$.tw.
- 34 or/20-33
- 35 19 and 34
- 36 limit 35 to yr="2002-2008" (127)

Appendix 2 Quality assessment: SIGN

Quality assessment of Mowatt et al 2008 (by SH and TSI)

		Methodology Checklist 1: Systematic Reviews and Meta-analyses	
Study identification (<i>Include author, title, year of publication, journal title, pages</i>) Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. Health Technol Assess 2008;12(17)			
Guideline topic:		Key Question No:	
Checklist completed by: Sigurður Helgason (SH) and Tuija S Ikonen (TSI).			
Section 1: Internal validity			
In a well conducted systematic review		In this study this criterion is::	
1.1	The study addresses an appropriate and clearly focused question.	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	A description of the methodology used is included.	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	<i>The literature search is sufficiently rigorous to identify all the relevant studies.</i>	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Study quality is assessed and taken into account.	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered SH Adequately addressed TSI Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or -	++ SH / ++ TSI	

2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	
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SECTION 3: DESCRIPTION OF THE STUDY Please print answers clearly

3.1	What types of study are included in the review? <i>(Highlight all that apply)</i>	RCT Case-control	CCT Other	Cohort SH /TSI
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Appendix 3 QUADAS tool

QUADAS quality assessment tool (39)

Mandatory items (as in the Cochrane handbook):

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Is the reference test likely to correctly classify the target condition?
3. Is the time period between reference test and index test short enough to be reasonably sure that the target condition did not change between the two tests?
4. Did the whole sample, or random selection of the sample, receive verification using a reference standard of diagnosis (reference test)?
5. Did patients receive the same reference test regardless of the index test result?
6. Was the reference test independent of the index test i.e. the index test did not form part of the reference test?
7. Were the index test results interpreted without knowledge of the results of the reference test?
8. Were the reference test results interpreted without knowledge of the results of the index test?
9. Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?
10. Were uninterpretable / intermediate test results reported?
11. Were withdrawals from the study explained?

Additional items

12. If a cut-off value has been used, was it established before the study was started (pre-specified cut-off value)?
13. Is the technology of the index test likely to have changed since the study was carried out?
14. Did the study provide a clear definition of what was considered to be a "positive" test result?
15. Was treatment started after the index test was carried out but before the reference test was performed?
16. Was treatment started after the reference test was carried out but before the index test was performed?
17. Were data on observer variation reported?
18. Were data on instrument variation reported?
19. Were data presented for appropriate patient sub-groups?
20. Was an appropriate sample size included?
21. Were objectives pre-specified?

Appendix 4 Quality assessment of original studies

The QUADAS tool was used in a modified form where eleven questions (1, 3, 4, 7, 8, 10 and 11, 12, 14, 17 and 19) of the original QUADAS tool (Appendix 3) were used.

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
3. Is the time period between reference test and index test short enough to be reasonably sure that the target condition did not change between the two tests?
4. Did the whole sample, or random selection of the sample, receive verification using a reference standard of diagnosis (reference test)?
7. Were the index test results interpreted without knowledge of the results of the reference test?
8. Were the reference test results interpreted without knowledge of the results of the index test?
10. Were uninterpretable / intermediate test results reported?
11. Were withdrawals from the study explained?
12. If a cut-off value has been used, was it established before the study was started (pre-specified cut-off value)?
14. Did the study provide a clear definition of what was considered to be a "positive" test result?
17. Were data on observer variation reported?
18. Were data on instrument variation reported?
19. Were data presented for appropriate patient sub-groups?

Select from QUADAS items*	1	3	4	7	8	10	11	12	14	17	19
Cademartiri 2007	+	+	+	+	+	+	+	+	+	+	+
Hausleiter 2007	+	?	+	+	+	+	+	+	+	+	+
Herzog 2007	+	+	+	+	+	+	+	+	+	-	+
Leber 2007	+	+	+	+	?	+	+	+	+	+	+
Mejboom 2007 a	+	+	+	+	+	+	+	+	+	+	+
Mejboom 2007 b	+	+	+	+	+	+	+	+	+	+	+
Muhlenbruch 2007	+	?	+	+	+	+	+	+	+	+	-
Oncel 2007	+	+	+	+	+	+	+	+	+	+	+
Schlosser 2007	+	+	+	+	?	+	+	+	+	-	-

Comments:

Cademartiri 2007

Item 10 and 11. No withdrawals or uninterpretable results? Selection into the study?

Hausleiter 2007

Item 1. The authors state that the patients have an intermediate pre-test probability for having CAD. The description of the study population is not very detailed but they included both patients with chest pain, dyspnea or intermittent arrhythmias with an equivocal stress test or in the absence of a positive stress test as well as asymptomatic patients with a positive stress test. The last group might account for 18.9% of the patients.

Item 3. The only statement on the time period between MSCT and ICA is "invasive coronary angiography was performed after MSCT angiography, usually on the same or next day after MSCT angiography".

Leber 2007

Item 7 and 8. Blinding is not described but MSCT performed and likely analysed the day before ICA.

Item 19. Sub-groups 50-74% stenosis and >75%.

Mejboom 2007a.

Item 1. Not consecutive. Patients referred over 24 months for ICA. Is this same material as Mejboom 2007b?

Mejboom 2007b.

Item 1. Not consecutive. Patients referred over 24 months for ICA. Is this same material as Mejboom 2007a?

Muhlenbruch 2007

Item 1. Significant stenosis defined as $\geq 70\%$.

Item 3. All patients underwent CTA and CCA within a short timeframe (mean 2.4 ± 3.2 days).

Item 19. Not separate subanalysis for known CAD patients.

Schlosser 2007

Item 8. No information is given on this issue but in the text the following answers Item 7. "MDCT images were read by a radiologist and a cardiologist in consensus blinded to the clinical data and the results of ICA".

Item 19. Not separate subanalysis for low risk patients.

Appendix 5 Demographic data

Demographic data of the selected studies for accuracy analysis.

Study id	Homogenous population of low or intermediate risk	N of patients analysed / total	Mean age	Symptoms	Risk category	Patients with CAD \geq 50 % present on ICA
Cademartiri 2007	yes	72	53.9 \pm 8.0	atypical or typical chest pain	low to intermediate	28 %
Hausleiter 2007	yes 16-slice (53 %) 64-slice (47 %)	243	62.0 \pm 9.9	chest pain, dyspnea, arrhythmia, positive stress test	intermediate	42 %
Herzog 2007	yes	55	67 (49 - 73)	atypical chest pain	low	35 %
Leber 2007	yes	88 / 90	58 \pm 8	typical or atypical chest pain, dyspnea	intermediate	24 %
Mejboom 2007	subgroup analysis of all risk groups	254 105 83 66	63 \pm 9 61 \pm 8 50 \pm 12	typical or atypical chest pain	high intermediate low	78 % 39 % 18 %
Mejboom 2007	UAP and non-ST-AMI 11 % vs. 13 % both, known CAD 12 % vs. 10 %	402 F 123 M 279	F 62 \pm 11 M 58 \pm 11	acute or stable AP	not reported	F 51 % M 68 %
Muhlenbruch 2007	high risk cut-off 70%	51	58.5 \pm 7,9	positive stress test symptomatic	high	88 %
Oncel 2007	risk not mentioned	80	56 (63 - 72)	chest pain or positive stress test	not reported	77 %
Schlosser 2007	yes	61 / 63	62.4 (33 - 78)	atypical chest pain ambiguous stress test	not defined	not reported

Effectiveness

Tuija Ikonen, Heikki Ukkonen, Sigurdur Helgason, Iris Pasternack, Marjukka Mäkelä

Introduction

For the assessment of effectiveness of multislice computed tomography (MSCT) coronary angiography, it would be optimal to compare two management pathways: one with MSCT as a rule out diagnostic test for coronary artery disease (CAD), and one without. A complete management path includes also the selection of treatment options. Pre-assumptions for this path are

- 1) patients have low or moderate likelihood of CAD, related to factors such as age, gender, symptoms, and risk factors for CAD,
- 2) there is a clinical need to rule out CAD because previous testing has not confirmed the presence or absence of the disease, and
- 3) the established diagnosis of CAD is esteemed to be useful for making decisions concerning the treatment options.

Information obtained from MSCT should always have clinical impact, either in the sense of ruling out CAD and consequent ex-juvantibus (diagnosis made on basis of the treatment outcome) unnecessary medical treatment, or verifying the diagnosis of CAD with optimal treatment protocol and possibility to avoid coronary disease end-points such as acute myocardial infarction (AMI), invasive treatment or death.

In the current medical literature there are only few, if any, studies that look into the effectiveness of MSCT as a part of management path. For the effectiveness assessment, however, it is of importance to formulate the relevant questions based on the process e.g. the diagnostic path rather than on the existing studies of accuracy, where MSCT is compared with invasive coronary angiography (ICA) and where effectiveness of MSCT is derived from the studies of effectiveness of ICA. Further work is needed to fill in the missing pieces of information.

Methodology

Literature review

For the review of the literature on MSCT angiography, we searched Medline (936), Premedline (50) and CRD (= HTA, EED, DARE). The search was performed between the December 5th and 7th, 2007. A completion search was performed from Premedline (84) and a specific search strategy for effectiveness on the 21st of May, 2008. Search strategies for each database are presented in Appendix 1.

The search strategy resulted in over 1000 references across all databases. Specific search for effectiveness gained 6 references. Two researchers independently selected relevant titles and abstract. In disagreement a consensus was sought.

Inclusion criteria were:

- Suspected coronary artery disease (CAD) in patients with typical or atypical non-acute chest pain, or a subgroup analysis of patients without known CAD, preferably in the group of low or intermediate pre-test likelihood of CAD.
- MSCT using 64-slice technology, or a subgroup analysis of 64-slice technology.
- Selecting proper treatment, e.g. risk factor reduction, medical treatment, invasive treatment for the patients who have undergone MSCT.
- Consequences of using MSCT, including incidental findings of the image area.
- At least 6 months follow-up for assessing clinical effectiveness of MSCT.

Exclusion criteria were:

- Assessment of high risk population or known CAD (e.g. invasive treatment), only.
- CAD diagnosed in adjunction with other diseases of the myocardium, heart valves or ascending aorta.
- Techniques lower than 64-slices, only.
- Diagnosis and treatment of acute chest pain, myocardial infarction/acute coronary syndrome.
- Screening and follow-up of asymptomatic high-risk or low-risk population.
- Monitoring treatment effect after coronary balloon dilatation (PTCA), stenting, or bypass operation (CABG).

In addition to Mowatt's HTA report (4), three studies looking at 64-slice MSCT as a part of diagnostic chain were obtained with follow-up over 6 months (1-3). In the retrospective study of Rubinshtein there were 100 patients with no previous invasive angiograms or treatments for CAD. In the study of Pundziute the proportion of patients with previous myocardial infarction was 33 %, and majority of them had a previous revascularisation (PCI). Suspected CAD was the indication for MSCT in 65 % of the patients (n=65). Pundziute et al. combined data from both 16 and 64-slice technologies. The third study reported a 15 ± 3 months follow-up of 421 symptomatic patients with intermediate risk after abnormal myocardial perfusion stress imaging and a consequent 64-slice CT angiography (1). Of the patients, 34 % had a positive history of CAD based on a previous angiogram or known acute myocardial infarction (AMI).

Quality Assessment

There is no straightforward way to assess the quality of the varying study types of diagnostic effectiveness studies. Therefore we had no formal quality assessment of these three studies included. The quality of the HTA of Mowatt et al. has been assessed by two assessors (SH and TSI), who performed quality assessment by using a quality assessment tool (SIGN - Methodology: Critical appraisal: Notes and checklists. Methodology Checklist 1: Systematic Reviews and Meta-analyses <http://www.sign.ac.uk/guidelines/fulltext/50/checklist1.rtf> and <http://www.sign.ac.uk/guidelines/fulltext/50/notes1.html>). See Appendix 2.

Assessment elements

Comparative accuracy of a replacement technology

Based on the accuracy and safety data, is there evidence that MSCT is more specific in ruling out coronary artery disease (CAD) and need for invasive procedure, compared to another test?

Results

What is the accuracy of MSCT against invasive coronary angiography (ICA)?

MSCT has usually lower specificity (approximately 87%) than sensitivity (appr 96%) when compared to ICA as reference standard for the diagnosis of coronary artery disease (CAD), both in patient level and in segment level analysis. If MSCT would have similar sensitivity but better specificity (against ICA) than another test that aims at diagnosing CAD, it could be seen a more effective diagnostic modality, because effective treatments exist. It would then find the CAD patients as well as the comparative technology (if similar sensitivity), and there are less false positive among those with positive test results (if better specificity). Increased sensitivity does not automatically imply improved effectiveness while the extra cases found with the more sensitive test could react differently to the treatment, so the results of treatment trials are not directly applicable. See more in issues J0001 and J0003 in the accuracy domain.

Is MSCT more specific than stress radionuclide imaging against ICA

According to Mowatt et al (4), the sensitivity of single photon emission computed tomography (SPECT) against invasive coronary angiography (ICA) for detecting a significant stenosis was either 81%, 87% or 88%, depending on the type of analysis undertaken, while specificity was 64%, 65% or 69% from two reviews and in a study re-analysing the results of one of the reviews (37,38). The pooled estimates for MSCT accuracy against ICA in a patient-level analysis are for comparison: sensitivity 99% and specificity 89% (5).

Schuijf et al compared 64-slice MSCT and Stress-rest myocardial perfusion imaging (MPI, technetium 99m) in a subset of 86 of 114 patients with an intermediate likelihood of coronary artery disease (CAD) and without previous CAD diagnosis. 58 patients were further analysed by ICA. Sensitivity of MSCT and SPECT in detecting a significant stenosis against ICA as reference standard were 100 % and 81% respectively, and specificities were 59 % vs 48 % (11).

The study of Danciu et al (1) compared MSCT directly to radionuclide stress imaging. From the population of 421 intermediate risk patients, majority (81.5 %) was considered not to have a significant CAD on 64-slice MSCT after unspecific or abnormal stress myocardial perfusion imaging (MPI). The group was heterogeneous including patients with no or mild coronary artery disease (CAD) on MSCT, mismatch between myocardial perfusion stress imaging (MPSI) and MSCT findings or occluded by-pass graft. During the follow-up of 15 months 6 patients required ICA and one of them underwent revascularisation. In this patient group classified as intermediate risk after stress MPI, and low-risk after MSCT, patients had a 0.3 % rate of the combined end-point

of death, acute myocardial infarction and revascularisation. The authors concluded that the use of MSCT improved specificity of the diagnostic path after stress MPI by ruling out significant CAD in 46 % of the patients in who the ruling out was not possible by radionuclide imaging (1). See also issue J0002 in the accuracy domain.

In conclusion: MSCT appears to be more sensitive and more specific than stress radionuclide imaging against common reference standard ICA.

Comment

It has to be remembered that MSCT is a tool to assess the coronary anatomy and plaques of CAD, whereas the functional studies define the extent of ischemia as functional consequences of the plaques. Therefore these methods are not completely comparable in the diagnostic path.

Safety

What is the mortality related to MSCT compared to invasive coronary angiography(ICA)?

Results

None of the included studies reported any mortality from MSCT or invasive coronary angiography (ICA). It is generally accepted that there is a small risk of fatal complications associated with ICA, whereas MSCT being less invasive does not have the same risk profile. Mortality of ICA is in order of 0.1 %. (5). See also safety domain.

Comment

There are studies regarding 64-slice MSCT mortality that have been presented as abstracts.

What is the incidence of radiation induced morbidity?

Results

In the HTA of Mowatt et al. (4) the radiation risk was reported in 12 full text studies. Technical factors that enhance image quality in 64-slice also result in a higher radiation dose compared with invasive CA. Both Hausleiter et al (6) and the Technology Evaluation Center estimated the effective dose for 64-slice CT to be around 11.0 mSv compared with 2.1 mSv or 4 to 8 mSv for invasive coronary angiography (ICA). Using ECG-dependent dose modulation the CT radiation dose can be reduced further by 30 to 50% during systole. The International Commission on Radiological Protection quote typical effective dose values of 5 to 12 mSv for CT angiography, 5 to 10 mSv for ICA, 13 to 16 mSv for sestamibi myocardial perfusion imaging and 35 to 40 mSv for thallium myocardial perfusion imaging. Across the studies reporting this information for the patient group as a whole, the CT radiation dose ranged from 6 to 11 mSv to 10 to 14 mSv (7,8). Women tended to receive a higher radiation dose than men. Across the studies reporting CT radiation dose separately for men and women, for men this ranged from 7.45 mSv to 15.2 mSv and for women from 12.2 mS to 21.4 mSv (9).

Comment

None of the included studies answered these questions directly. These questions are answered more profoundly in the Safety domain. Radiation dose depends on the devices and used programmes. The level of the multimodal technology itself does not provide enough information to assess actual dose and consequent potential radiation harms of the used method. More specific details about the technology for calculations are required.

Change-in management

Does 64-slice CT improve the physician's ability to make correct diagnosis of CAD in patients with low or intermediate risk for CAD?

Methods

The answers were obtained from the three full text studies included for obtaining effectiveness data (1,2,10)

Results

Rubinshtein et al. assessed 100 patients by MSCT, who were suspected to have coronary artery disease (CAD) because of chest pain but who only had a negative or non-diagnostic exercise treadmill test (ETT). The ETT results were negative in 59 patients and non-diagnostic in 41. Obstructive CAD was present on MSCT in 22 % of patients with negative and 39 % of patients with non-diagnostic ETT examination, and 26 of 29 positive findings were confirmed by invasive coronary angiography (ICA). Two patients were false positive on MSCT. In one patient there was a 2-vessel disease instead of 1-vessel disease suggested by MSCT (10) Of the 71 patients diagnosed not to have obstructive lesions on MSCT, ICA was performed in 15 due to continuing symptoms within 2 weeks. Of these significant CAD (70 % stenosis) was found in one patient. In patients with unequivocal or negative stress test, CAD was correctly diagnosed in 26 of 29 patients by using MSCT, with a positive predictive value (PPV) of 90 %, and among the 71 patients who were condemned not to have CAD, there was only one positive diagnosis that was failed within a short term follow-up. Thus, MSCT led to improved detection of the diagnosis of CAD in majority of the patients with suspected CAD.

Furthermore, calculated from the figures given in Rubinshtein's study, in the group of negative ETT in 73 % of patients CAD was correctly ruled out by MSCT and in 76 % by ETT. MSCT excluded CAD in 61 % of patients with non-diagnostic ETT, thus in this group, MSCT was more specific than ETT in ruling out CAD.

In the study of Pundziute et al. 100 patients with known or suspected CAD were assessed with MSCT. 20 patients did not have any signs of CAD, and 32 were diagnosed to have a significant CAD (>50 % stenosis) on MSCT. During 16 months follow-up there were 33 events in 26 patients including one death of myocardial infarction (MI). All events occurred in patients with abnormal coronary arteries. Based on clinical judgement and stress test, a total of 24 patients underwent revascularisation, of which 7 had cardiac surgery. Patients with events had more extensive atherosclerosis on MSCT. In a multivariate analysis, the findings on MSCT predictive for CAD were the presence of plaques, obstructive CAD, left main/ left anterior descending artery (LM/LAD) disease, number of coronary segments with plaques and number of coronary segments with mixed plaques (2). Based on the study results MSCT was able to rule out 20 patients from the suspicion of CAD, of which patients none had cardiac events during the follow-up.

In the study of Danciu et al. from the population of 421 intermediate risk patients where the majority (81.5 %) was medically managed, 78 patients (18.5 %) were sent for ICA and when required for revascularisation after stress myocardial perfusion imaging (MPI) and MSCT-examination. The medically managed group was heterogeneous including patients with no or mild CAD, mismatch between myocardial perfusion stress imaging (MPSI) and MSCT, or occluded by-pass graft. During the follow-up of 15 months 6 patients required ICA, and one of them underwent revascularisation. In this patient group classified as low-risk after MSCT, the rate of the combined end-point of death, acute myocardial infarction (AMI) and revascularisation was 0.3%. Thus, the use of MSCT was able to rule out clinically significant CAD in the majority of patients (1).

Of the patients referred to ICA based on over 70 % stenosis (34 patients) or over 50 % stenosis and matching MPI stress defect (42 patients), revascularisation rates were 23/42 and 27/30. The positive predictive value of severe stenosis on ICA was 88 % (30/34 patients).

Comment

This element is beyond specific study questions in the assessed studies.

Does the use of 64-slice CT modify the use of invasive treatment for CAD?

Results

Mowatt's HTA reported two studies which dealt the usefulness of MSCT in decision making. Auseon and colleagues reported that, in the year following the introduction of 64-slice CT compared to the previous four years, the yearly rates of increase in diagnostic catheterisation volume and percutaneous interventions had not been significantly affected. Danciu and colleagues reported that in the first six months following the introduction of 64-slice CT, invasive coronary angiography (ICA) had been avoided in 82% of 486 patients (4).

Rubinshtein et al. (10) assessed 100 patients by MSCT, who were suspected to have coronary artery disease (CAD) because of chest pain but who only had a negative (n=59) or non-diagnostic (n=41) exercise treadmill test (ETT). Obstructive CAD was present on 64-slice CT in 29 patients, all of whom underwent ICA. Among them 26 patients were confirmed to have significant CAD. 18 patients underwent revascularisation. During the follow-up of one year, none of the 71 patients who were not primarily catheterized died or had myocardial infarctions (MI). Another 15 patients underwent ICA within two weeks and one of the ICAs led to CAD diagnosis. The information about consequent revascularisation is missing. Later, five patients underwent ICA, with percutaneous intervention in two of them. The authors considered at least one of these lesions to have been a missed diagnosis and the other one might have represented disease progression. By using 64-slice CT in the clinical pathway of this low or intermediate risk population, 51 ICAs were avoided, but at least one patient who later required invasive treatment was missed initially.

In the study of Pundziute et al, among 100 patients with suspected or known CAD, MSCT was able to rule out CAD in 20 patients and of these none had a cardiac event during the follow-up (2). In the study setting MSCT was not used as a part of diagnostic/therapeutic workup, wherefore it was not designed to answer the study question.

In the study of Danciu et al. from the population of 421 intermediate risk patients who were initially referred for ICA after stress myocardial perfusion imaging (MPI), the use of 64-slice MSCT-examination led to the decision of medical management in 343 patients (81.5 %), and only 78

patients (18.5 %) were sent for ICA, of whom 50 underwent revascularisation (1). However, 6 patients required late ICA due to continuing symptoms, of which one required late (over 1 month after MSCT) revascularisation.

Comment

There are no specific answers to these elements in included studies.

Does MSCT detect other disease conditions causing chest pain which have impact on the CAD treatment decisions?

Does MSCT detect other disease conditions (e.g. pulmonary nodules, vascular aneurysms) that lead to new diagnostic pathways or other treatments than CAD?

How does this impact the use of health technologies and resources, and the quality of life and mortality of patients?

Results

Not answered in the included studies.

Comment

Case studies might have been described, but they are beyond this analysis. Different risk groups might have different likelihoods of incidental findings. It would be important to assess the clinical relevance of the incidental findings.

How does the use of 64-slice CT modify the need for Emergency Room visits/contacts, unscheduled hospitalization or outpatient visits or modify the need of intensive care?

Results

Not answered in the analysed studies.

Health outcomes

Is there effective treatment for non-obstructive (<50% stenosis)/ obstructive CAD in patients with stable symptoms of angina pectoris?

Results

Concerning non-obstructive coronary artery disease (CAD), in Mowatt's HTA review there was a conclusion that 64-slice CT would also show lesser degrees of stenosis, and could therefore influence management other than revascularisation. For example, a patient with 30% stenosis might receive lifestyle advice, a statin, and perhaps intensified control of blood pressure or blood

glucose. Several studies have reported regression of coronary artery disease (CAD) after statin treatment, though usually modest (4).

Obstructive CAD is treated by medication, percutaneous coronary intervention (PCI) or by-pass surgery. The contemporary medical treatment has been shown to improve the prognosis in patients with CAD. PCI and by-pass surgery, although useful at controlling symptoms in symptomatic patients, have only limited prognostic benefit if any.

In patients with low or intermediate risk for CAD, what is the effect of 64-slice CT - invasive / non-invasive treatment on mortality?

Results

In Rubinshtein's study of 100 patients with negative or non-diagnostic treadmill examination, positive MSCT led to invasive coronary angiography (ICA) in 29 patients, and MSCT result suggested rule-out significant coronary artery disease (CAD) in 71 patients, of whom 15 were assessed with ICA within 2 weeks due to on-going symptoms, and one of patients was diagnosed to have CAD on ICA. During the follow-up of one year, none of the 71 patients died or had myocardial infarctions (MI). Later, five patients underwent ICA, with percutaneous intervention in two of them (10)

In the study of Danciu et al. from the population of 421 intermediate risk patients where the majority (81.5 %) was medically managed (N=343), 78 patients (18.5 %) were sent for ICA and when required for revascularisation after stress myocardial perfusion imaging (MPI) and MSCT-examination. The medically managed group was heterogeneous including patients with no or mild CAD, mismatch between myocardial perfusion stress imaging (MPSI) and CT-findings or occluded by-pass graft. During the follow-up of 15 months 6 patients required ICA, and one of them underwent revascularisation. In this patient group classified as low-risk after MSCT, the rate of the combined end-point of death, acute myocardial infarction (AMI) and revascularisation was 0.3%. There was no mortality in 343 patients on medical treatment considered to have low risk of CAD within 15 months after MSCT (1).

In patients with low or intermediate risk for CAD, how does the 64-slice CT - treatment modify the clinical end points of CAD (AMI, UAP, revascularisation) or symptoms of chest pain and need for health care compared to a comparator treatment path without use of 64-slice CT?

In patients with low or intermediate risk for CAD, how does the use of 64-slice CT - treatment modify the number of patients receiving effective treatment?

Results

With 64-slice CT it is possible to detect stenosis of lesser degree. Therefore its results could lead to secondary prophylaxis of coronary artery disease (CAD), such as lifestyle advice or a drug to lower lipids, blood pressure or blood glucose that otherwise would not have been initiated. However, the identified studies did not look specifically to this question.

In the study of Rubinshtein et al. none of the 71 patients treated conservatively based on MSCT-finding died or had acute myocardial infarction (AMI) during the follow-up of one year. Within the first two weeks 15 with continuous symptoms or clinical signs underwent invasive coronary angiography (ICA) and one patient with a significant CAD was found. It is not reported if revascularisation (PCI) was required. Later, five of the patients underwent ICA, with PCI in two of them. The authors considered at least one of these lesions to have been a missed diagnosis and the other one might have represented disease progression (10).

In the study of Danciu et al. during the follow-up of 15 months 6 patients from the medically treated group (343 patients) required ICA and one of them underwent revascularisation. In this patient group classified as low-risk after MSCT, the rate of the combined end-point of death, AMI and revascularisation was 0.3%. The use of MSCT instead of ICA possibly led to delayed diagnosis in one case (1).

The conclusion from these two patient series is that correct diagnosis might have been missed in few patients compared to use of ICA, but the consequences in terms of clinical events are rare.

Comment

Imaging modalities are tools to be used in proper context of the clinical path. All results need to be judged in the clinical context.

In patients with low or intermediate risk for CAD, how does the use of 64-slice CT - treatment modify the effectiveness of invasive or non-invasive treatment?

Results

When MSCT is used for add-on information to the clinical diagnosis, it might give possibility to enhance medical treatment. There are several studies about primary and secondary prevention at population level. However, in this specific context no studies have been found to improve the effectiveness of treatment path.

What is the effect of 64-slice CT on health-related quality of life in patients who are diagnosed to have obstructive CAD / non-obstructive CAD / no CAD?

Results

This element was not answered in the included studies.

What are the negative consequences of further testing and delayed treatment in patients with false negative test result on 64-slice CT?

Results

There were only few comments on this in analysed studies. In the study of Rubinshtein, among 71 patients without evidence of obstructive coronary artery disease (CAD), 15 patients with on-going symptoms had invasive coronary angiography (ICA), of which one showed a significant stenosis in the left anterior descending artery (LAD). No clinical consequences were described. Another five

patients underwent clinically driven ICA during the follow-up of one year. Among them were two with percutaneous angioplasty for LAD. No hard cardiac events were described.

What are the negative consequences of further testing and treatments in patients with false positive test result on 64-slice CT?

Results

Rubinshtein (10) assessed 100 patients by MSCT, who were suspected to have coronary artery disease (CAD) because of chest pain but who only had a negative or non-diagnostic exercise treadmill test (ETT). Obstructive CAD was present on 64-slice CT in 29 patients, all of whom underwent invasive coronary angiography (ICA). Among them 26 patients were confirmed to have significant CAD. Three were diagnosed as not significant CAD on invasive coronary angiography (ICA). No other negative consequences are described except that the ICA procedure might have been avoided with a proper diagnosis on MSCT.

What are the overall benefits and harms in health outcomes considering the amount of false positive and false negative?

Results

Answer was not found in the literature.

What is the effect of knowledge of test results in patients who are diagnosed to have obstructive CAD / non-obstructive CAD / no CAD?

Results

This element was not answered in the included studies.

Would the patient be willing to use MSCT for the diagnosis of CAD again?

Results

This element was not answered in the included studies.

Comment

Answer to this element might be found from studies using other than 64-slice MSCT, or from the studies included in the Social Domain.

Discussion

Very few studies were identified that dealt with the usefulness of 64-slice CT in the diagnostic path of patients with stable chest pain and low to intermediate risk of coronary artery disease (CAD). Based on accuracy data and what is known from large population studies of CAD prevention, 64-slice CT helps to identify and classify the patients between groups of primary and secondary prevention and patients between obstructive and non-obstructive disease. Further studies are needed

to find more specific and direct evidence to the questions asked in the elements of EUnetHTA effectiveness domain.

From the methodological point of view the questions from generic EUnetHTA diagnostic format were initially translated into the specific context of MSCT by two authors (TSI and HU). From the literature, only three studies were identified that looked at the diagnostic path and clinical follow-up of the patients after 64-slice CT examination. The answers were extracted from the studies with a specific interest to the target group of low and intermediate risk for CAD in patients with non-acute symptoms. Because of lack of appropriate studies, specific answers for majority of the issues were lean. On the other hand, some elements would have required a specific literature search with a wider or completely different focus, e.g. questions about mortality, or the reference standard, and the effective treatment for CAD.

Assessment of effectiveness for a diagnostic test requires different approach from the basic accuracy assessment and leads to a more complex setting. However, these questions are of major interest and they are essential requirements in the core of clinical work: does the effort paid for diagnostic work-up really benefit the patients?

References

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Assessment elements table

Element Identification Code (ID)	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT Or Comment (if regarded as a not relevant issue in this context)
D0019	Effectiveness	Comparative accuracy of a replacement technology	Based on the accuracy and safety data is there evidence that the replacing technology is more specific or safer than the gold standard or comparator test?	Yes	In patients with low or intermediate risk for CAD, is 64-slice CT more specific or safer than CA / radionuclide imaging /stress ECHO / the best medical treatment and clinical follow-up?
D0001	Effectiveness	Safety	What is the mortality related to the diagnostic technology?	Yes	What is the mortality related to MSCT compared to CA?
D0008	Effectiveness	Safety	What is the morbidity related to the diagnostic technology?	Yes	What is the morbidity related to MSCT? What is the incidence of radiation induced morbidity? What is the impact of MSCT on renal function?
D0020	Effectiveness	Change-in management	Does the use of the technology lead to improved detection of the disease?	Yes	In patients with low or intermediate risk for CAD, does 64-slice CT improve the physician's ability to make correct diagnosis of CAD?
D0021	Effectiveness	Change-in management	Does the use of the technology lead to a change in the physicians' management decisions?	Yes	Does the use of 64-slice CT change the physicians' prescription of primary or secondary prevention medication to the patients with low or intermediate risk for CAD? Does the use of 64-slice CT modify the use of invasive treatment for CAD?
D0022	Effectiveness	Change-in management	Does the use of technology detect other health conditions (e.g. incidental findings) which have impact on the treatment decisions concerning the target condition?	Yes	Does MSCT detect other disease conditions causing chest pain which have impact on the CAD treatment decisions? Does MSCT detect other disease conditions (e.g. pulmonary nodules, vascular aneurysms) that lead to new diagnostic pathways or other treatments than for CAD? How does this impact the use of health technologies and resources, and the quality of life and mortality of patients?
D0023	Effectiveness	Change-in management	How does the technology modify the need for other tests and use of resources?	Yes	How does the use of 64-slice CT modify the use of stress ergometry, stress ECHO, SPECT or CA in patients with low or intermediate risk for CAD, and what is the impact on resources?
D0010	Effectiveness	Change-in management	How does the technology modify the need for hospitalization?	Yes	How does the use of 64-slice CT modify the need for Emergency Room visits/contacts, unscheduled hospitalization or outpatient visits or modify the need of intensive care?
D0024	Effectiveness	Health outcomes	Is there an effective treatment for the condition the technology is detecting?	Yes	Is there effective treatment for non-obstructive (<50% stenosis)/ obstructive CAD in patients with stable symptoms of AP?
D0025	Effectiveness	Health outcomes	What is the effect of the test-treatment intervention on mortality?	Yes	In patients with low or intermediate risk for CAD, what is the effect of 64-slice CT - invasive / non-invasive treatment on mortality?
D0005	Effectiveness	Health outcomes	How does the test-treatment intervention influence the magnitude and frequency of morbidity?	Yes	In patients with low or intermediate risk for CAD, how does the 64-slice CT - treatment modify the clinical end points of CAD (AMI, UAP, revascularisation) or symptoms of chest pain and need for health care compared to a comparator test - treatment or a treatment path without use of 64-slice CT? In patients with low or intermediate risk for CAD, how does the use of MSCT - treatment modify the number of adverse outcomes from MSCT versus other diagnostic tests? In patients with low or intermediate risk for CAD, how does the use of 64-slice CT - treatment modify

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Pilot assessment to test the HTA Core Model. Not for decision-making.

					the number of patients receiving effective treatment?
D0026	Effectiveness	Health outcomes	How does the technology modify the effectiveness of subsequent interventions?	Yes	In patients with low or intermediate risk for CAD, how does the use of 64-slice CT - treatment modify the effectiveness of invasive / non-invasive treatment?
D0013	Effectiveness	Health outcomes	What is the effect of the technology on health-related quality of life?	Yes	What is the effect of 64-slice CT on health-related quality of life in patients who are diagnosed to have obstructive CAD / non-obstructive CAD / no CAD?
D0027	Effectiveness	Health outcomes	What are the negative consequences of further testing and delayed treatment in patients with false negative test result?	Yes	What are the negative consequences of further testing and delayed treatment in patients with false negative test result on 64-slice CT?
D0028	Effectiveness	Health outcomes	What are the negative consequences of further testing and treatments in patients with false positive test result?	Yes	What are the negative consequences of further testing and treatments in patients with false positive test result on 64-slice CT?
D0029	Effectiveness	Health outcomes	What are the overall benefits and harms in health outcomes considering the amount of false positive and false negative?	Yes	What are the overall benefits and harms in health outcomes considering the amount of false positive and false negative? What are the impacts of risks of radiation and kidney failure?
D0030	Effectiveness	Patient satisfaction	Does the knowledge of the test result improve the patient's quality of life?	Yes	What is the effect of knowledge of test results in patients who are diagnosed to have obstructive CAD / non-obstructive CAD / no CAD?
D0018	Effectiveness	Patient satisfaction	Would the patient be willing to use the technology again?	Yes	Would the patient be willing to use MSCT for the diagnosis of CAD again?

Appendix 1 Search Strategies

Multislice CT, Basic search for EUnetHTA

Database: Ovid MEDLINE(R) <1950 to November Week 2 2007>

Search date: 7.12.2007

Search strategy:

-
- 1 exp Coronary Disease/di, ra [Diagnosis, Radiography]
 - 2 (coronary adj2 (disease\$ or occlus\$ or vessel\$ or arter\$ or stenosis\$ or restenosis\$ or aneurysm\$ or thrombosis\$ or vasospasm\$ or obstruct\$)).tw.
 - 3 calcinosis/di, ra or myocardial ischemia/di, ra
 - 4 1 or 2 or 3
 - 5 exp Coronary Angiography/
 - 6 exp Tomography, X-Ray Computed/
 - 7 5 and 6
 - 8 (angiograph\$ and tomograph\$).tw.
 - 9 7 or 8
 - 10 4 and 9
 - 11 (msct or mdct).tw.
 - 12 (("8" or "16" or "32" or "40" or "64") adj2 (slice\$ or row\$)).tw.
 - 13 (multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi-detect\$" or "multi detect\$" or multisect\$ or "multi-sect\$" or "multi sect\$").tw.
 - 14 11 or 12 or 13
 - 15 10 and 14
 - 16 animals/
 - 17 humans/
 - 18 16 not (16 and 17)
 - 19 15 not 18
 - 20 limit 19 to yr="1990 - 2008"

Multislice CT, Effectiveness

Database: Ovid MEDLINE(R) <1950 to May Week 2 2008>

Search date: 23.5.2008

Search strategy:

-
- 1 exp Coronary Disease/di, ra [Diagnosis, Radiography]
 - 2 (coronary adj2 (disease\$ or occlus\$ or vessel\$ or arter\$ or stenosis\$ or restenosis\$ or aneurysm\$ or thrombosis\$ or vasospasm\$ or obstruct\$)).tw.
 - 3 calcinosis/di, ra or myocardial ischemia/di, ra
 - 4 1 or 2 or 3
 - 5 exp Coronary Angiography/
 - 6 exp Tomography, X-Ray Computed/
 - 7 5 and 6
 - 8 (angiograph\$ and tomograph\$).tw.
 - 9 7 or 8
 - 10 4 and 9
 - 11 (("64" or sixty-four or sixtyfour) adj2 (section\$ or slice\$ or row\$)).tw.

- 12 (msct or mdct or multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi-detect\$" or "multi detect\$" or multisect\$ or "multi-sect\$" or "multi sect\$").tw.
- 13 11 or 12
- 14 10 and 11
- 15 animals/
- 16 humans/
- 17 15 not (15 and 16)
- 18 14 not 17
- 19 18 not (news or letter or comment or editorial).pt.
- 20 ("change-in manage\$" or "change-in patient manage\$").tw.
- 21 "diagnostic before and after".tw.
- 22 test-treatment path\$.tw.
- 23 clinical path\$.tw.
- 24 ((pre-test or pretest) adj2 manage\$).tw.
- 25 ((post-test or posttest) adj2 manage\$).tw.
- 26 diagnostic triag\$.tw.
- 27 ((clinical or therapeutic) adj2 decision\$).tw.
- 28 decision analy\$.tw.
- 29 Decision Making/
- 30 Triage/
- 31 or/20-30
- 32 19 and 31 (9)

Appendix 2 Quality assessment

Quality assessment of Mowatt et al 2008 (by SH and TSI)

		Methodology Checklist 1: Systematic Reviews and Meta-analyses	
Study identification (<i>Include author, title, year of publication, journal title, pages</i>) Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. Health Technol Assess 2008;12(17)			
Guideline topic:		Key Question No:	
Checklist completed by: Sigurður Helgason (SH) and Tuija S Ikonen (TSI).			
Section 1: Internal validity			
In a well conducted systematic review		In this study this criterion is::	
1.1	The study addresses an appropriate and clearly focused question.	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	A description of the methodology used is included.	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	<i>The literature search is sufficiently rigorous to identify all the relevant studies.</i>	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Study quality is assessed and taken into account.	Well covered SH/TSI Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered SH Adequately addressed TSI Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –	++ SH / ++ TSI	

2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	
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Costs and economic evaluation

Irina Cleemput, Cécile Camberlin, Pirjo Räsänen, Victor Sarmiento González-Nieto, Belén Corbacho, Torbjørn Wisløff, Kersti Meiesaar

Introduction

The interest in the costs and cost-effectiveness of multi-slice computed tomography (MSCT) coronary angiography comes from the possible savings from avoiding unnecessary invasive coronary angiographies (ICA). If MSCT is used for screening purposes, its aim is to detect subclinical atherosclerosis; the idea being that if you can treat such manifestations in an early phase, future costs of expensive interventions may be avoided or delayed and the quality and length of life may increase. However, these beneficial effects on costs and health effects remain to be proven while limitations and potential harms have to be considered. Concerns are the exposure to high-dose radiation, the potential of misdiagnosis (false positives), the administration of beta-blockers and the injection of iodinated contrast.

Research in this domain aims at finding out the following: "Is MSCT angiography a cost-effective alternative to standard work-up for the diagnosis and treatment of coronary artery disease in patients at low to intermediate risk for cardiovascular events?" The comparator in this economic evaluation of MSCT is the standard work-up as defined in the clinical trial (5) upon which the economic evaluation is based. This trial is frequently cited to demonstrate MSCT's cost-effectiveness. There is only very little literature on the economics of MSCT in the patient group examined in this HTA. This is actually not so surprising given the lack of evidence for the impact of diagnostic procedures on patient outcomes in the patient population with low to intermediate risk for cardiovascular events. In view of this lack of evidence, one could question the usefulness of a cost-effectiveness analysis.

Methodology

Literature review

For the review of the economic literature on MSCT angiography, we searched MEDLINE, Pre-MEDLINE, EMBASE, EconLit, HTA database and NHSEED. The search was performed between November 30th and December 6th, 2007. Search strategies for each database are presented in the appendix 2.

The search strategy resulted in 290 unique references across all databases. Two researchers independently selected relevant titles and abstract. For references selected by one researcher, but not the other, a consensus was sought.

Inclusion criteria were:

- population: low to medium risk, non-acute chest pain

- intervention: MSCT
- outcome: avoided invasive procedures (intermediary outcome), quality-adjusted life years (QALYs) or simply life years gained (LYG) (final outcome)
- design: full or partial economic evaluation, cost-outcome description

Exclusion criteria were

- focus on EBCT (electron beam computed tomography) or MSCT of less than 64 slices
- absence of economic information
- MSCT in high-risk population
- MSCT in patients with acute chest pain at the emergency department
- letters, editorials and papers that were not in English

After the first selection round, 53 titles and abstracts were selected for full text retrieval. Scanning the full text led to the 50 exclusions. Three studies were retained: Dewey et al. 2007 (3), Otero et al. 2007 (9) and Goldstein et al. 2007 (5). Three additional studies were identified by handsearching: Rubinshtein et al. 2006 (10), Cole et al. 2007 (2) and a primary economic evaluation as part of an HTA on MSCT from AETSA 2008 (7).

None of the three studies that were retained for the literature review used final outcome parameters in the analysis. Moreover, no single full economic evaluations, including an incremental cost-effectiveness analysis, were found in literature. Nevertheless, some of these studies are frequently cited to demonstrate cost-effectiveness of MSCT. One of these is the RCT of Goldstein et al. (5), alongside which economic data were collected. The study provides interesting information on both the therapeutic impact of MSCT and outcomes on 6 months follow-up. Unfortunately, however, the data have not been fully explored to assess the technology's cost-effectiveness relative to standard diagnostic care. Because we aim to fully explore the data provided by this work for our economic evaluation of MSCT relative to standard of care, we briefly discuss the study of Goldstein et al. (5).

Economic evaluation

The economic evaluation was performed according to the methodological guidelines for pharmaco-economic evaluations in Belgium (1).

Design

For the evaluation of the incremental costs and effects of a diagnostic strategy with MSCT and a standard diagnostic strategy in low-risk patients with chest pain, we used the data presented in the report of the RCT and economic evaluation of Goldstein et al. (5). Although we are well aware that it might be too early to examine the intervention's cost-effectiveness given the lack of evidence on the utility of diagnostic techniques in the target population, we performed this rudimentary economic evaluation mainly for the sake of testing the core HTA model for diagnostic procedures. Goldstein et al. (5) performed a RCT of MSCT for the evaluation of acute chest pain. One hundred ninety-seven (197) patients aged 25 years or older, at low risk for coronary events, with no history of coronary artery disease (CAD) and presenting at the emergency department with acute chest pain were randomized to "Standard of Care" or MSCT. Their ECG at time=0 and time=4 hours were normal as well as their serum biomarkers. The standard of care diagnostic protocol to rule out myocardial infarction included serial ECG and cardiac enzymes, followed by rest-stress myocardial perfusion SPECT imaging before referring home or to catheterization laboratory. The MSCT strategy included calcium scoring and angiography, followed by conventional ICA when positive, discharge home when normal and by nuclear stress testing when MSCT results are intermediate or

inconclusive. Outcomes included number of tests complications, major adverse cardiovascular events (death, acute myocardial infarction (AMI), unstable angina), number of correctly diagnosed patients and time to diagnosis. A diagnosis was judged correct based on the results of a catheterization or the presence or absence of major adverse cardiovascular events during the index admission or the 6-month follow-up period. Among the 99 patients following the MSCT arm, 96 (95%) were correctly diagnosed: 88 without CAD (including 1 readmission for a negative ICA) and 8 with a positive ICA. Twenty-four (24.2%) had to have a nuclear stress imaging due to non-diagnostic MSCT and 4 patients had an ICA that turned to be negative. In the emergency department setting, MSCT was able to immediately identify or exclude CAD in 75% of cases. No test complications or major cardiovascular events were noticed in either arm in the 6-month follow-up period. Eight patients in each group required a late office or emergency department visit for recurrent chest pain. Fewer patients required additional non-invasive evaluations (the protocol was not described) in the MSCT than in the "Standard of Care" arm (2% versus 7%; $p=0.10$). The median time to diagnosis was 3.4 hours in the MSCT arm (25th percentile: 2.3 hours, 75th percentile 14.8 hours) versus 15 hours in the "Standard of Care"-arm (25th percentile 7.3 hours; 75th percentile 20.2 hours). As a result from reduced time in the emergency department, costs were significantly lower for MSCT patients amounting to \$1 586 (25th percentile \$1 413; 75th percentile to \$2 059) against \$1 872 for the standard of care arm (25th percentile \$1 727; 75th percentile \$2 069).

The authors conclude that MSCT is safe and highly effective to give a correct diagnosis over a 6-months period. However, MSCT still has limitations in determining the physiological significance of intermediate coronary lesions. They warn against a possible oculostenotic reflex, caused by the inability of MSCT to provide coronary blood flow data. Further studies are recommended to determine the optimal use of MSCT.

Although this study is frequently cited to demonstrate the cost-effectiveness of MSCT, it does not strictly satisfy the criteria of a full economic evaluation. No incremental calculations were made, no incremental cost-effectiveness ratio (ICER) was calculated and costs were incompletely taken into account, e.g. costs of ICA, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or repeated evaluations during follow-up. Costs were calculated based on data from the hospital billing department and based on the emergency department's cost-to-charge ratio. Although not clearly stated in the methods section of the article, the cost-to-charge ratio seems to be a cost per hour of use of the emergency department. The authors were contacted to obtain more details about the ratio used, but no response to the email was received. Costs of the procedure were included (MSCT \$507 and nuclear imaging \$538).

While the authors are very enthusiastic about MSCT for the evaluation of acute chest pain, it should be noted that the number of invasive procedures (ICA, PCI and CABG) is higher in the MSCT-arm than in the "Standard of Care"-arm, while the outcomes in terms of mortality and morbidity up to 6 months are not any different between the arms.

Moreover, despite the apparent safety of both strategies (absence of adverse complications), 10% of the patients in the MSCT arm had to be radiated twice (MSCT+nuclear testing) and 4% even three times (MSCT+nuclear testing+ICA). Iodinated contrast also presents a potential harm in MSCT evaluation. Although 8 ICAs out of 12 were positive in the MSCT-arm and only 1 out of 7 in the "Standard of Care"-arm, this does not necessarily mean anything for the prognosis of the patients with a positive ICA.

The numbers of patients were too small to evaluate the true incidence of false positive cases and false negative cases, especially in a population with a low prevalence.

Although the data from this RCT were directly used for the economic evaluation, we did not use the same approach as the authors for the economic analysis. We decided to extrapolate the economic results of the study by Goldstein et al. (5) to include the costs of invasive angiography, revascularisations and complications up to six months after initial admission to the emergency department for acute chest pain. The basic idea is that the cost-effectiveness of MSCT depends not only on the costs and effects of the diagnostic strategy, but also the costs and effects of its sequelae, i.e. the changes in therapeutic behaviour and the consequent impact on patient outcomes. Therefore, it is insufficient to consider only the technique's diagnostic accuracy (sensitivity and specificity) in an economic evaluation. An economic evaluation should also incorporate the technique's effect on patients' final outcomes (LYG or QALYs gained).

The design of our economic evaluation can be considered as a kind of retrospective piggy-back economic evaluation based on a data from one RCT. More specifically, the economic evaluation is based on the clinical results and the description of procedures performed in the patients in both diagnostic arms of one RCT. Based on these results and descriptions, costs and effects as relevant for the economic evaluation were estimated. The construct of the decision tree is entirely based on the movements of patients observed in that RCT. In that sense, the decision tree is a limited representation of the expected reality, as the number of patients in the RCT was limited and not all branches of a more realistic model could be filled with data from the trial. However, with the limited data available in literature, it was unfortunately unrealistic to fill a decision tree that includes all possible real-life scenarios.

A simple decision tree was constructed in Excel, where the numbers of patients moving from one intervention to another were derived directly from the RCT. The structure of the decision tree is presented in Appendix 2.

Analytic technique

Because outcomes in terms of mortality or major cardiovascular events are not different between the two diagnostic arms in the study, an analysis of the "cost-per-LYG" based on these data would ultimately boil down to a cost-minimisation analysis. However, invasive coronary angiography has a demonstrated impact on the quality of life of patients undergoing this procedure (12,13). Therefore, it is worth looking at the QALY gains or losses of the two diagnostic work-up paths being compared. A cost-utility approach is therefore performed, calculating the incremental cost-per-QALY gained associated with MSCT as compared to "Standard of Care".

Perspective

The perspective taken is that of the Belgian health care payer, including both the National Institute for Health and Disability Insurance (RIZIV/INAMI) and the patients. For the calculation of the costs of the two diagnostic work-up arms, we calculate the total reimbursement by the RIZIV/INAMI and add, if applicable, the patients' out-of-pocket expenses.

Target population

The target population of our model is as in the RCT: adult patients with acute chest pain who are deemed at low risk for coronary events after an initial work-up in the emergency department (ECG, biomarkers). Population characteristics in both groups are presented in Table 1.

Table 1: Characteristics of patients included in the economic model

	MSCT N=99	“Standard of Care” N=98	P-value
Age, mean in yrs	47	50	0.08
Male, %	43	57	0.05
Body Mass Index	28	28	0.78
Hypertension, %	39	38	0.88
Diabetes, %	8.2	12.2	0.35
Family history of early coronary disease, %	40	44	0.56
Current smoker, %	15	20	0.35
Goldman Riley criteria, %			
0- very low risk	100	99	1
1- low risk	0	1	
2- moderate risk	0	0	

Comparator

The comparator to MSCT angiography is the “Standard of Care” as defined by Goldstein et al. (5). This includes non-invasive coronary tests, i.e. serial ECG and cardiac biomarkers at 0, at 4 and at 8 hours and rest-stress myocardial perfusion single-photon emission computed tomography imaging. Common procedures to both diagnostic arms were the electrocardiograms and cardiac biomarkers at 0 and at 4 hours. Patients were randomised if both of these were normal. Therefore, the difference in primary diagnostic protocol between the “intervention”, i.e. MSCT, and the comparator, i.e. “Standard of Care”, is one cardiac biomarker and SPECT as part of the initial diagnostic strategy in the “Standard of Care” group.

Costs

Initial diagnostic strategy

The costs of the initial diagnostic strategy were calculated on the basis of the prevailing reimbursement tariffs and out-of-pocket expenses of the procedures associated with the strategy.

For MSCT angiography no reimbursement tariff exists (yet). Therefore, we used the reimbursement and patients’ out-of-pocket expenses for “chest CT” as a proxy for the costs of MSCT angiography from the perspective of the Belgian health care payer. Usually other costs are associated with procedures than the costs of the procedure itself. For example, when a patient enters an emergency department and gets a MSCT angiography after which he is immediately discharged, the hospital can charge other costs to the RIZIV/INAMI such as a physician’s fee.

To identify the resource use, and especially the lump sums a hospital can charge if a patient is either discharged the same day after MSCT or “Standard of Care” or is hospitalised for ICA that is eventually not followed by an invasive procedure, we presented different scenarios to the accounting service of a hospital who then retrieved the actual bill of a patient fitting into the

respective scenarios to identify what can be charged in each of the cases. The scenarios presented to the hospitals were the following:

- a patient enters the emergency department for chest pain, undergoes a standard diagnostic work-up and subsequently a conventional ICA which turns out to be negative
- a patient enters the emergency department for chest pain, undergoes a diagnostic work-up including a chest CT (used as a proxy for MSCT) and a nuclear stress test and is then discharged home
- a patient enters the emergency department for chest pain, undergoes a chest CT and is immediately discharged home
- a patient enters the emergency department for chest pain, undergoes the standard of care, including nuclear stress test and is then discharged home

If no bill could be retrieved for an actual patient fitting in one of these scenarios, medical experts and accounting services simulated what would be charged in these cases. This was the case for the scenarios where a nuclear stress test is performed at the emergency department, on the basis of which it would be decided to send the patient home. According to the medical administration, no single patient fitted in this scenario according to their register. This would mean that the scenario presented in the study by Goldstein et al. (5) might not be realistic in Belgium. Because we nevertheless had to calculate a cost for this scenario, as we had to adhere to the diagnostic protocols suggested in the trial, we simply added the procedure cost of a radionuclide myocardial perfusion scintigraphy (MPS) to the cost of a patient satisfying the other criteria of the scenario where MPS was included.

For ICA that is not followed by revascularisation, we obtained a patient bill from one hospital, on the basis of which we identified the procedures that are charged in such a case.

Revascularisation: PCI and CABG

The costs of PCI and CABG were derived from a Belgian HTA on drug eluting stents (DES) (8). These cost data were based on actually observed cost data of all patients having received a bare metal stent (BMS) or DES in 2004 in Belgium. A distinction was made between the costs associated with PCI with BMS and PCI with DES and between treatment with one or another stent-type in diabetic and non-diabetic patients. The distribution of the costs for a hospitalisation episode due to PCI and CABG was taken into account in the sensitivity analysis.

Point estimates, along with their distribution used in the sensitivity analysis, are presented in table 2.

Table 2. Average cost and parameters of the distributions of PCI and CABG in diabetic and non-diabetic patients

Costs	Mean	S.E.M.	distribution	lower bound	upper bound	source
PCI with stent (BMS) in non-diabetic patients	6298	255	normal	3018	24221	KCE report 66A; www.kce.fgov.be
PCI with stent (DES) in non-diabetic patients	7000	1541	normal	3371	68450	KCE report 66A; www.kce.fgov.be
PCI with stent (BMS) in diabetic patients	7190	773	normal	2118	17444	KCE report 66A; www.kce.fgov.be
PCI with stent (DES) in diabetic patients	7732	770	normal	1836	51591	KCE report 66A; www.kce.fgov.be
CABG in non-diabetic patients	15319	804	normal	7650	56287	KCE report 66A; www.kce.fgov.be
CABG in diabetic patients	17439	2459	normal	8742	52521	KCE report 66A; www.kce.fgov.be

From the same HTA, we derived the distribution of BMS and DES across diabetic patients and non-diabetic patients respectively. The data are as follows:

	Diabetic patients	Non-diabetic patients
BMS	21,7%	88,2%
DES	78,3%	11,8%

Outcomes

The outcomes are valued based on data from literature about the quality of life impairment associated with PCI, CABG and ICA. SPECT and MSCT are assumed to have no impact on health-related quality of life (HRQoL).

Serruys et al. (13) studied HRQoL in 600 patients who had undergone PCI with stenting and 605 patients having undergone CABG. The instrument was the EuroQol (EQ-5D). EQ-5D health states were translated into an index value on a scale from 0 (dead) to 1 (perfect health) based on the UK off-the shelf utility values for EQ-5D health states (4). This study found that healthy, on average 60-year old, patients have a quality of life index of 0.86 (s.d. 0.16). At the time of intervention, patients had an index of 0.69 (s.d. 0.20) in case of PCI and 0.68 (s.d. 0.20) in case of CABG. One month after the intervention, quality of life values were 0.84 (s.d. 0.16) and 0.78 (s.d. 0.17) for PCI and CABG respectively. At six months after the intervention, there was no longer a significant difference between the quality of life of patients who had undergone PCI and patients who had undergone CABG and both patient groups had already reached the quality of life index of 0.86, which is equivalent to baseline values in healthy patients of the same age.

Scuffham and Chaplin (11,12) used these values to calculate the quality of life loss due to PCI and CABG in an economic model. They assumed a quality of life loss due to PCI of 0.17 for 1 month, which boils down to 5 quality-adjusted life days lost. For CABG, they assumed a quality of life loss of 0.18 for one month and 0.08 for the subsequent 2.5 months. This is equivalent to 11.4 quality adjusted life days lost due to CABG. Other authors have used similar QALY decrements. Kuntz et al. (6), for instance, estimated the number of quality-adjusted life days lost due to PCI and CABG at 2 and 10 days respectively.

We used the quality of life values and their observed distribution as reported by Serruys et al. (13) to define the number of quality adjusted life days lost. Assumptions had to be made about the duration of quality of life impairment due to these procedures as for obvious reasons no continuous data are available for quality of life. Similarly to Scuffham and Chaplin (11,12) we assume that the baseline values at time of intervention as reported by Serruys et al. (13) hold for one month in case of PCI and CABG and that in addition CABG patients suffer from a quality of life reduction of 0.08 compared to healthy individuals at that age during 2.5 months following the intervention. Unlike Scuffham et al. (11,12), however, we take the distributions in observed quality of life values into account in our estimates of the variability in quality of life impairment. For angiography without PCI we did not find specific utility values. We therefore assumed the same quality of life impairment as for PCI, albeit for a shorter period of time, i.e. 0.5 months instead of 1 month.

The quality of life values and their distributions for each of the states, on the basis of which the QALY decrements are calculated, are presented in Table 3.

Table 3. Distributions of quality of life index values used to calculate the number of quality-adjusted life days lost

Health state	Duration of state	Quality of life index values, mean	Standard deviation	Distribution	Lower bound	Upper bound
Baseline		0,86	0,16	Normal	0.2	1
PCI procedure	1 month	0,69	0,2	Normal	0.25	1
CABG procedure	1 month	0,68	0,2	Normal	0.25	1
CABG follow-up	2.5 months	0,78	0,17	Normal	0.5	1

The impact of symptom relief from revascularisation on HRQoL was not taken into account in our economic evaluation because the RCT gave no information on this aspect.

Time horizon

The time horizon used in the economic model is the one for which data are available from the RCT, i.e. from admission to the emergency department up to 6 months follow-up. We assume that longer time horizons would not change the results of the economic analysis, because there is insufficient proof that early diagnosis of CAD or early revascularisation of CAD in patients with no documented ischemia would change lifetime outcomes.

As for the outcomes, we assume that only invasive coronary procedures (ICA, PCI and CABG) have an impact on the number QALYs. The absolute difference between the numbers of QALYs in both procedures remains therefore de facto the same in extended time periods if the difference in the number of invasive procedures remains the same. Obviously, the relative impact of the quality of life loss due to the procedures decreases if the time horizon increases.

If the observed trend in the RCT of more revascularisations in the MSCT arm continues in longer follow-up periods, the difference between the costs and outcomes of both diagnostic strategies will only increase. The RCT is, however, underpowered to allow such hypothesis.

Sensitivity analysis

Bootstrapping was performed to obtain confidence intervals around the cost and outcome estimates in the economic evaluation. 1000 bootstrap samples were drawn from the defined distributions. The distributions used in the bootstrapping for cost and outcome variables are presented in the paragraphs where the sources and assumptions with respect to the cost and outcome variables are discussed. Bootstrapping was performed in @RISK.

We verified the conclusions of Goldstein et al. by calculating the costs of both diagnostic strategies up to the point where the decision to perform CCA is taken. Costs of CCA or revascularisation were not included. On the basis of this analysis; Goldstein et al. concluded that the MSCT procedure is less costly than the “Standard of Care” procedure. Outcomes, however, were not measured in terms of QALYs but in terms of “time to diagnosis”, which is, as explained earlier, not relevant for

resource allocation decisions in health care. Health care decision makers are interested in obtaining the highest improvement in health with a given amount of resources.

Discounting

Because the time horizon of the evaluation is less than one year, there is no need to discount costs and outcomes.

Assessment elements

Resource utilization

What types of resources are used when delivering MSCT and its comparators?

What amounts of resources are used when delivering MSCT and its comparators?

Results

Types of resources and volumes of resource use for which no real observational data were available are presented in Table 4.

Table 4. Resource for MSCT, standard of care and conventional coronarography

	Both strategies*	MSCT diagnostic path	Standard diagnostic path (standard tests+MPS)	Conventional coronarography
Procedure fees	2 blood tests (cardiac biomarkers)	MSCT procedure	1 additional blood test (cardiac biomarkers)	Coronarography
	2 ECG		MPS procedure fee	Additional blood tests
Products		Iodinated contrast	Radio-isotope (1/6 kit sestamibi)	Iodinated contrast
Physician fees		Radiologist's fee	Radiologist's fee	Radiologist's fee
		Cardiologist's fee in ED	Cardiologist's fee in ED	Cardiologist's fee
				Surveillance fee per hospitalisation day
Lump sums		1 "mini lump sum" (if MSCT scan is not followed by hospitalisation)	1 "mini lump sum" (if MPS is not followed by hospitalisation)	2 hospitalisation days – per diem price
		Lump sum medical imaging		Lump sum clinical biology per day
				Lump sum medical imaging
				Lump sum for hospital admission

* these costs are not taken into account as they are equal between the two strategies. Only incremental costs are calculated.

The corresponding cost figures for these items are presented in Table 5. The distributions mentioned are the ones used for the sensitivity analysis. Distributions are only defined for cost items that are variable across hospitals. Other amounts, e.g. those defined in the Belgian “nomenclature”, are deterministic and have hence no distribution.

Table 5. Cost items included in the analyses

	Cost item	Mean (RIZIV + Patient)	Standard deviation	Distribution	Lower limit	Upper limit
Procedures	Cardiac biomarkers	10.33 (7.75+2.58)	-			
	MSCT procedure fee	121.35 (118.87+2.48)	-			
	SPECT procedure fee	318.11 (280.93+37.18)	-			
	Coronarography procedure fee	484.56 (484.56+0)	-			
	Additional blood tests in case of ICA	25.69 (25.69+0)	-			
Products	Contrast agent MSCT	44.68 (44.68+0)	-			
	Radio-isotope SPECT	37.18 (37.18+0)	-			
Physician's fees	Radiologist's fee	25.96 (18.52+7.44)	-			
	Radiologist's fee (sum for all procedures in case of ICA)	39.87 (33.33+6.54)	-			
	Cardiologist's fee in ED	35.25 (31.18+4.07)	-			
	Surveillance honorarium per hospitalisation day	24.84 (19.88+4.96)	-			
Lump sums	Hospital per diem price	20.83	3.61	normal	15.77	42.67
	“Mini” lump sum	56.39	12.798	normal	41.27	124
	Lump sum clinical biology (per hospital admission)	143.92	30.88	normal	94.03	233.17
	Lump sum clinical biology (per day)	21.89	5.82	normal	11.84	45.48
	Lump sum medical imaging (per day)	50.72	12.07	normal	22.13	88.74

For the calculation of the costs of PCI and CABG, there was no need to first identify all resources and secondly measure them, as all resources used and their costs were included in the cost figures of the national database.

Unit costs

What are the unit costs of the resources used when following a diagnostic protocol with MSCT and a standard diagnostic protocol?

Results

The results of the base-case analysis are presented in Table 6.

Table 6. Results of the base-case economic analysis

Diagnostic path	Cost per patient, mean (95% C.I.)	QALYs lost per patient, mean (95% C.I.)
MSCT, index hospitalisation	914.92 (875;955)	0.0014 (0;0.004)
MSCT follow-up	88.55 (83.15;94.49)	0.00014 (0;0.0046)
Total	1003.48 (959;1047)	0.0016 (0;0.0045)
Standard of care, index hospitalisation	461.38 (444;484)	0.0003 (0;0.0009)
Standard of care, follow-up	62.53 (58.63;66.49)	0.00028 (0;0.0009)
Total	523.91 (505.12;548.03)	0.00056 (0;0.0018)

According to these results the MSCT diagnostic strategy is on average €479.56 more expensive than the standard of care strategy.

Indirect costs

What is the impact of a diagnostic strategy with MSCT on indirect costs?

Results

In the RCT used as a basis for the economic evaluation, more patients in the MSCT arm underwent revascularisation than in the “Standard of Care” arm. Revascularisation requires hospitalisation for, on average, 3 to 7 (dilatation/stenting, PCI) or 13 to 18 (bypass operation, CABG) days in Belgium (<https://tct.fgov.be/etct/anonymous?lang=nl>; visited on April 10, 2008). This would imply higher indirect costs associated with MSCT.

We have not calculated this impact in monetary terms, as indirect costs are not part of the reference case analysis according to the Belgian guidelines for pharmacoeconomic evaluations, which were followed in this study (1). Moreover, as it was already clear from the direct cost calculation that MSCT is more expensive than “Standard of Care”, indirect costs would only add to the cost difference between MSCT and “Standard of Care”. This is a qualitative conclusion that can be drawn, without having to quantify the precise impact on productivity.

Outcomes/consequences

What are the incremental effects of a diagnostic protocol with MSCT relative to a standard diagnostic procedure?

Results

The economic model based on one RCT and data from literature about HRQoL after invasive procedures, showed that MSCT leads to a higher loss in QALYs: 0.0016 QALYs are lost in the MSCT as compared to 0.00056 QALYs in the “Standard of Care”. This is equivalent to about 6 hours of life in perfect health more lost in the MSCT arm than in the ICA arm.

Is the technology cost-effective compared to current procedures?

What is the incremental cost-effectiveness ratio for MSCT versus standard diagnostic procedure?

Results

Base-case results

The costs of MSCT were found to be higher than the costs of the “Standard of Care”. In addition, more QALYs were lost with MSCT than with the “Standard of Care”, although this difference (6 hours) can be considered negligible. Therefore, we conclude that for this patient population, the diagnostic strategy with MSCT is dominated by the “Standard of Care”.

Sensitivity analysis

We tested the primary results of Goldstein et al. (5) and found that both the costs of the MSCT and the “Standard of Care” diagnostic strategy are lower if the costs of ICA during the index hospitalization and the costs of late diagnostic testing and revascularizations are not included in the cost estimates. The corresponding costs per patient for both diagnostic arms in Belgium are presented in Table 7.

Table 7. Average cost of MSCT and “Standard of Care” when cost of invasive interventions is not included

	Cost per patient (€)	QALYs per patient
MSCT	347.71 (331;370)	0
Standard of care	383.26 (366;406)	0

In this case, costs of the strategy with MSCT are indeed lower than the costs of the standard of care strategy. Because in this scenario the model stops right before the decision to do an ICA is made and because no quality of life loss is assumed due to nuclear stress testing or MSCT, the number of QALYs is the same in both diagnostic arms.

Discussion

Our economic model, based on observed data from one RCT, showed that the total costs of MSCT angiography in patients at low or intermediate risk for coronary events and no documented ischemia are higher than the “Standard of Care”, defined as 3 cardiac biomarker tests (at 0, 4 and 8 hours), 2 ECGs and nuclear stress testing. The outcomes of the diagnostic strategy with MSCT as a filter for nuclear stress testing, i.e. only patients with intermediate or inconclusive MSCT test results undergo a nuclear stress test, are worse than the outcomes of the standard of care strategy. Because more

patients in the MSCT arm undergo revascularisation, and revascularisation impacts on HRQoL, this result is not surprising.

Goldstein et al. (5), however, did not reach the same conclusion, mainly because they stopped their costing procedure when the decision to do an invasive angiography was taken. Their endpoint, therefore, was an intermediate one. The relevance of it can be questioned in general but especially in this patient population. The general argument against the use of intermediate endpoints in economic evaluation is that they are not relevant for the policy maker or the patient. The policy maker is interested in how he can obtain the highest health benefit at a given cost. The patient is interested in how he can obtain the highest health benefit. The fact of reaching more or less quickly a decision to do an ICA is not relevant if eventually this has no impact on final outcomes such as LYG or QALYs gained.

The results of our economic evaluation only pertain to the diagnostic and treatment path followed by actual patients observed in the trial and to the period of observation in the trial. The advantage of this approach is that no assumptions have to be made about the future events and interventions, thereby reducing the uncertainty of the results. The disadvantage of the approach, however, is that it also introduces a level of uncertainty in the sense that it is uncertain to what extent the results would hold if larger patient populations were treated. The patient numbers in each health state were too small to reliably estimate transition probabilities and make the model more generic. For instance, none of the patients in the “Standard of Care”-arm who underwent a late ICA were revascularised. This might be a coincidence due to the small number of patients undergoing a late ICA. The RCT was not powered to detect such potential relevant differences. In real life, with very large patient numbers, the situation might be different, and some patients might undergo revascularisation if late ICA is positive. To increase the generalisability of the results, more data on the long-term consequences of both diagnostic interventions would be needed (need for revascularisation, AMI, death). Data from larger data sets would allow us to define transition probabilities and hence build a more generic model.

As far as the limited duration of the trial, and consequently the economic model is concerned, we know from the clinical literature review that the prognosis of patients who present with atypical chest pain is generally good. Early intervention in patients with CAD but no documented ischemia diagnosed by MSCT angiography does not necessarily improve long-term outcomes in these patients.

We conclude that there is no economic rationale for using MSCT angiography in low-risk patients with atypical chest pain.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT 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 following a diagnostic strategy that includes MSCT as a filter for nuclear stress testing and what types of resources are used when following a standard diagnostic protocol?
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 following a diagnostic strategy that includes MSCT as a filter for nuclear stress testing versus a standard diagnostic protocol?
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 the resources used when following a diagnostic protocol with MSCT and a standard diagnostic protocol?
E0004	Costs and economic evaluation	Indirect Costs	What is the impact of the technology on indirect costs?	Yes	What is the impact of a diagnostic strategy with MSCT 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 effects of a diagnostic protocol with MSCT relative to a standard diagnostic protocol?
E0006	Costs and economic evaluation	Is the technology cost-effective when compared to current procedures?	What is the incremental cost-effectiveness ratio?	Yes	What is the incremental cost-effectiveness ratio of MSCT angiography compared to a "standard of care" diagnostic procedure that includes nuclear stress testing and 3 cardiac biomaker assays?

Appendix 1: Search strategy for literature review

Embase

Date of search: 06.12.2007

Number of hits: 51 (for entire strategy)

No.	Query	Results	Date
#1.	'computer assisted tomography'/exp	278,698	06 Dec 2007
#2.	'multidetector computed tomography'/exp	2,507	06 Dec 2007
#3.	'angiocardiology'/exp	48,033	06 Dec 2007
#4.	coronary AND ('angiography'/exp OR 'angiography')	52,937	06 Dec 2007
#5.	'computed tomographic angiography'/exp	3,011	06 Dec 2007
#6.	computed AND tomographic AND ('angiography'/exp OR 'angiography')	5,125	06 Dec 2007
#7.	coronary AND ('artery'/exp OR arter*)	249,531	06 Dec 2007
#8.	coronary AND ('vessel'/exp OR vessel*)	47,812	06 Dec 2007
#9.	mdct* OR msct* OR multi*row* OR multi*detect* OR multi*spiral* OR multi*slice*	7,439	06 Dec 2007
#10.	((#3 AND (#7 OR #8)) OR #4)	52,937	06 Dec 2007
#11.	(#2 OR ((#1 OR #5 OR #6) AND #9))	5,779	06 Dec 2007
#12.	#10 AND #11	1,111	06 Dec 2007
#13.	'coronary artery bypass graft'/exp OR cabg OR (coron* AND by*pass)	56,110	06 Dec 2007
#14.	'calcium'/exp OR 'artery calcification'/exp OR 'calcification'/exp OR calci*	556,705	06 Dec 2007
#15.	'coronary stent'/exp OR 'drug eluting stent'/exp OR stent*	50,257	06 Dec 2007
#17.	'ischemic heart disease'/exp OR (ischemi* OR myocard* OR arteriosclero* OR ('angina'/exp AND pectoris) OR (((('chest'/exp OR thora*) AND 'pain'/exp) OR 'thorax pain'/exp) OR atherom* OR coronar* OR stenosis) OR 'coronary artery disease'/exp	859,250	06 Dec 2007
#18.	#13 OR #14 OR #15 OR #17	1,383,870	06 Dec 2007
#19.	#12 AND #18	1,111	06 Dec 2007
#22.	'clinical trial'/exp OR 'clinical trial' OR random* OR rct* OR cohort* OR 'cohort analysis'/exp	1,052,965	06 Dec 2007
#23.	'diagnostic accuracy'/exp OR 'sensitivity and specificity'/exp	185,276	06 Dec 2007
#24.	#22 AND #23	26,805	06 Dec 2007
#25.	#19 AND #24	86	06 Dec 2007
#26.	#25 AND [humans]/lim AND [2000-2007]/py	85	06 Dec 2007
#27.	((('fiscal:ab,ti,de OR financial:ab,ti,de OR finance:ab,ti,de OR funding:ab,ti,de) OR ((variable*:ab,ti,de OR unit*:ab,ti,de OR estimate*:ab,ti,de) AND cost*:ab,ti,de) OR ('socioeconomics'/ OR 'cost benefit analysis'/ OR 'cost effectiveness analysis'/ OR 'cost of illness'/ OR 'cost control'/ OR 'economic aspect'/ OR 'financial management'/ OR 'health care cost'/ OR 'health care financing'/ OR 'health economics'/ OR 'hospital cost'/ OR 'cost minimization analysis'/)) OR ('economic evaluation'/ OR 'cost'/ OR 'reimbursement'/ OR 'cost utility analysis'/ OR 'drug cost'/ OR 'energy cost'/ OR 'hospital cost'/ OR 'hospital running cost'/ OR 'biomedical technology assessment'/))	608,245	06 Dec 2007
#28.	#26 AND #27	8	06 Dec 2007

#29. #28 AND [embase]/lim AND [2000-2007]/py AND [2000-2007]/py	8	06 Dec 2007
#30. #19 AND #27	59	06 Dec 2007
#31. #30 AND [humans]/lim AND [embase]/lim AND [2000-2007]/py	51	06 Dec 2007

CRD: HTA(13), NHS-EED(7), DARE (6)

Date of search: 06.12.2007

Number of hits: 26 (for entire strategy) HTA(13), NHS-EED(7), DARE (6)

Search history

Search Matching records

# 1 MSCTA OR MSCT OR MDCT OR MDCTA	14
# 2 CT OR "compute tomograph*" OR CTA	843
# 3 multi*detector* OR multi*row* OR multi*slice* OR multi*spiral*	24
# 4 #2 AND #3	24
# 5 #4 OR #1	31
# 6 #4 OR #1 RESTRICT YR 2000 2007	26

Econlit(Ovid)

Date of search: 06.12.2007

Coverage period database: 1969 to November 2007

Number of hits: 15 (for entire strategy)

#	Search History	Results
1	(MSCT\$ or MDCT\$ or CTA or multi\$slice\$ or multi\$detector\$ or multi\$row\$ or multi\$spiral\$).mp. [mp=heading words, abstract, title, country as subject]	15

Ovid MEDLINE(R)

Date of search: 30.11.2007

Coverage period database: 1950-November, week 2, 2007.

Number of hits: 215 (for entire strategy)

- 1 exp tomography, x-ray computed/ or multi-slice computed tomography.mp. (191800)
- 2 (mdct or msct or ((multi\$row\$ or multi\$detect\$ or multi\$spiral\$ or multi\$slice\$) and ((compute\$ and tomograph) or ct))).mp. (3695)
- 3 1 or 2 (192051)
- 4 exp coronary angiography/ (32102)
- 5 (coronar\$ and angiograp\$).mp. (49714)

- 6 exp coronary vessels/ (38297)
- 7 (coronar\$ and (vessel\$ or arter\$)).mp. (173752)
- 8 exp myocardial ischemia/ (273633)
- 9 (myocard\$ or ischemi\$ or arteriosclero\$ or angina pectoris or chest pain or atherom\$).mp. (579065)
- 10 (calcium or calcinos\$ or calcification\$).mp. (412807)
- 11 exp stents/ or stent\$.mp. (37840)
- 12 exp coronary artery bypass/ or cabg.mp. or by\$pass.mp. (86191)
- 13 exp coronary stenosis/ or stenosis\$.mp. (115427)
- 14 or/3-6 (269182)
- 15 or/7-12 (1109590)
- 16 3 and 14 and 15 (20105)
- 17 limit 16 to humans (19529)
- 18 limit 17 to yr="2000 - 2007" (9908)
- 19 clinical trial\$.mp. or clinical trial.pt. or random\$.mp. or RCT.mp. or exp *cohort studies/ (858660)
- 20 exp *"sensitivity and specificity"/ (1496)
- 21 18 and 19 and 20 (0)
- 22 (price\$ or pricing\$).mp. (14212)
- 23 ec.fs. (235528)
- 24 cost\$.tw. (200524)
- 25 exp "Costs and Cost Analysis"/ (133793)
- 26 22 or 23 or 24 or 25 (396432)
- 27 21 and 26 (0)
- 28 18 and 26 (215)

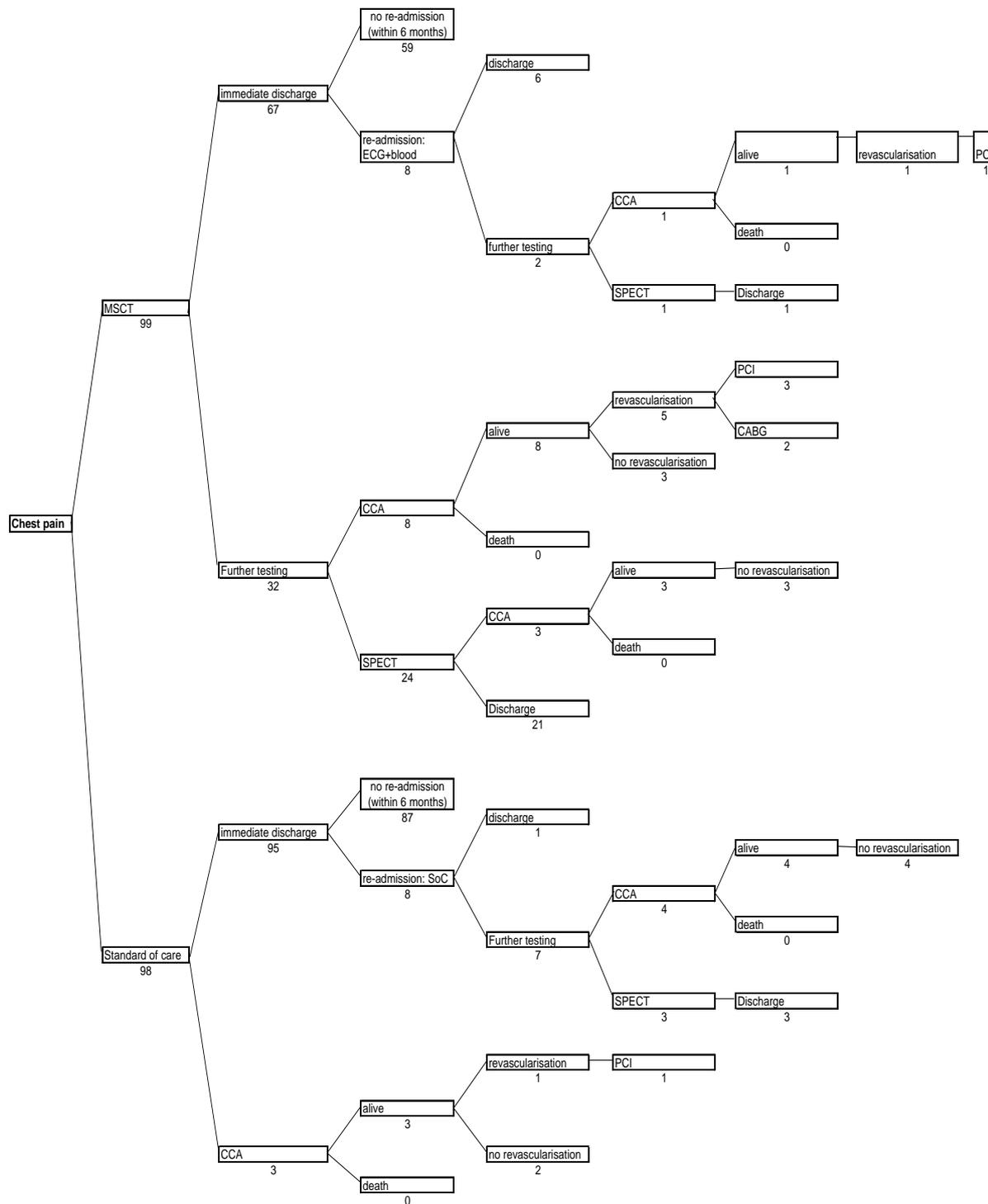
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

<p>Date of search: 3.12.2007 Coverage period database: November 30, 2007 Number of hits: 0/4/59</p>
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- 1 (MDCT or MSCT or ((multi\$row\$ or multi\$detect\$ or multi\$spiral\$ or multi\$slice\$) and ((compute\$ and tomograph\$) or CT)).tw. (416)
- 2 (coronar\$ and angiograp\$).tw. (758)
- 3 (coronar\$ and (vessel\$ or arter\$)).tw. (3097)
- 4 2 or 3 (3246)
- 5 (myocard\$ or ischemi\$ or arteriosclero\$ or angina pectoris or chest pain or atherom\$).tw. (7296)
- 6 (calcium or calcinos\$ or calcification\$).tw. (5231)
- 7 stent\$.tw. (1453)
- 8 (CABG or by\$pass).tw. (1923)
- 9 stenosis\$.tw. (1728)
- 10 5 or 6 or 7 or 8 or 9 (15777)
- 11 1 and 4 and 10 (59)**

- 12 (clinical trial\$ or random\$ or RCT or cohort).tw. (25267)
- 13 11 and 12 (4)
- 14 (price\$ or pricing).tw. (543)
- 15 econom\$.tw. (3696)
- 16 cost\$.tw. (7752)
- 17 14 or 15 or 16 (10872)**
- 18 11 and 17 (4)**

Appendix 2: Structure of the decision tree for the economic model



Ethics

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Introduction

Ethical analysis within an HTA aims at analyzing the moral questions raised by the technology itself and by the implications of implementing or not implementing a health technology, as well as ethical issues that are inherent in the HTA process. In principle, this may be accomplished by systematically eliciting the values which are placed on a technology and its implementation by different stakeholders. This can be done either through conducting own primary research or through literature and document analysis. These different values are then analyzed 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 consider only the use or non-use of one technology in a specific setting from the ethical viewpoint, but rather accompany and advise the whole HTA process from prioritizing topics, defining research questions, choosing the methodology to summarizing results and drawing conclusions.

Once the importance of ethical analyses is admitted, the question of how to integrate ethics in HTA reports raises. In fact, ethical evaluations can be conducted very differently depending on the resources in the HTA organization, the technology in question and, above all, the research methodology.

Ethical analysis is built into the HTA Core Model on two levels. The more general inclusion of ethical considerations in the whole HTA process is presented in the chapter "Introduction". It emphasizes the somewhat different nature of ethics as a domain within HTA. The results of more practical reflection on the consequences and implications of the use of a technology are recorded in the assessment elements.

In the ethical analysis domain of the Core Model the assessment elements represent a standard set of questions, based primarily on the work of Hofmann (2005). This set – that has been also used for the MSCT coronary angiography – is suggested to guide value analysis referring to the technology and its implementation as well as discussing compatibility and congruency with prevalent societal moral values.

Methodology

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. Primary sources, e.g. information from patients and patient organizations, is vital for

assessments, but for time and resource reasons there was no opportunity to elicit primary information (e.g. patients perspectives on outcomes used in clinical trials) for this assessment.

Literature searches

A three-part literature search was applied:

1. Database searches for articles relating to multi-slice computed tomography (MSCT) coronary angiography. The searches were performed in three well known databases: PubMed, EMBASE and Euroethics. A search strategy constructed combining the words “ethics” (AND) “MSCT coronary angiography” yielded not a single paper. Consequently the present ethical analysis has been carried out relying on information provided in „general“ articles on MSCT coronary angiography.
2. Additional references were taken from reference lists of retrieved publications as well as from recently published journal articles.
3. Additional searches combining the general search terminology for “multislice CT” supplied by Finohta with terms derived from the ethical issues were performed in the unfiltered PubMed database as well as the PubMed “bioethics subset”. The additional searches are documented in Appendix 1.

Information selection

The studies that have been considered eligible are those published in English language from January 2002 to December 2007, in which there was an empirical assessment of MSCT coronary angiography with at least 16 slices in patients presenting mild and stable symptoms of chest pain with low or moderate risk for coronary artery disease.

Assessment of study / publication quality

No assessment of methodological study quality was undertaken.

Assessment elements

Principal questions about the ethical aspects of technology

Is MSCT coronary angiography a new, innovative mode of care, an "add on" to a standard mode of care, intended as a triage to other tests or a replacement of a standard?

Results

MSCT coronary angiography is emerging as a non-invasive clinically reliable diagnostic tool to detect coronary stenosis. It is an imaging method that generates a three-dimensional image of the coronary vessels from a series of two-dimensional computerized tomography images. The scan, equipped with 8-, 10-, 16-, 32-, or 64-slices, consists of a CT angiography of the thorax characterized by a retrospective synchronization technique based on the ECG, that is recorded simultaneously with the MSCT scan. The vascular enhancement is obtained by means of administration of a bolus of iodinated contrast material (CM), through an antecubital vein (100-140

ml of CM 300-400 mgI/ml at 4 ml/s). The development of MSCT is still in progress. It started with 4-slice CT. Currently 320-slice CT is being introduced. Imaging of cardiac vessels is clinically challenging due to continuous motion during cardiac cycle.

The anatomical visualization provided by MSCT differs from the one of conventional coronary angiography because it is not a simple “lumenology“ but it is capable to provide information on the vessel wall and on neighbouring structures, which until now can only be achieved by invasive techniques such as intravascular ultrasound or optical coherence tomography.

A preliminary note with regard to its clinical applications is that patients who have risk factors for coronary artery disease (CAD), stable symptoms of chest pain, no previous history of myocardial infarction, and ECG not pointing at acute ischemia are usually referred to exercise ECG. Positive finding in exercise ECG is usually sufficient to determine the diagnosis of coronary artery disease and initiation of medication. If the diagnosis remains open, MSCT is proposed as a non-invasive alternative to invasive coronary angiography. Negative findings on MSCT obviate invasive angiography, but those with positive MSCT findings (i.e., significant stenosis) would still need to be confirmed by invasive coronary angiography.

Further, with regard to patients where exercise ECG is not feasible e.g. patients unable to move their legs, MSCT can be a replacement test to determine the diagnosis of and treatment for CAD. Finally, MSCT has also been proposed as an additional non-invasive cardiac test that may be complementary to other non-invasive tests currently available (e.g., stress tests) (Hoffmann et al. 2006).

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

Results

MSCT coronary angiography seems not to impose challenges to religious, cultural or moral convictions, or to the beliefs of some groups, or to changes of current social arrangements.

What can be the hidden or unintended consequences of MSCT coronary angiography and its applications for different stakeholders?

Results

The intended use (in whom, how, with what benefits / harms to expect) of MSCT coronary angiography is specified by manufacturers and through documents (safety data, trial results) required and accepted as prerequisite for market approval by regulatory bodies (see technology description). Nevertheless, MSCT requires a higher exposure of the patient to ionizing radiation than with other radiological techniques. Although the long-term risks associated with radiation exposure from single examinations are relatively low, it raises a concern about repetitive and unnecessary use on patients and risks for radiologists and other staff. Unnecessary exposure of tissue (as part of a necessary examination) can also be a consequence of widespread use of the method. So far the optimal candidates are not yet determined. It may even be regarded as a

possibility to rule out cardiac disease in people with no clinical symptoms as has occurred with the marketing of whole body MRI.

The information provided by MSCT is not limited to the coronary vessels. Anomalies in other structures (e.g. pulmonary nodules, aortic anomalies, etc) can be incidentally discovered in an MSCT. These findings may prompt a diagnostic chain including more invasive manoeuvres. This is especially problematic for patients as well as for the treating physicians since the clinical relevance of such incidental findings without clinical manifestations can be unclear.

The use of MSCT for triple rule-out of myocardial infarction, pulmonary embolism and aortic dissection in patients with chest pain at the emergency department has also been suggested, which would widen the use of MSCT and place it close to emergency units.

Questions about effectiveness and accuracy

What are the proper end-points for assessment of MSCT coronary angiography and how should they be investigated?

Results

The ultimate end-point for diagnostic tests is patient outcome and societal efficacy (Fryback and Thornbury 1990). If there are no studies showing results on this area, assessment of therapeutic efficacy in combination with results on diagnostic thinking efficacy and diagnostic accuracy efficacy may be acceptable. The latter are especially suitable in situations where the technology is intended to completely replace an existing one taking its place in a well established diagnostic chain. In contrary, in such situations where the technology adds to an existing diagnostic chain, its value should be assessed relying on patient outcomes. It is also important to notice that “even high-quality diagnostic imaging may be non-contributory in certain instances, and radiology of lesser quality may be of great value in others.” Therefore it is important that if such lower level efficacy is accepted as end-points, further study has to be promoted in order to find evidence on the “hard endpoints” (Fryback and Thornbury 1990:89).

Are the accuracy measures of MSCT coronary angiography decided and balanced on a transparent and acceptable way?

Results

See accuracy domain.

Autonomy

Does the implementation or use of MSCT coronary angiography challenge patient autonomy?

Results

It is important to highlight that MSCT adds to diagnostic imaging technologies as ECG, invasive coronary angiography (ICA), etc. Typical patients present mild and stable symptoms of chest pain and are not suffering from an acute pathology – therefore, their decision making capabilities should not be (severely) compromised. Still, some characteristics of MSCT in comparison to other investigative technologies may be difficult to understand. Consequently, patients must be thoroughly informed of them in order to make an informed decision for or against the use of MSCT.

The main points to consider are:

1. MSCT is a non-invasive procedure but compared to ICA, it does not offer the possibility to treat the discovered pathologies in the same session (interventions of myocardial revascularization).
2. The effective radiation dose of a contrast enhanced cardiac CT scan is 5-20 mSv. In comparison, diagnostic ICA has a mean effective radiation dose of 2–7 mSv. Consequently, patients must be informed that – even if still extremely low – the risk of inducing cancer is higher for MSCT coronary angiography than that for ICA. See more details in the safety domain.
3. The vascular enhancement is obtained by means of administration of a bolus of iodinated contrast material, through an antecubital vein. Iodinated contrast media are generally safe. Nevertheless, they can occasionally cause allergic reactions and renal failure. Allergic reactions are usually mild but may progress to life-threatening situations (0,02-0,04%) (See safety domain). Contrast-induced nephropathy (CIN) is a serious complication of the use of iodinated contrast media and it is especially related to some pre-existing risk factors.
4. Drugs are used in many procedures in order to achieve better image quality: β -blockers to lower the heart rate and short-acting nitro-glycerine preparations to improve the visualisation of coronary artery lumen. Special attention must be given to patients for which β -blockers and nitrates are contraindicated. It is to be evaluated whether the potential serious adverse effects caused by these drugs could interfere with their decision making capabilities.
5. Besides the injection of iodinated contrast material, the breath hold is also necessary to visualize the coronary artery lumen. Therefore, it is important to prepare the patient for the sensations experienced from the injection of the contrast agent and to perform repeated test breath holds. This is an element that could interfere with their autonomy.
6. MSCT may produce incidental findings from adjacent structures, which still do not explain the symptoms which lead to the diagnostic work-up of coronary artery disease (CAD), e.g. a pulmonary or a lymph node. Such an incidental finding may put the patient and the clinician in the need of clarifying its clinical relevancy. Diagnostic work-up of incidental findings may require invasive investigations. This is problematic since incidental findings do not relate to the original motive of consultation but often force the patient into an additional diagnostic work-up with all its consequences. In such situations, there is a risk of “labelling” the patient with an additional condition until the incidental finding have been clarified (e.g. if a node is incidentally found a patient may get a “cancer” label until it has been ruled-out, with all its implications for the patient such as anxiety, etc.). When something truly pathological is found, (e.g. in fact malignant cells), the patient would be referred to aggressive treatments. The problem is that the true meaning of incidental findings is not known. In the worst case, someone would have been treated for something

which in his/her lifetime would have not had any clinical relevancy had it been not incidentally discovered. This is a problem that has been discussed e.g. in the context of prostate cancer screening.

7. Finally, it should be considered that even if patients are provided with sufficient information on procedures, possible benefits and risks, they may not be able to understand the information in the situation they are in. On the other hand, informed consent can be used in radiology, not only to respect and promote patients autonomy, but also for other less patient oriented purposes, such as judicial, economic and responsibility-reduction (Hofmann et al 2008).

Is MSCT coronary angiography used for patients/people that are especially vulnerable?

Results

In this context “vulnerability” means that patients in the situation of treatment have not the full capabilities of decision-making, due to critical illness, age (children) or mental disturbances.

In this assessment we concentrate on the use of the MSCT angiography in patients presenting mild and stable symptoms of chest pain with low or moderate risk for coronary artery disease, so there is no direct issue on decision-making capabilities concerning consenting to this treatment. In cardiac MSCT, radiation is targeted at chest, therefore subjecting females to high organ doses of the breast, The lifetime excessive risk of breast and lung cancer for girls and young women after single MSCT is much higher than for individuals aged 55 years or older, recently estimated at 1.75-5.5% after a single scan (see Safety domain).

Can MSCT coronary angiography entail special challenges/risk that the patient/person needs to be informed of?

Results

For a description of formal requirements of an “informed consent” procedure see legal domain. Risk assessment is particularly complex because certain negative outcomes are apparent immediately whereas others are manifest only years later (such as the statistical risk of cancer induction). With regard to immediate risks, MSCT is absolutely contraindicated in subjects who have hypersensitivity to iodinated contrast agent. Relative contraindications exist with respect to conditions that are known to limit diagnostic image quality: history of allergies or allergic reactions to other medications; renal insufficiency (serum creatinine level of > 1.5 mg/dL), congestive heart failure, history of thromboembolic disorders, multiple myeloma, hyperthyroidism, pheochromocytoma, atrial fibrillation, inability to perform breath hold for 15 s (Hoffmann et al. 2006).

Further, sublingual administration of short-acting nitro-glycerine (2 tablets, equal to 0.8 mg) immediately before a scan has been used sometime to improve the visualization of the coronary artery lumen. Current data on the effects of nitro-glycerine in MSCT coronary angiography are not available. Case-control studies are warranted to establish the benefits of the use of nitro-glycerine, which include improved visualization of the coronary arteries, especially in women, subjects with diabetes, and subjects with hypertension. Nitro-glycerine is contraindicated in subjects taking phosphodiesterase inhibitors, such as sildenafil or vardenafil, and in subjects with hypersensitivity

to organic nitrates, increased intracranial pressure, symptomatic hypotension, and severe anaemia (Hoffmann et al., 2006).

Risks that manifest only later are very difficult to assess. To estimate the practically immeasurable risk of cancer from low-level radiation, various mathematical models are required to extrapolate dose-risk data from highly exposed populations. Currently, a linear relationship between dose and risk is used in the risk model for low-level exposures. For example, for any individual aged 55 years or older, lifetime risk of developing cancer after a single MSCT cardiac exam is low and ,generally, is considered to be below 1.0 %. In the study of Coles it is estimated that the risk of inducing a fatal cancer is 0,07 % for MSCT and 0,02 % for invasive coronary angiography (ICA) (See safety domain). Recently published data (Abdulla et al. 2007, Dewey et al., 2008) suggest that the effective radiation dose of MSCT coronary angiography is higher in the examination of women than of men, mainly as a result of the fact that the radiosensitive female breast is in the x-ray path. Therefore, it can be observed that the radiation risk of MSCT coronary angiography would need to be weighed especially in female patient (See safety domain).

Finally, there are some risks related to diagnostic accuracy of MSCT coronary angiography. In general, the studies have demonstrated the high degree of accuracy of 64-slice MSCT in the detection of significant stenosis in smaller coronary artery segments and side branches. A high negative predictive value suggests that there is a good probability that 64-slice MDCT rules out the presence of hemodynamically significant CAD. The probability is high, but it is not complete. Consequently, there may be risks in terms of delay of diagnostic decisions making. See more details in the safety domain.

Does the implementation of MSCT challenge or change professional values, ethics or traditional roles?

Results

The anatomy of the heart and coronary arteries does not constitute a main backbone of the knowledge and daily clinical practice of the radiologist. Cardiac imaging has been until now remitted to cardiologists, and it is still not a daily radiology practice. So, radiologists and cardiologists must try working together in order to ensure safe and effective care. Furthermore, there is potential for conflicts derived from the expansion of one of the professions and reduction of the other. This can be for example problematic in fee-for-service systems, where the two professions would compete for the same patients. In the worst case, this can lead to unnecessary duplication of investigations.

Another challenge is posed by the problem of “self-referral”, when the referring physician has a financial interest in the health care institution he or she is referring to. In the context of MSCT the problem of self-referral is especially of concern within the cardiologist profession, when the cardiologist is at the same time the owner of the CT equipment. A few approaches have been suggested to safe-guard against unethical self-referral: a) the use of evidence-based guidelines; b) physician and laboratory credentialing; c) periodic case conferences; d) oversight/reviews processes; e) consultation with other providers; f) full disclosure/ transparency and discussions with patients regarding alternatives, including an option for a second opinion (Wann et al., 2007)

Human dignity

Does the implementation or use of MSCT coronary angiography affect human dignity?

Results

Human dignity is affected if a certain technology exposes patients to unbalanced risks. MSCT coronary angiography seems not to impose such challenges.

Human integrity

Does the implementation or use of MSCT coronary angiography affect human integrity?

Results

MSCT coronary angiography seems not to impose such challenges.

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 MSCT coronary angiography? Who will balance the risks and benefits in practice and how?

Results

Harms of MSCT have been discussed in more detail in other assessment elements within this domain. On the other hand, MSCT has several benefits for patients over conventional angiography, including: volumetric acquisition, which permits visualization of the anatomy from multiple angles and in multiple planes after a single acquisition; improved visualization of soft tissues and other adjacent anatomic structures; less invasiveness and thus fewer complications. Benefits of CT angiography over magnetic resonance imaging (MRI) include wider availability of scanners, higher spatial resolution, absence of flow-related phenomena that may distort MRI images, and the capability to visualize calcification and metallic implants such as endovascular stents or stent grafts. In summary, there is currently no other diagnostic method that could totally replace it in the diagnostic chain or could as such be nominated as the reference test (see accuracy domain). Nevertheless, not everyone agree that the net health outcome is favourable. For example, the Technology Evaluation Center (2005) – an American center that has pioneered the development of scientific criteria for assessing medical technologies through comprehensive reviews of clinical evidence – thinks that “The evidence is insufficient to determine whether the use of MSCT improves net health outcome or whether it is as beneficial as any established alternatives”. In general, major doubts are related to the fact that all potential clinical applications are uncertain and data on cost-effectiveness are scarce.

Can MSCT coronary angiography 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?

Results

Besides patients, the relevant stakeholder groups that may directly or indirectly be affected from the use of MSCT coronary angiography are care providers, the professionals, payers, and manufacturers. Due to time limitations, in this assessment we concentrate on the benefits of some relevant stakeholder groups.

Providers (hospitals etc.)

Implementing MSCT coronary angiography requires extra financial resources. How high these extra costs are, and by whom they are borne, depends on the regulation of the hospital financing systems in the respective countries. In fee-for-service systems MSCT might offer the chance for extra profits for care providers, whereas in systems with flat rate hospital financing the provision of MSCT might impose extra costs on health care providers (e. g. Kearney et al., 2006). Taking into consideration the high value that is put on technically advanced, “cutting edge” medical technology by patients as well as by society it is attractive for providers to advertise that patients receive the most innovative care in their facilities.

Professionals

MSCT coronary angiography is a very recent technique, so it is difficult to know if MSCT is accepted by physicians. We report here the opinions of professionals' associations.

According to American College of Cardiology Foundation (ACCF) (Hendel et al., 2006) MSCT is appropriate

- for the detection of coronary artery disease (CAD) in symptomatic patients and evaluation of chest pain syndrome in intermediate pre-test probability of CAD and if ECG is uninterpretable or the patient is unable to exercise;
- for the evaluation of intracardiac structures, if there is a suspicion of coronary anomalies;
- for assessing cardiac morphology in complex congenital heart diseases, including anomalies of coronary circulation, great vessels, and cardiac chambers and valves; and in patients with new onset heart failure to assess aetiology.

The American Heart Association (AHA) published a scientific statement on assessment of CAD by cardiac computed tomography in October 2006 (Budoff et al., 2006). The recommendations specific to MSCT include:

- CT coronary angiography is appropriate for the assessment of obstructive disease in symptomatic patients;
- Imaging of patients for monitoring stent placement cannot be recommended;
- There is no data on the prognostic implications of MSCT for non-calcified plaque (NCP) assessment; therefore, its use for this purpose is not recommended.

Manufacturers

MSCT scanners were introduced in 1998 with the release of 4-slice CT scanners. In 2004, 64-slice CT scanners were introduced. All major CT manufacturers offer 64-slice CT scanners, such as: AADCO Medical Inc, Analogic Corp, Anexa Corp, Beekley Corp, Composites Horizons Inc, Covidien (formerly Tyco Healthcare Mallinckrodt), DeJarnette Research Systems Inc, Eizo Nanao, Technologies Inc, Gamma Medica-Ideas, GE Healthcare, Hitachi Medical Systems America Inc, Imaging3 Inc, MEDRAD Inc, Mercury Computer Systems Inc, NeuroLogica Corp, Philips Medical

Systems, R2 Technology Inc, a Hologic Co, Siemens Medical Solutions USA Inc, Thinking Systems Corp, Toshiba America Medical Systems, Unfors. MSCT has revived CT technology that was on the edge of being out-phased.

Justice and Equity

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

Results

This question warrants 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, it is unclear whether benefits outweigh harms in the context of MSCT coronary angiography. Up to now, an evidence-based decision whether a particular patient or a group of patients „need“ or does not need MSCT coronary angiography can not be made. Taking into consideration the widespread development of MSCT coronary angiography the question arises whether for the implementation of MSCT fairness, justness and solidarity could also mean to efficiently protect patients in whom harm might outweigh possible benefits from receiving the technology.

If future evidence will be able to determine a patient group that is clearly in need of MSCT, economic considerations might impair the principles of fairness, justness and solidarity. The price of MSCT is generally high (see also costs and economic evaluation domain). Who carries these extra costs 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 for the technology.

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

Results

The main moral problems around MSCT result from two types of considerations: the first is that it is unclear whether net harm or net benefit will result from its implementation. 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.

The second consideration is that MSCT involves risks related to radiation exposure. To assess technologies with this type of risks in some countries, practical guidelines have been published.

Rights

Does the implementation or use of MSCT coronary angiography affect the realisation of basic human rights?

Results

In the context of health care mainly 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 MSCT in different patient groups has been discussed in other assessment elements (benefits and harms for patients) as well as aspects of distributive justice. Using MSCT coronary angiography seems not to affect the realisation of basic human rights. Nevertheless, recently published data (Dewey et al., 2008) suggest that the effective radiation dose of MSCT coronary angiography is higher in the examination of women than men, mainly as a result of the fact that the radiosensitive female breast is in the x-ray path. This aspect should also be taken into consideration when establishing criteria/guidelines for the implementation of MSCT (to avoid favouring men, since they are less exposed to this specific risk and to avoid unnecessary risks for women).

Legislation

Is legislation and regulation to use MSCT coronary angiography fair and adequate?

Results

European Union directions do not include specific instructions for issues directly linked to MSCT technology, such as authorisation, patents/licenses, price and reimbursement regulations, product safety, guarantee and liability. They regulate the market of health technologies in a more general fashion (i.e. through CE certification for new technologies). See also legal domain.

The use of ionising radiation in medical imaging procedures is regulated by European law. There are quality criteria for operation, exposure, radiation protection and image quality (Bongartz, et Al. 2004). In many countries though, the fulfilment of the European law is lacking. From ethical point of view, the legislation seems not to be fully efficient to protect the best interest of the patients at the moment.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research Question in the context of DES
F0001	Ethical aspects	Principal questions about the ethical aspects of technology	Is the technology a new, innovative mode of care, an "add on" to a standard mode of care or a replacement of a standard?	Yes	Is MSCT coronary angiography a new, innovative mode of care, an "add on" to a standard mode of care or a 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?	No	Can MSCT coronary angiography 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	What can be the hidden or unintended consequences of MSCT coronary angiography and its applications for different stakeholders?
F0017	Ethical aspects	Questions about effectiveness and accuracy	What are the proper end-points for assessment and how should they be investigated?	Yes	What are the proper end-points for assessment of MSCT coronary angiography and how should they be investigated?
F0018	Ethical aspects	Questions about effectiveness and accuracy	Are the accuracy measures decided and balanced on a transparent and acceptable way?	Yes	Are the accuracy measures of MSCT coronary angiography decided and balanced on a transparent and acceptable way?
F0004	Ethical aspects	Autonomy	Does the implementation or use of the technology challenge patient autonomy?	(Yes)	Does the implementation or use of MSCT coronary angiography challenge patient autonomy?
F0005	Ethical aspects	Autonomy	Is the technology used for patients/people that are especially vulnerable?	No	Is MSCT coronary angiography used for patients/people that are especially vulnerable?
F0006	Ethical aspects	Autonomy	Can the technology entail special challenges/risk that the patient/person needs to be informed of?	Yes	Can MSCT coronary angiography entail special challenges/risk that the patient/person needs to be informed of?
F0007	Ethical aspects	Autonomy	Does the implementation challenge or change professional values, ethics or traditional roles?	Yes	Does the implementation of MSCT challenge or change professional values, ethics or traditional roles?
F0008	Ethical aspects	Human Dignity	Does the implementation or use of the technology affect human	No	Does the implementation or use of MSCT coronary

			dignity?		angiography affect human dignity?
F0009	Ethical aspects	Human integrity	Does the implementation or use of the technology affect human integrity?	No	Does the implementation or use of MSCT coronary angiography 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 MSCT coronary angiography? Who will balance the risks and benefits in practice and how?
F0011	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 MSCT coronary angiography 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?
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 MSCT coronary angiography on justice in the health care system? (Are principles of fairness, justness and solidarity respected?)
F0013	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 MSCT coronary angiography treated in the health care sector?
F0014	Ethical aspects	Rights	Does the implementation or use of the technology affect the realisation of basic human rights?	No	Does the implementation or use of MSCT coronary angiography affect the realisation of basic human rights?
F0016	Ethical aspects	Legislation	Is legislation and regulation to use the technology fair and adequate?		Is legislation and regulation to use MSCT coronary angiography fair and adequate?

Appendix 1: Additional search strategies

Search **within** 1250 Hits from Pubmed, using the basic search on MSCT:

Connector	Field	Terminology	Results
	Keywords	Informed Consent	21
OR	Keywords	Jurisprudence	22
OR	All non-indexed text fields	ethic* OR moral* OR justice OR autonomy OR beneficence OR beneficence	22
OR	All non-indexed text fields	{burden*benefit ratio } OR {burden benefit ratio } OR {fact value distinction*} OR {facts and values} OR {patient preference*} OR {valule based} OR {value judgement*} OR {norm*} OR {normative} OR {non-malfeasance} OR {nonmalfeasance}	180
OR	All non-indexed text fields	{benefit AND harm} OR {technology-driven} OR {technology driven} OR {normative effective*}	180
OR	All non-indexed text fields	{fairness} OR {equity} OR {access AND care}	180
OR	All non-indexed text fields	{innovation*} OR {triage*}	211
OR	All non-indexed text fields	{cultural} OR {conviction*} OR {religion*} OR {belief} OR {ideology} OR {philosophy}	211
OR	All non-indexed text fields	{family} OR {famili*} OR {relatives} OR {stigma} OR {label} OR {adverse event*} OR {adverse effect*}	237
OR	All non-indexed text fields	{autonomy} OR {informed consent} OR {false positiv*} OR {false negativ*} OR {counseling}	259
OR	All non-indexed text fields	{dignity } OR {human integrity} OR {human right*}	259
OR	All non-indexed text fields	{resource allocation} OR {solidar*} OR {fairness} OR {justness} OR {equity} OR {availability} OR {access}	283
OR	All non-indexed text fields	{legislation } OR {regulation} OR {legal*}	289

Search within the bioethics subset of PubMed:

Number	Query	Results
1	(((((("Coronary Angiography"[Mesh])) AND ((("Tomography, X-Ray Computed"[Mesh]))) OR ((angiograph* AND tomograph*))) AND ((bioethics[sb]))	36

Organisational Domain

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Introduction

The research within the organisational domain aims at finding out 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 multi-slice computed tomography (MSCT) and the objective is to assess the organizational effects of the introduction of a 64-slice-MSCT in coronary angiography compared to the conventional invasive coronary angiography as a golden standard for coronary artery disease (CAD).

MSCT can have the potential to reduce the number of invasive coronary angiographies. It can also have other possible consequences in the management pathway of CAD. Still, from an organizational point of view, the introduction of MSCT does not induce major new changes in management.

Methodology

Organisational aspects are rarely analyzed within clinical studies and HTA reports, so the analysis required several activities. A systematic review of the literature was crucial but not enough to answer the research questions of this domain. In an initial search no relevant scientific evidence was found. To complement our search, we reviewed also grey literature using a commonly used web search engine (Google) and consulted websites of manufacturers, regulatory agencies, and health technology assessment agencies. Since organisational aspects are strictly linked to their own contexts, it is useful to integrate results with the experience of local experts in this area.

Strict PICO-framing (Patient, Intervention, Control, Outcome) is often not pertinent in the issues of organisational domain, neither from the view point of data retrieval nor reporting. Organisational features of an imaging modality are not strictly linked to a particular technology or patient population. Rather, they are similar over a wider range of similar technologies (here imaging technologies using radiation) and across indications and patient populations. Rarely a device like MSCT is purchased only for the management of cardiac patients. If MSCT is available, it is used for all possible patient groups and indications. Therefore, evidence of organisational features of imaging other anatomical areas, or another cardiac conditions than coronary artery disease, may be equally relevant for this assessment. In this Core HTA we recognise the framing used in other domains. The PICO framing for organisational domain would be thus: P=patients with a suspicion of CAD and low to moderate risk for CAD; I=management pathway with MSCT; C=management pathway without MSCT; O= correctly treated patient. In some issues we use broader scope and include other issues than strictly in the PICO.

Literature search:

Published literature was obtained by searching Ovid MEDLINE, CINAHL (Cumulative Index to Nursing & Allied Health Literature), and CRD Database (DARE, NHS, EED, HTA).

Basic searches for the Core HTA on coronary MSCT have been done by information specialist Jaana Isojärvi in Finohta by utilising general terms to define the technology and disease. The search strategy is available as an appendix in the General design chapter. Additional literature searches were performed by adding domain-specific key words in the search strategy.

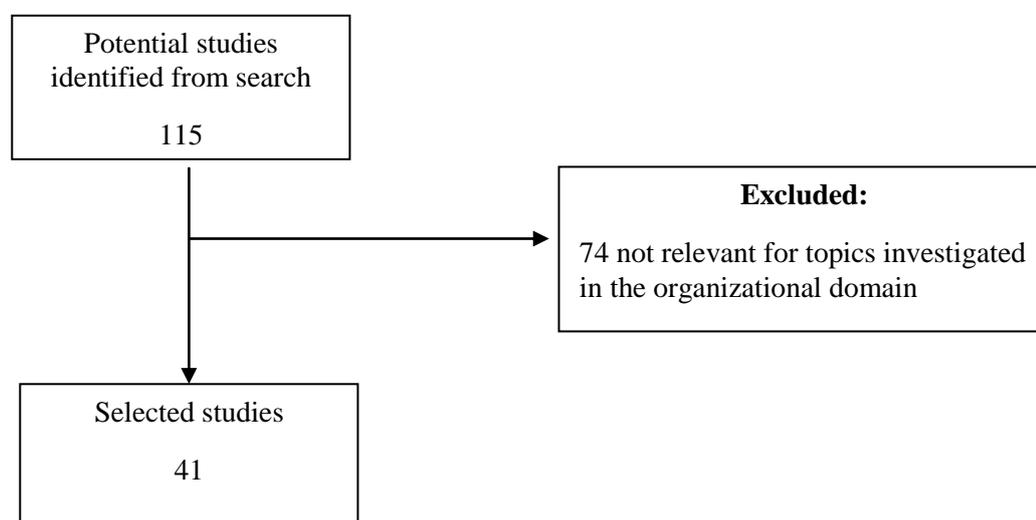
Selection criteria and method:

A study was eligible for inclusion if it met each of the following inclusion criteria:

- Included patients with coronary artery disease;
- 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.

A total of 115 studies were identified. 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 41 papers. Figure 1 shows a QUORUM flowchart¹ of study selection.

Figure 1: Selection of studies for inclusion



Quality assessment

Quality assessment criteria for clinical studies are not pertinent in the investigation of organizational aspects. We are currently not aware of suitable quality criteria for articles looking at health care organisation.

Assessment elements

Process

What kind of work flow and patient flow processes is needed when implementing MSCT?

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature. Semi-structured interviews to a clinician in staff at an Italian university hospital were performed.

Results

MSCT could have a crucial role as a diagnostic tool where findings of preliminary conventional tests (ECG, exercise ECG, stress test) show an intermediate probability of coronary artery disease (CAD) or are uninterpretable or the tests are not possible to perform. These patients could be referred to MSCT instead of directly undergoing to coronary angiography. Introduction of MSCT means an additional step in the diagnostic part of the management chain. The potential of MSCT to reliably rule out CAD could reduce the number of invasive coronary angiographies (ICA). If MSCT will replace a significant percentage of them, the ICAs will be performed only as interventional procedure and not more as a diagnostic test (5). Evidence shows that MSCT allows a faster diagnosis for CAD compared to conventional ICA. This may have a significant impact on the work flows because of the possibility to reduce length of stay, costs and work charges (2).

MSCT coronary angiography could be used also for those low risk patients in whom invasive coronary angiography is not indicated. In that group MSCT could affect the treatment or prognosis if it resulted in improved allocation of preventive medications and life style changes.

It has been also pointed out that MSCT-CA (MSCT coronary angiography) could have a potential role in the management of patients with severe CAD (Acute Coronary Syndrome - ACS). Patients with ACS and STEMI (ST-segment elevation myocardial infarction) are referred for primary PCI (percutaneous coronary intervention). If referred for thrombolysis, and this is successful, MSCT-CA could be performed to assess extent and severity of CAD which may be useful for further patient-management or prognosis. In patients with UA/NSTEMI (unstable angina/non-ST-segment elevation myocardial infarction) MSCT-CA could be used to assess the extent and severity of CAD which may be useful for clinical decision making for medical treatment, PCI or CABG (coronary artery bypass grafting) (3).

The introduction of MSCT changes hospitals work flows as new departments are involved in the patients' management path. The MSCT scan must be analyzed by a radiologists; this implies new procedures which involve a close collaboration between cardiologist and radiologist. The resulting interdisciplinary cooperation will likely affect current practice patterns.

MSCT coronary angiography practices require a more customized examination with more cooperation between referring clinician and reading physician than in traditional CT practices and in angiography laboratories where a smaller number of examinations are performed by a physician

who is directly involved in clinical decision making. It will also impact on current models of training (4).

Comment

MSCT has the potential to change the organization of treatment of several diseases, including CAD which is the focus of this Core HTA. The rapid technical development of CT requires constant adaptation of acquisition protocols.

What kind of patient and relative involvement in treatment or care has to be mobilized when implementing MSCT?

Methods

Analysis of selected studies extracted from the literature review. We found additional information by internet search of grey literature.

Results

A study (6) shows that performing MSCT scan requires a collaborative behaviour and cooperation with the patient. Before the scanning process, the patients should perform multiple breath-holding exercises. They improve the capability of the patients to hold breath for longer times and make them familiar with the scanning procedure resulting in decreased anxiety.

The patients should refrain from eating four hours before the procedure; otherwise, they may have nausea after the contrast material administration. In addition, they must void their bladder before the examination to prevent increased heart rates associated with anxiety over a full bladder.

Compliance of the patients is best achieved when all information about the procedure, the risks and advantages of the test is given to them. A clear explanation of the technology and brief clinical information is essential. Possible heat sensation caused by the injection of the contrast medium is worth to be explained, as well as the side effects caused by the premedication be used. The patient should know how important it is for the image quality to stay still throughout the image acquisition.

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

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature.

Results

The available data support the notion that MSCT coronary angiography may be an alternative to invasive coronary angiography in symptomatic patients with a low to intermediate likelihood of having coronary artery disease. The introduction of MSCT can have the potential to reduce the number of invasive coronary angiography. This could improve the health care process in terms of quality.

We have considered the Joint Commission's, an organization committed in improving quality and safety in health care, definition for quality (7). Performing MSCT scan doesn't affect all the dimensions of quality. The Appropriateness and effectiveness dimensions could be most likely affected by the introduction of MSCT, because it allows avoiding unnecessary examination. Moreover, MSCT can affect the Efficiency dimension because it allows a decrease of hospital stay, procedure time and costs. Finally, performing MSCT scan may improve the safety: the contrast complications and radiation exposure related to MSCT (8) seem to be smaller than the rare but severe risks from an invasive procedure (death, stroke, bleeding, infection). See Table 1

Table 1

	CT coronary angiography	Invasive coronary angiography
Hospital stay	1 hour	Usually at least 4 to 5 hours, including the time before the procedure and bed rest after procedure
Procedure time	<5 minutes	Roughly 1 hour including patient preparation time but not including recovery area stay
Cost	Around \$2,000	Around \$10,000 or more
Risk of procedure	Very small: related to contrast medium and radiation exposure	Small: anyway there is a probability of death, stroke, bleeding, infection and contrast related complications

Table adapted from Schussler J.M. et al. Computed tomographic coronary angiography: experience at Baylor University Medical Center/Baylor Jack and Jane Hamilton Heart and Vascular Hospital. BUMC PROCEEDINGS 2005;18:228-233.

What kind of staff, training and other human resources is required when using MSCT?

Methods

Analysis of selected studies extracted from the literature review. Systematic review using Pubmed with the following keywords: "Ct angiography" and "training". Additional information was found by internet search of grey literature.

Results

Computed tomography (CT) is one of the most rapidly evolving techniques for assessing cardiovascular anatomy. Multidisciplinary teams of specialists from radiology, cardiovascular medicine, and cardiothoracic surgery are best suited to lead the clinical and scientific evaluation of non-invasive coronary imaging with MSCT. The complex nature of the imaging devices and anatomy as well as the rapidly advancing uses of these modalities requires the trainee to be introduced to this modality (9).

Since MSCT coronary angiography is a multidisciplinary procedure it may best

be interpreted jointly by cardiologists and radiologists. Some radiologists may lack the clinical experience to interpret the findings in the setting of a specific clinical scenario. Conversely, cardiologists may be unfamiliar with the interpretation of CT images, especially if extra-cardiac structures are included despite a field of view limited to the heart (10). The appropriate approach to MSCT coronary angiography would be a team that includes multiple skills of individuals trained in radiology and in cardiology (11).

Table 1 General training needs and strengths of cardiologists and radiologists

	CARDIOLOGIST	RADIOLOGIST
NEEDS	<ul style="list-style-type: none"> ▪ Increased knowledge of CT operations, CT components, CT physics, and image formation ▪ Radiation safety review ▪ Understanding of contrast kinetics, administration and safety 	<ul style="list-style-type: none"> ▪ Concepts of gating CT cardiovascular studies and retrospective reconstruction ▪ Review of 3D cardiac anatomy ▪ Understanding of clinical implications of technology (i.e. where it fits in)
STRENGTHS	<ul style="list-style-type: none"> ▪ Understanding of cardiovascular testing modalities in clinical practice ▪ Detailed knowledge of how cardiac findings will impact care ▪ Understanding 3D cardiac structure 	<ul style="list-style-type: none"> ▪ Understanding of CT operation, image formation, and radiation safety ▪ Comfort with review of CT images and workstations ▪ Understanding of contrast administration and dynamics

Table adapted from Tony De France, Cardiac CT angiography training picks up steam. Diagnostic Imaging, 2006 (12) .

The American College of Cardiology (ACC)/AHA developed recommendations for attaining and maintaining the minimum experience, cognitive and technical skills necessary for the competent performance of cardiovascular CT (13). They are:

- General
 - o Physics of CT and radiation generation and exposure
 - o Scanning principles and scanning modes for noncontrast- and contrast-enhanced vascular imaging
 - o Principles of intravenous iodinated contrast administration for safe and optimal vascular imaging
 - o Prevention, recognition, and treatment of adverse reactions to iodinated contrast
 - o Prevention, recognition, and treatment of adverse reactions to β -blockers' administration
 - o Principles of image post-processing and appropriate applications
- Cardiovascular anatomy, physiology and pathophysiology
- Cardiovascular pathology
- Symptoms and signs of diseases related to cardiovascular pathology

For appropriate use of this technology, it is possible to define three levels of expertise (9). All cardiology fellows must attain at least the first level of expertise.

- Level 1: This entails understanding the basic principles, indications, applications, and technical limitations of CT and the interrelation of this technique with other diagnostic methods. During cumulative 4-week training, a trainee should be actively involved in Cardiovascular Computed Tomography (CCT) interpretation under the direction of a qualified (preferably Level 3-trained) physician-mentor. There should be a mentored interpretative experience of at least 50 cases. This level will not qualify a trainee to perform CT or to interpret CT independently.
- Level 2 is defined as the minimum recommended training for a person to independently perform and interpret CCT. To accomplish this, he/she should devote an additional 1 month, interpreting a minimum of 150 contrast studies. The non-contrast and contrast studies may be evaluated in the same patients. Of these, at least 35 cases should be performed under appropriate supervision. Competence at this level implies that the person is sufficiently experienced to interpret the CT examination accurately and independently. Continued exposure to special CT procedures such as hybrid studies with nuclear imaging and integration of images into electrophysiologic procedures is appropriate during Level 2 training.
- Level 3 of expertise would enable the trainee to direct a CT laboratory. A total of 6 months of training is required, with an additional 6 months experience that can be obtained concurrently with training in other imaging modalities. To attain Level 3, candidates should be involved with interpretation of at least 100 non-contrast and 300 contrast CCT examinations. For at least 100 of these cases, the candidate must be physically present and be involved in the acquisition and interpretation of the case.

As is true for many other procedures, a minimum number of cases are necessary to ensure continued proficiency in quality of care. Maintenance of vascular CT expertise requires both ongoing Continuing Medical Education (CME) and regular performance and interpretation of cardiovascular CT examinations. Physicians should periodically attend postgraduate courses and workshops that focus on cardiovascular CT, especially those that emphasize new and evolving techniques and developments. In addition, physicians should seek to compare the quality, completeness, and results of their own examinations with those presented at scientific meetings and in professional publications. A minimum of 50 examinations per year is recommended in order to maintain the physician's skills (13).

The British Cardiovascular Society working group highlighted that there is undoubtedly a need for consultants to be trained in non-invasive cardiac imaging (5). Professional groups need to develop new training curricula that might be open to trainees from both cardiology and radiology backgrounds. Since the complementary expertise cardiology and radiology teams bring to Cardiovascular magnetic resonance (CMR) and Multi detector computed tomography (MDCT), it was recommended, wherever possible and depending on local circumstances, that there should be training available to both cardiology and radiology physicians who aim to become experts in the field, and this should be organised through close collaboration between cardiology and radiology consultants who have specialist expertise in these modalities. The training curriculum for specialist registrars (SpRs) is being revised to increase the profile of non-invasive imaging. Regional training schemes are clearly defined and focused imaging modules throughout SpR training. A final module in cardiac imaging is recommended for all those who have decided this is their career path and should be offered in all units training SpRs. A curriculum for such a final year is considered essential, but should be flexible and regularly reviewed in what is likely to be an area of rapid change (5).

What kind of co-ordination and communication of activities does MSCT require?

Methods

Analysis of selected studies extracted from the literature review. We found additional information by internet search of grey literature.

Results

Performing and evaluating coronary MSCT will need the implementation of an integrated process involving different units of the organization, clinical actors and stakeholders. An integrated process of care presumes the standardization of coordination and communication mechanisms among the different actors. MSCT involves different medical specialties, imaging scientists, and manufacturers of MSCT systems. Multidisciplinary teams of specialists from radiology, cardiovascular medicine, and cardiothoracic surgery are best suited to lead the clinical and scientific evaluation of non-invasive coronary imaging with MSCT. Interdisciplinary cooperation will likely affect current practice patterns. Modern practices require a more customized examination with more cooperation between referring clinician and reading physician than in traditional CT practices and in angiography laboratories (4).

It is also important taking into account the communication with patients. 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 be submitted the procedure or not. It is crucial that they understand the whole procedure and the risks involved, as well as all the other options available to be cured. Patient should be provided with a full information set; the entire clinical path should be explained as well as the single procedure of MSCT diagnosis.

According to the Council Directive 97/43/Euratom, 30 June 1997, informed consent needs to be received for performing MSCT (14). The format designed by several institutions from different countries entitles 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 (linked to the contrast agent administration, radiation exposure and β -blocker administration) and also the possible other diagnostic options and their risks. Radiologists should cooperate with cardiologists in order to avoid any possible lack of information as well as any possible replication or conflicting information. The referring physician should also inform the patients about the test procedure in order to increase the patients' comfort and reduce anxiety.

The manufactures of MSCT have developed a protocol regarding patient preparation. The protocol is available on the Internet (15).

Structure

What consequences will MSCT have for decentralisation or centralisation?

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature.

Results

Literature search did not allow to focus the analysis on patients with suspected CAD and low to moderate risk of the disease. Rather, information on organizational impact of the introduction of MSCT is referred generally. The choice between centralization or decentralization is dependent on the specific uses of MSCT.

According to Loewinger and Budoff (16), MSCT could be utilized in emergency department setting as a possible 'triple rule-out' for myocardial infarction, pulmonary embolus, and aortic dissection, improving efficiency and efficacy. In terms of centralization/decentralization decision it could mean that MSCT facilities are suitable for hospitals with emergency department. Also Hoffman et al 2006 (17) underlined that MSCT-based detection of significant coronary stenoses, in emergency department setting, has the potential to decrease the number of unnecessary hospital admissions, without reducing appropriate admission rates. Another study (18) suggests the use of MSCT also in risk assessment of CAD, so that primary preventive strategies could be performed more selectively and cost-effectively.

Probably, at the moment, there is no clear trade-off between centralization and decentralization, Clinical (epidemiological and medical) reasons could suggest a wider extension of the use of MSCT. According to Gani et al (19), there has been increasing interest in MSCT recently, especially with the advent of 64-slice CT. On the other hand, costs constraint has prevented a wide distribution of MSCT in hospitals, even if Gaylord asserts that the costs would be affordable even to smaller hospitals (20). However there is still no quantitative evidence on the amount and on the value of these potential savings that decentralization could bring (21).

What kinds of investments are needed (materials or premises) when introducing MSCT?

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature. A semi-structured interview with purchase managers was performed.

Results

The standard technological equipment to perform coronary CTA (Computed Tomography Angiography) should comprise (22):

<i>Specification</i>	<i>64-Slice scanner</i>
Tube current (mAs)	500–950
Tube voltage (kV)	120–140
Tube rotation time (ms)	375–500
Temporal resolution (ms)	165–210
Slice collimation (mm)	0.5–0.6
Scan length (s)	6–13
Contrast dose (mL)	50–80

Table adapted from 23 Udo Hoffmann et al. Coronary CT Angiography. J Nucl Med 2006; 47:797–806.

Some authors have stated that the equipment standards required for MSCT coronary angiography comprise a multi-detector CT scanner capable of creating a minimum of 64 slices per gantry rotation (24) include:

- ECG: Interface with CT system for the acquisition - prospective and retrospective reconstruction
- Angiographic automatic injector for contrast media
 - Dual-syringe
 - Automatic, programmable
 - Interface with CT system for the synchronisation between bolus injection and scan
 - High pressure infusion line, 18-20G cannula
 - Maximum flow $\geq 5\text{ml/sec}$
- Workstation for reconstruction (6,23,8,25,26,27,28,29,30,31,32,33,34,35,36)
 - The type of software depends on the kind of analysis needed to perform: MIP, MPR, VR (Volume Rendering), CPR (Curve Planar reformation), advanced tools of vascular tests, calcium scoring, etc.
 - DICOM
- Availability of the RIS-PACS system for the electronic recording of the test scans and image reconstruction. The system is strongly advised although it does not determine the performance of the technology.

Introduction of MSCT coronary angiography in a health care organization involves high costs related to the purchasing investment and to the utilization in the routinely clinical practice. Decisions have differed by organizations, depending on their clinical goals, business strategy, local market conditions, PACS readiness and progressiveness of their cardiac programs. In the table below, a list of costs have been reported in order to measure the economic impact of MSCT introduction.

Item	Cost (€)
Purchase of the MSCT scanner*	1,100,000
Construction and installation**	40,000
Radiation screen*	200,000
Electricity requirements per month**	1,200
Maintenance and service per year**	100,000

* Information collected through semi structured interview with purchase managers

**Data from³⁰ (Marc Dewey et al. Noninvasive Detection of Coronary Artery Stenoses with Multislice Computed Tomography or Magnetic Resonance Imaging. *Ann Intern Med.* 2006;145:407-415).

The cost of personnel varies in different countries according to the national labour market regulations. It is very unlikely that any centre could justify the installation of a dedicated cardiac CT scanner. The provision of MSCT would be best achieved through shared cardiac time on scanners being used for current (albeit expanding) radiological indications. It is essential though that all new CT scanner installations have a cardiac capability (5).

In conclusion, introducing MSCT into clinical practice means significant investment that only few centres can afford. The costs of the investment will influence the diffusion of the technology in the health care system. The decision on acquisition of MSCT means not only costs and resource utilization but also cost savings connected to the avoidable coronary angiographies. The invasive coronary angiographies could be performed only as an interventional procedures and not anymore as a diagnostic test. Moreover, the health benefits of patients have to be considered, in terms of infarctions and other heart diseases avoided, which could lead into indirect cost savings.

What is the likely budget impact of MSCT for the payers (e.g. government)

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature.

Results

The introduction of a new technology raises the question about whether and how the service provided with the new technology will be reimbursed. The decisions in terms of reimbursement rates have a direct effect on the choices of the providers, in particular on the composition (kinds and amount) of the provided services.

In the United States Medicare's national coverage policy for computed tomography (CT) does not specifically address coverage of coronary CT angiography. The policy states that CT scans may be covered as diagnostic services if reasonable and necessary, and if performed on an FDA-approved model of CT equipment. The local Medicare contractors have discretion to determine the specific circumstances under which a CT scan is covered. In March 12, 2008 the Centers for Medicare and Medicaid Services (CMS) has decided to make no change to section 220.1 of the National Coverage Determination Manual titled "Computed Tomography" (Pub. 100-3, 220.1). It has been decided that no national coverage determination on the use of cardiac computed tomography angiography for

coronary artery disease is appropriate at this time and that coverage should be determined by local contractors through the local coverage determination process or case-by-case adjudication (37).

A group of radiologists and lab directors, the American College of Radiology (ACR), vendors, and contrast developers are lobbying CMS to change the CPT codes, arguing that such low reimbursement doesn't reflect the reality of expense and time in using the technology. CT angiographies have largely replaced catheter angiography so it is not only cost-effective in time and materials, it also exposes patients to less risk. But as Medicare rates do not reflect the work involved, hospitals are losing money. A traditional catheterized angiogram costs \$5,000 (38), while a CTA costs \$299 plus Carrier Priced (in Hospital Outpatient Department) (39).

Similarly the Italian system does not have a specific fee for MSCT angiography utilization. These examinations are covered in an outpatient basis. In Lazio region the fee linked to Thorax TC with or without "contrast" is applied. Below there are the ICD 9 CM codes reported for the service and the related fees for three Italian regions.

Code ICD 9 CM	Service
87.41.1	Computed axial tomography of thorax with or without contrast. [lung, thorax aorta, airtube, oesophagus, sternum]
88.42.1	Aortography (digital angiography of aorta and of aortic arch)

Region	Fee	
	<i>87.41.1</i>	<i>88.42.1</i>
Lazio	€ 137,89	€ 283.28
Emilia Romagna	€ 137,90	€ 283.30
Veneto	€ 210.75	€ 288.95

A German study has shown that in a high-referral centre (30 coronary MSCT examinations per day), already with the present reimbursement rate (€ 124,43 – reimbursement minus contrast agent costs) the break-even point could be reached after a short period of 23 months. However, since such high referral rates are rather unlikely, MSCT coronary angiography would only be profitable in a reasonable time frame after investment if reimbursement were three-times higher than with the present outpatient reimbursement system in Germany⁴⁰.

Management

What management problems and opportunities are attached to the new technology?

What management problems and opportunities are attached to MSCT?

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature.

Results

The use of MSCT requires multidisciplinary clinical skill to manage MSCT use in clinical practice and multidisciplinary competences for assessment activities (clinical, economical and

organizational. Close collaboration of multiple disciplines can be challenging to implement, but on the other hand it may lead to important synergies.

Who decides which patients are to undergo MSCT coronary angiography and on what basis?

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature.

Results

Decision about testing with MSCT requires the competence of different professionals in different situations:

- Patient could be admitted from emergency department (ED) by the ED physician who needs MSCT to rapidly evaluate patients for life-threatening illnesses. MSCT may allow safer and earlier discharges of patients with chest pain compared to traditional rule-out protocol (41).
- Patient could undergo a MSCT exam because the GP asks it for him. In that case the exam will be scheduled.
- Patient could undergo a MSCT in a pre-operative phase because the cardiologist needs more information for surgery. MSCT may provide useful information for the selection of potential candidates for percutaneous mitral annuloplasty (29).

Culture

How is MSCT accepted?

Methods

Analysis of selected studies extracted from the literature review and a search in Google.

Results

Recently, multislice computed tomography (MSCT) has gained increasing acceptance within the cardiology and radiology communities as a valuable, diagnostic imaging tool (43). Technological advances have facilitated its rapid expansion. MSCT and other noninvasive coronary artery imaging procedures are becoming important gatekeepers, helping to select patients for invasive cardiac catheterization.

Traditional stress-test approach is time-consuming, expensive, and is often not feasible or equivocal. MSCT coronary angiography has been shown to be helpful in patient management: it has reduced the time to make the diagnosis by about 75% and also reduced the costs (46). A cultural resistance by practitioners is possible as the new technology requires new and more specialized skills. Anthony N. DeMaria, MD, MACC, editor-in-chief of the *Journal of the American College of Cardiology*, also sees "a blurring of the boundaries between disciplines, and perhaps the emergence of new types of cardiologists, a cardiovascular imaging specialist."

While mean direct costs of MSCT are lower than in the alternative modalities, administrators often, incorrectly, predict decreasing revenues. This could lead to a resistance from the management to the

introduction of MSCT. Although the mean payment for MSCT coronary angiography was substantially lower than other tests, the experience of South Carolina Heart Center, Columbia, SC shows an increase in revenue, considering direct and indirect costs including physician time, ancillary labor, and equipment costs.

Additionally, unlike traditional angiography, MSCT does not require any procedural time for the cardiologist. The available work units from the shift of angiography modalities result in increased capacities for interventional time, making additional revenues (43) possible. A study of Goldstein et al. outlined that, compared with patients treated according to the standard of care, diagnoses were significantly shorter and cheaper in the MSCT coronary angiography group.

Outcomes: Multislice CTA vs standard of care (43)

Outcome	Multislice CTA	Standard of care	p
Diagnostic time (h)	3.4	15.0	<0.001
Cost (\$)	1586	1872	<0.001
Reevaluations over 6 months (%)	2	7	0.10

Schonenberger et al. have prospectively compared patient acceptance of the two new non-invasive tests (MSCT and MRI) with that of the invasive reference standard – conventional invasive coronary angiography (ICA) – in a consecutive cohort of 111 patients with suspected coronary artery disease. MSCT was considered significantly more comfortable than MRI ($p < 0.001$), and the patients indicated a significantly lower degree of helplessness during MSCT than during angiography ($p < 0.001$). Patients were significantly more concerned prior to the tests about conventional coronary angiography than about either of the two non-invasive tests ($p < 0.001$). Overall satisfaction was higher for MSCT than for MRI and ICA. From the patients' perspective the main reasons for the high acceptance of MSCT are: it is uncomplicated, non-invasive, painless, and fast. This subjective assessment is corroborated by the comparison of the total duration of the different tests, which shows that MSCT was significantly faster (17.4 min) than both MRI (58.4 min, $p < 0.001$) and ICA (58.0 min, excluding time necessary for interventions, $p < 0.001$) (47).

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

Methods

Analysis of selected studies extracted from the literature review. Additional information was found by internet search of grey literature.

Results

Government agencies are important drivers in the development of biomedical imaging through support of biomedical research and through policy guidance on the ethical responsibilities of investigators, especially those using animals and human participants in research. Government support of research in biomedical imaging is critical to the growth of new knowledge and to new applications of this knowledge in the clinical arena.

Scientific and professional societies are also essential partners in the expansion of biomedical imaging and in developing and delivering imaging innovations. The education of members, scientists, and health care providers from other disciplines, as well as patients and the public, about new imaging technologies and their benefits for biomedical research and clinical medicine is a responsibility best shouldered by scientific and professional societies.

Academic institutions are the home of most basic and translational research in biomedical imaging. They are also the training ground for the next generation of basic and clinical imaging scientists.

Corporations are also important stakeholders and innovators in the area of biomedical imaging. Companies developing imaging probes—radiopharmaceuticals, optical agents, and magnetic resonance (MR), ultrasound (US), and CT contrast agents—and imaging device companies have invested millions of dollars in a research infrastructure to support the development process.

Foundations and voluntary health agencies also play important roles in the development of new technologies and therapies to benefit patients and the public. They can help facilitate two-way communication between researchers and those who use the products and services created through research, including clinicians and patients.

The ultimate stakeholders in biomedical imaging are, of course, *patients and the public*. Because of rapidly emerging advances in molecular biology, genetics, and proteomics, it is likely that health care as we know it today will be transformed tomorrow into a more effective and efficient process that benefits patients and all of society. Biomedical imaging will play a major role in bringing this potential to fruition (48).

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 Multi Slices Computed Tomography (MSCT) (64 slices) procedures, and what kind of changes or consequences can their use cause in the organisation. The investigation of MSCT's impact on management and structure of organization was very complex, because organisational aspects are rarely analysed within clinical studies and HTA reports and hence little evidence is available in the scientific literature. The traditional systematic literature review was not completely suitable to obtain full information on organisational aspects, and it was necessary to complement the search with analysis of other sources.

The impact of MSCT-64 on clinical pathways of patients could lead into reducing length of stay and avoiding repeated evaluations for recurrent chest pain. Introducing MSCT-64 into practice does not lead into completely novel organisational challenges. Comparative imaging systems have been introduced before. The incremental features of MSCT require some changes though, mainly in the co-operation across disciplines.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT Or Comment (if regarded as a not relevant issue in this context)
G0001	Organisational aspects	Process	What kind of work flow and patient flow processes are needed?	yes	What kind of work flow and patient flow processes is needed when implementing MSCT?
G0002	Organisational aspects	Process	What kind of changes can the implementation of a new technology generate in the quality of care?	yes	What kind of changes can the implementation of MSCT generate in the quality of care?
G0003	Organisational aspects	Process	What kind of patient and relative involvement in treatment or care has to be mobilized?	yes	What kind of patient and relative involvement in treatment or care has to be mobilized when implementing MSCT?
G0004	Organisational	Process	What kind of staff, training and other human resources is required?	yes	What kind of staff, training and other human resources is required when using MSCT?
G0005	Organisational aspects	Process	What kind of co-operation and communication of activities have to be mobilised?	yes	What kind of co-ordination and communication of activities does MSCT require?
G0006	Organisational aspects	Structure	What consequences the implementation of the new technology will have in respect of decentralisation or centralisation?	yes	What consequences MSCT will have in respect of decentralisation or centralisation?
G0007	Organisational aspects	Structure	What kinds of investments are needed (material or premises)?	yes	What kinds of investments are needed (materials or premises) when introducing MSCT?
G0008	Organisational aspects	Structure	What is the likely budget impact of the implementation of the technology for the payers (e.g. government)?	yes	What is the likely budget impact of MSCT for the payers (e.g. government)?
G0009	Organisational aspects	Management	What management problems and opportunities are attached to the new technology?	yes	What management problems and opportunities are attached to MSCT?
G0010	Organisational aspects	Management	Who decides which patients are to undergo a treatment and on what basis?	yes	Who decides which patients are to undergo MSCT coronary angiography and on what basis?
G0011	Organisational aspects	Culture	How is the new technology accepted?	yes	How is MSCT accepted?
G0012	Organisational aspects	Culture	How will the other interest groups of the new technology be taken into account in the planning / implementation of the new technology?	yes	How will the other interest groups of MSCT be taken into account in the planning / implementation of MSCT?

Appendix 1 Search strategy

Database: Ovid MEDLINE(R) <1950 to October Week 4 2007>

Search date: 1.11.2007

Search strategy:

-
- 1 Tomography, X-Ray Computed/ (186962)
 - 2 ("64-slice\$" or "multislice\$" or MSCT or "multi-detect\$" or "multidetected\$" or MDCT).tw. (5665)
 - 3 1 or 2 (189092)
 - 4 exp delivery of health care/ (531676)
 - 5 work process\$.tw. (483)
 - 6 4 or 5 (532064)
 - 7 3 and 6 (1230)
 - 8 (centraliz\$ or centralis\$ or decentralis\$ or decentraliz\$).tw. or centralized hospital services/ (9607)
 - 9 3 and 8 (50)
 - 10 health manpower/ or exp health personnel/ (282682)
 - 11 (staff\$ or personnel\$).tw. (100334)
 - 12 (competenc\$ or skill or skills).tw. (81951)
 - 13 Staff Development/ (4742)
 - 14 10 or 11 or 12 or 13 (423765)
 - 15 3 and 14 (827)
 - 16 exp communication/ (249186)
 - 17 cooperative behavior/ (12335)
 - 18 (collaborat\$ or cooperat\$).tw. (103369)
 - 19 16 or 17 or 18 (354762)
 - 20 3 and 19 (1435)
 - 21 Investments/ (6084)
 - 22 exp Health Care Costs/ (29701)
 - 23 (cost or costs or fees or fee or finance or finances or financial).tw. (200579)
 - 24 Resource Allocation/ (5795)
 - 25 21 or 23 or 24 (210775)
 - 26 3 and 25 (2364)
 - 27 Leadership/ (17810)
 - 28 (leadership\$ or management\$).tw. (413474)
 - 29 27 or 28 (424183)
 - 30 3 and 29 (12558)
 - 31 2 and 6 (65)
 - 32 2 and 8 (2)
 - 33 2 and 14 (26)
 - 34 2 and 19 (34)
 - 35 2 and 25 (125)
 - 36 2 and 29 (257)
 - 37 31 or 32 or 33 or 34 or 35 or 36 (449)

Social aspects

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Introduction

The social domain takes the patient as a point of departure in its analysis of the manifold social implications of health technology. The focus of the domain is on the diverse social arenas where the patient lives and acts during the period of sickness and treatment. Application of diagnostic technologies possibly interacts with peoples social arenas in two ways: first, directly by application of the technology and second, by generating a diagnosis and the patient having to face its consequences.

In the context with MSCT, direct social interactions may concern the way and circumstances of accessing an examination, preparatory procedures, perceptions (such as pain, discomfort, anxiety) during the procedure, aftercare and cost related aspects. Social interactions related to the diagnosis of Coronary Heart Disease (CHD) could involve communication and support needs before and after the examination, self perception and future life planning as a patient with a chronic disease. While the direct interactions are specific for MSCT the diagnosis related aspects also refer to other diagnostic modalities for CHD. Therefore, the emphasis in the following chapter is laid more on the direct interactions.

This study analyzed views of patients and professionals on social aspects utilizing and adapting assessment elements defined in the Social aspects of the EUnetHTA Core Model. Data were taken from a systematic overview of the (very limited amount) of published literature as well as from interviews conducted with patients and professionals concerning their views on the implementation of 64-slice computerized tomography coronary angiography also called as multi-slice computer tomography (MSCT) in the diagnostics of coronary artery disease.

Methodology

Literature overview

Literature searches concerning social aspects of MSCT coronary angiography were performed in Medline, Premedline (via the PubMed system), the CRD databases (HTA, EED, DARE) and the ISI Social Sciences Citation Index (SSCI). In the first step the basic search for literature on MSCT supplied by Finohta (see Appendix 1 in General design chapter) was adapted for the use in PubMed. A search run on June 4th 2008 yielded 1275 hits. These hits were transferred to a Reference Manager database and in the second step combined with search terms for articles dealing with social aspects of MSCT. Search terms were deducted from the issues formulated in the core model (both models developed during the project were

used). The combination yielded 376 potentially relevant citations in the Pubmed, 1 in the SSCI and 22 in the CRD databases. The abstracts of these 399 citations were in the third step further screened using the following inclusion criteria:

- Abstracts mentioning patients reception/ perceptions/ reactions of MSCT
- Abstracts mentioning outcomes of MSCT, other than accuracy parameters
- Abstracts mentioning information and communication issues concerning MSCT
- Abstracts mentioning the integration of MSCT in processes of care from the perspective of patients, relatives or clinicians

Exclusion criteria were:

- Indications for MSCT use other than coronary artery disease (CAD)
- Studies and reviews reporting accuracy results only

After elimination of duplicates the abstract screening left 34 potentially relevant publications (Appendix 2). These were ordered in full-text. Full-text screening of the 34 abstracts led to exclusion of 32 publications. A table with excluded studies and reasons for exclusion can be found in the Appendix 3.

Two studies, one prospective case series (Schroeder et al., 2004) and one comparative patient survey (Schoenenberger et al., 2007) fulfilled the inclusion criteria. Relevant information on study design and results were extracted. (Tables are found in Appendix 4).

Interview studies

Individual semi-structured interviews on patients and professionals were conducted. The interview themes were prepared on the basis of the pre-defined social and psychological topics and issues in the Core Model. The issues included questions such as the following:

- what kind of changes can the use of the technology produce to patients' social relations?
- what kind of reactions can the use of the technology give rise to in patients?
- what kind of consequences can the use of the technology produce to patients' self-perception?
- how does the information gained from the diagnostic study influence patient's psychological and social well being?

The patients were asked to describe their views for three different timeframes: before the intervention, during the intervention and after the intervention.

Patients that had been examined by MSCT during February-March 2008 in the Turku University Central Hospital (TUCH) were asked for informed consent by their physician. Eleven patients consented, and seven of them were finally available for interviews (patient characteristics see table 1). In addition, we interviewed three cardiologists who refer patients to MSCT coronary angiography in Turku, two from TUCH and one from a private clinic Pulssi.

Table 1: Patient characteristics in the interview study

Patient Number	Gender, occupational status, age
1	Male, pensioner, 68
2	Male, pensioner, 68
3	Male, pensioner, age not given
4	Male, pensioner, 72
5	Male, in working life, 37
6	Female, in working life, 52
7	Female, unemployed, working parttime, age not given

One researcher (JK) interviewed all patients at their homes and two researchers (TI and JK) the professionals, one guiding the discussions and the other taking notes during the sessions. All interviews were recorded, then transcribed to written texts and summarized into English (Appendices 5 and 7).

The study was financed by the Finnish Office for Health Technology Assessment (Finohta) within the National Development Centre for Welfare and Health (STAKES).

Assessment elements

Major life areas

In which social areas of the patients may the use of the MSCT generate change?

Results

Interview studies: Patient expressed concern over the influence of the diagnosis (results from the MSCT examination) and its consequences (e.g. bypass surgery) on everyday life (patients 2 and 6) and on the ability to work and thereby the economical situation (patients 6,7,8). This perception was shared also by the experts, who state that a diagnosis of CAD will have multiple consequences (e.g. need for treatment, rehabilitation) for the future life of the patients (experts 1,2,3).

Literature review: no information.

Who are the significant others that are involved in the use of MSCT coronary angiography in addition to the patient?

Results

Interview studies: Other persons than the patient, namely spouses and/or friends are involved in the use of the technology in that way that patients seek their mental support (calm down fear, insecurity and uneasiness) before the examination, awaiting the diagnosis (patients 1,2,3,4,5,7).

Literature review: no information.

What kind of support and resources are needed or might be released as MSCT is put to use?

Methods

Questions asked in the interview studies:

- Did you have to make some special arrangements in your daily life because of the upcoming diagnosis?
- Did you need to mobilize some special resources (e.g. money, time) for the diagnosis? How long did it take?
- Did you need any kind of psychological, social or practical support before the diagnosis?
- Did you need any support during your stay at the hospital, when the diagnostic testing was done?
- Have you needed to make some special rearrangements in your daily life after the diagnosis?
- Have you needed any kind of support?
- Have you needed to mobilize some special resources as a consequence of the diagnosis?

Results

Interview studies: Before MSCT the patients did not need any support (patient 6) or they had talked about the upcoming MSCT examination with their spouse or the nearest ones (patients 1,2,3,4,5,7). The financial resources needed were 493 € at the private clinic (patient 1), or normal health care costs (22 € - patients 2,3,4,5,6,7) at the city hospital. The patients also needed to spend some time (range 30 minutes to 2 hours) for the investigation and stay at the hospital. The patients needed no support during the MSCT.

After the intervention the patients had various paths depending on the result of the MSCT. Some patients had another consultation with their doctor and changes in medication (patient 1) or were sent to further investigations (patients 2,3,4). One patient will have bypass surgery, and would need support after the operation (patient 2). Some patients returned to their regular life, because nothing serious was found (patients 5,6,7). The waiting time for the results was mentioned by three patients (5,6,7) as a period of uneasiness, although these waiting times seem to differ in length. This point is also mentioned by one of the experts (1) as an aspect that patients have to be prepared for.

While the patients did not report needing social support after the MSCT, experts mention that the diagnosis of coronary artery disease (CAD) triggers the need for support by e.g. support groups (expert 2) or rehabilitation measures (expert 3).

Literature review: In the comparative study of patient acceptance of MSCT, MRI or angiography for the diagnosis of suspected CAD (with every patient undergoing all three examinations) patient-perceived degree of concern before the examination was measured on a 1-5 point Likert-Scale (1=none to 5=very high). Before MSCT and MRI the measured degree of concern was $1,51 \pm 0,85$ or $1,64 \pm 0,93$ (mean \pm SD), which was significantly lower than before angiography ($2,75 \pm 1,23$) (Schoenenberger et al., 2007). In the same study, 63 out of 111 patients pointed out the “fastness” of the examination as an advantage of MSCT over MRI or angiography.

What kinds of changes does the use of MSCT coronary angiography generate in the patient's role?

Results

Literature review: no information.

Interview studies: Nothing special or discussions with spouse or friends. Experts (2,3) pointed out that after the MSCT diagnosis (which either confirms or excludes coronary artery disease, CAD) it will be possible for most patients to keep up or resume his or her normal activities. CAD is considered a treatable disease, which still allows the patients to continue in their working life. On the other hand they mentioned that in a minority of cases a CAD diagnosis as a result of MSCT lead to the perception that retirement would be adequate – although stress tests are normal and the disease is adequately treated (expert 3).

What kind of changes does the implementation and use of MSCT coronary angiography mean for the patients physical and psychological functioning?

Methods

Questions asked in interview studies:

- Did the diagnosis produce any harm for you?
- Was the diagnosis necessary for you? Benefits? Adverse effects?

Results

Interview studies: During the MSCT the patients reported pain (patients 2, 3), and a hot wave (patients 3,5,7). After the examination two patients (4,6) felt exhausted or not well. One patient reported no adverse effects. All patients reported that the MCST was necessary for them, because the results changed their care or medication (patients 1,2,3,4,6), or because nothing was found and it released them from their worries (5,7).

Literature review: In the comparative study of MSCT, MRI and angiography patients reported very little pain during the MSCT examination (maximum experienced pain $0,9 \pm 4,5$ (mean \pm SD) on 1-100 VAS). The respective values for MRI ($5,2 \pm 1,6$) and angiography ($24,6 \pm 23,4$) were much higher ($p < 0,001$). 11% of all patients pointed out “painlessness” as one advantage

of MSCT over MRI and angiography. Also, comfort during the test (measured on a 1-5 point Likert-Scale 1=best, 5=worst) was perceived better for MSCT ($1,49 \pm 0,64$) compared to MRI ($1,75 \pm 0,81$) ($p > 0,001$). The perceived degree of helplessness was lower during MSCT ($1,19 \pm 0,48$) than during MRI ($1,39 \pm 0,89$) or angiography ($1,52 \pm 0,86$) ($p < 0,001$ for comparison MSCT – angiography).

Overall satisfaction on a five-point Likert-Scale was also highest for MSCT ($1,32 \pm 0,51$) compared to MRI ($1,58 \pm 0,89$) and angiography ($1,46 \pm 0,61$), although the differences were not statistically significant (Schoenenberger, 2007).

In a consecutive case series with 455 ± 166 days of follow-up between 92% and 98% of patients with low or intermediate probability of coronary artery disease (CAD) examined with MSCT as the first-line investigation were satisfied or very satisfied with the procedure in the Cardiac imaging outpatient clinic. Slightly better values (98% and 96% satisfaction) were found in the groups of patients, where CAD was excluded or no severe stenoses were detected. Clinical condition and quality of life were also improved or equal in all patients of these groups. In the groups with pathological findings or uninterpretable images the clinical condition at follow-up was deteriorated in 4% and 10% of patients and the quality of life was reported worse by 2% and 10% of patients at follow-up. Statements on the patient's social roles were not given in the publication (Schroeder, 2005).

Individual

How do patients and important others react and act upon MSCT coronary angiography?

Methods

Questions asked in interview studies:

- What kind of consequences did the upcoming diagnosis have on your psyche and on your different social arenas?
- How did you react on the upcoming diagnosis?
- How did you react during the diagnosis?
- What did the waiting time of the results of the MSCT mean for your psyche and social life?
- How did you react as a consequence of the diagnosis?

Results

Interview studies: Some patients indicated not being afraid, having discussed the coming examination with their spouse (patients 1,2,5), family (patient 4) or friends (patients 4,5,6,7), some felt a little excited (patients 3,6), some did not even remember the coming MSCT (patient 2). Some told that they were a little unsure or afraid of what consequences a possible disease would generate in their economic situation and working life (patients 6,7). The tube used in the examination and possible allergy raised also some concerns (patient 7). During the MSCT the patients had no special reaction, except the pain (see above). The patients commented that the waiting time was short, but at the same time most difficult for some of them. Some patients were excited to hear the results. After hearing the results of the MSCT the patients' reactions were variable: positive, surprise, released or no special reactions.

In the expert interviews the opinion was expressed (expert 2) that patients have to be prepared to live with the “label” CAD for the rest of their lives. Doctors have to realize how important it is to prepare patients for the oncoming diagnosis.

Literature review: no information

Communication

What is patients' and significant others' knowledge and understanding of MSCT coronary angiography?

Methods

Questions asked in interview studies:

- What kind of route did follow to you come to the diagnosis?
- Was your opinion asked when choosing the CTCA for the diagnostic method?
- What kind of instructions did you get for preparing to the diagnosis?
- Did you get enough information before the diagnosis?
- How did the diagnosis work from your opinion?
- What kind of activities did you have to perform during the diagnosis?

Results

Interview studies: All patients have had several previous consultations (tolerance test) in health care about their chest pain, some for several years. Their physician sent them to the investigation, except one patient, who himself had to put pressure on and convince the doctors for the MSCT in the private clinic. The patients were instructed that they should not eat that morning before the MSCT, or they did not remember anything special. One patient did not get any instructions and searched for them on the Internet.

The patients felt that they got enough information during the MSCT. The patients told that they could have been informed better about a feeling of a hot wave or possible strong pain during the MSCT. Everything worked very well during the examination. The MSCT required no activities of the patients. The patients just needed to lie down, and hold their breath for some ten seconds.

During expert interviews it turned out that the indications for MSCT are not handled uniquely. Two experts agreed though, that MSCT should not be used for screening purposes. There is agreement in the expert's answers that the patient pathway usually starts in the health centre or district hospital, continues to a cardiologist who then may or may not refer to MSCT. Depending on the patient's condition, waiting times to see a cardiologist can stretch from 1 to 4 months.

Literature review: Patients in the comparative study rated the preparation and information prior to the test on a five-point Likert-Scale (1=very good; 5=poor). The average values were $1,27 \pm 0,52$ (mean +/- SD) for MSCT, $1,35 \pm 0,64$ for MRI and $1,48 \pm 0,72$ for angiography.

How is the information regarding the use of MSCT processed and exchanged?

Results

Interview studies: By discussion between the doctor, nurses and the patient.
Literature review: no information.

What are the consequences of using MSCT coronary angiography for decision making?

Results

Interview studies: According to the patients, MSCT provided information to the doctors and patients that led to changes in care or medication (patients 1,2,3,4) or exclusion of diagnosis (patients 5,6,7).

Literature review: In the follow-up study of 142 consecutive patients, in 77 patients CAD was ruled out or clinically irrelevant stenoses were detected by MSCT. These patients were given a recommendation against angiography. The recommendation was followed in 73 patients, 4 patients had an angiography against recommendation, two of them with positive results (which leads to a false negative rate of 2,6 % (2 out of 77)). 59 patients with relevant stenoses or uninterpretable images were given a recommendation for angiography, 26 of which were performed. Seven angiographies yielded negative results which leads to a false positive rate of 11,8% (7 out of 59)) (Schroeder, 2005).

Discussion

MSCT can still be considered a “technology under development” (e.g. from 4-slice to the currently available 256-slice technology). Without clear indications it is not surprising, that the scientific literature mostly deals with its clinical efficacy (in the sense of “accuracy” for the diagnosis of different cardiac and extra-cardiac conditions). Only very few publications report social aspects and patient perceptions of the technology as specified for this report. Against this background, semi-structured interviews with patients and experts were conducted complementing the literature analysis to at least outline possible social and patient-related aspects of MSCT for the diagnosis of coronary artery disease.

Major life areas: Major life areas that may be somehow changed by the use of MSCT are patient’s everyday life at home as well as working life. Relating to the technology use itself, it seems that changes are just minor – since the technology maybe applied in an ambulatory setting, requires no time-consuming preparation, is fast and requires no special aftercare. For the patients the availability of a partner (spouse, family, friends) with whom the upcoming examination and its potential results may be discussed, seemed sufficient psychological preparation. The consequences seem to be larger, when related to the possible diagnosis. Some patients perceive the diagnosis “CAD” (and to some extent its therapeutic consequences) as a threat to their ability to lead an independent life or to continue with their working life –although there is the general view that a properly treated CAD must not limit a patients ability to work. In this context, also economic losses are feared. This view is shared

by experts, who state that a diagnosis of CAD “may change the whole life of the individual”. The meaning of CAD diagnosed by MSCT may be of particular relevance if the technology is used in populations with high numbers of false positive results (low risk populations, screening).

Individual: Patients in the interviews reported some minor physical limitations that were directly related to the MSCT examination, especially experience of pain, heat sensations and to some degree exhaustion after the examination. These results are somewhat contradictory to the data reported in the literature, where patients undergoing MSCT as well as MRI and angiography for the diagnosis of CAD only reported very low values for pain and discomfort during MSCT. Overall, very high rates of satisfaction with the examination were reported. It must be noted though, that the literature data are derived from two studies only. Psychological consequences (in the sense of uneasiness, insecurity) were again more related to the expectation of the diagnosis rather than to the technology itself. Both patients and clinicians pointed out that especially the waiting time before final results are communicated is a critical period that patients have to be prepared for. Although patients expressed no need for special aftercare, experts pointed out that a diagnosis of CAD may trigger the need for support groups or comprehensive rehabilitation measures.

Communication: In the interviews as well as in the literature review patients were mostly satisfied with the information supplied before the examination. This again may have to do with the fact that the examination itself generates only minor physical, psychological and organisational consequences. Furthermore, all patients in the interviews expressed that they considered the examination “necessary”, regardless whether the findings were positive or negative. Indirectly this supports the view that communication did not raise any unrealistic hopes or expectations.

It has to be noted, that these results have to be regarded as preliminary. There were only two studies so far analysing patient perceptions of MSCT, both with certain methodological limitations. The patients' and experts' interviews were conducted in Finland and it remains to be discussed, whether other aspects (e.g. financial aspects) may be of major importance in other health care systems. Ideally, patient related outcomes such as quality of life, psychological and physical wellbeing and impact of diagnosis on patients' major life areas and interpersonal relations should be investigated in future (controlled) implementation studies.

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT Or Comment (if regarded as a not relevant issue in this context)
H0001	Social aspects	Major life areas	Which social areas does the use of the technology influence?	yes	In which social areas of the patients may the use of the MSCT generate change?
H0002	Social aspects	Major life areas	Who are the important others that the use of the technology may affect in addition to the patient?	yes	Who are the important others that are involved in the use of MSCT coronary angiography in addition to the patient?
H0003	Social aspects	Major life areas	What kind of support and resources are needed or might be released as the technology is put to use?	yes	What kind of support and resources are needed or might be released as MSCT is put to use?
H0004	Social aspects	Major life areas	What kinds of changes does the use of the technology generate in the patient's role in the major life areas?	yes	What kinds of changes does the use of MSCT coronary angiography generate in the patient's role?
H0005	Social aspects	Major life areas	What kind of changes does the implementation and use of the technology mean for the patients physical and psychological functioning in his or her major life areas?	yes	What kind of changes does the implementation and use of MSCT coronary angiography mean for the patients physical and psychological functioning?
H0006	Social aspects	Individual	How do patients and important others react and act upon the technology?	yes	How do patients and important others react and act upon MSCT coronary angiography?
H0007	Social aspects	Communication	What is patients' and important others' knowledge and understanding of the technology?		What is patients' and important others' knowledge and understanding of MSCT coronary angiography?
H0008	Social aspects	Communication	How is the information regarding the use of the technology processed and exchanged?	yes	How is the information regarding the use of MSCT processed and exchanged?
H0009	Social aspects	Communication	What are the consequences in decision making?	yes	What are the consequences of using MSCT coronary angiography in decision making?

Appendix 1: Search strategies

PubMed

Search terms	Hits	potentially relevant
{support} OR {ressource}	208	13
{employment } OR {return to work} OR {length of stay} OR {hospital stay} OR {discharge}	17	4
{leisure} OR {activities} OR {ADL}	2	0
{family } OR {relations} OR {relatives} OR {carer}	73	1
{social} OR {psychologic*}	2	0
{wellbeing} OR {well-being} OR {recovery}	5	1
{information} OR {understanding} OR {informed consent}	166	13
{attitude} OR {perception} OR {preference} OR {self conception} OR {self-conception} OR {satisf*} OR {expectation}	15	1
{insecurity} OR {worr*} OR {hope} OR {anxiety} OR {stigmat*}	3	0
{leisure} OR {lifestyle} OR {life-style} OR {life style} OR {daily activities} OR {ADL}	2	0
{quality of life} OR {QoL}	2	0
{Care*} OR {rehabilitation}	47	7
Sum	376	40
After duplicate elimination		31

Social Science Citation Index

An abbreviated search in the Social Science Citation Index ® yielded one hit, which was of no relevance for the Core Topic Assessment.

Step	Search terms (2003-2008)	Hits
#1	TS=(coronary AND (disease* OR occlus* OR vessel* OR arter* OR stenos* OR restenos* OR aneurysm* OR thrombos* OR vasospasm* OR obstruct*)) OR TS=(angina pector* OR calcinos* OR myocardial ischem*)	4.378
#2	TS=(multi row OR multislice OR multi-slice OR multi slice OR multidetect* OR multi-detect* OR multi detect* OR multisect* OR multi-sect* OR multi sect*) OR TS=(msct OR mdct)	1.048
#3	TS=(angiograph* AND tomograph*) OR TS=("coronary angiograph*" OR "computer tomograph*" OR "computed tomograph*" OR "computerized tomograph*")	667
#4	#1 AND #2 AND #3	1

The one publication retrieved turned out to be not relevant after abstract screening.

CRD databases

References retrieved from the DARE/HTA/EED searches were supplied by FINOHTA (n=22). Abstract screening (using the same in- and exclusion criteria as noted above) left 4 (one included in the PubMed searches as well) possibly relevant publications which were also ordered in fulltext.

Appendix 2: Potentially relevant citations (n=34)

PubMed

- (1) Bax JJ, Schuijff JD, van der Wall EE. [Non-invasive imaging for the detection of coronary artery disease]. *Ned Tijdschr Geneesk* 2007 Apr 7;151(14):799-804.
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CRD-Databases

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- (2) Ontario Ministry of Health and Long-Term Care: Multi-detector computed tomography angiography for coronary artery disease. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS), 2005
- (3) Medical Services Advisory Committee: Diagnostic and therapeutic modalities for coronary artery disease. Horizon Scanning 003. Medical Services Advisory Committee. 2003

Appendix 3: Publications excluded after fulltext screening

Reference	Study type	Social aspects mentioned	Remarks
PubMed			
Bax, 2007	Narrative review on multiple imaging technologies	none	
Beanlands, 2007	Systematic review on accuracy and prognosis data	none	
Cardemattiri, 2005	Narrative review of (technical) patient preparation to achieve optimal image quality	none	
Dewey, 2004	Narrative comparison of different non-invasive diagnostic modalities for CAD	none	
Gallagher, 2008	Narrative review on the "Triple rule out" strategy	none	
Gani, 2007	Narrative comparison of different non-invasive diagnostic modalities for CAD	none	
Goldstein, 2007	RCT MSCT versus standard care	time to definite diagnosis	given in hours; no patient perspective
Hamon, 2006	Meta-Analysis of diagnostic studies	none	Also contained in CRD-Database search
Hecht, 2008a			publication not accessible
Hecht, 2008b	retrospective Case series of MSCT after invasive angiography	none	
Hoffmann, 2006	Educational paper on Utility of MSCT	none	
Johnson, 2008	Survey on patient preparation practice, practical aspects only	none	
Kolnes, 2006	Diagnostic accuracy study in a local hospital	none	
Lesser, 2007	Accuracy and prognosis study	none	
Loewinger, 2007	Narrative Review on Utility of MSCT	none	
Philippe, 2004	Narrative Review on Utility of MSCT, MRI and invasive angiography	none	
Picano, 2006	Narrative review on the radiation exposure by different radiological examination	not specifically for MSCT	
Poon, 2006	Narrative Review on Utility of MSCT	none	
Raman, 2007	Vignette, illustrating clinical decisionmaking	none	
Roberts, 2008	Narrative Review on Utility of MSCT	none	
Rubinshtein, 2006	Evaluation of a chest pain unit including MSCT	proportion of hospitalised patients	not clear, how CPU care differed from routine ER care
Rubinshtein, 2007a	Proof-of-Concept study to establish the role of MSCT in ED triage	none	
Rubinshtein, 2007b	Double publication of the data from Rubinshtein 2007a		
Schoenhagen, 2006	Editorial – Need for evidence on diagnostic accuracy; need for multidisciplinary collaboration	not data based (multidisciplinary cooperation)	
Schoepf, 2003	Narrative Review on possible clinical utility	none	
Schoepf, 2007	Review of practical aspects of MSCT	none	
Schuij, 2005	Editorial Comment on Technical advances	none	
Schuij, 2007	Narrative Review on possible clinical utility	none	
White, 2007	Narrative Review on Utility of MSCT	none	
Zimmet, 2006	Narrative Review of result interpretation	none	
CRD Databases			
NHS QIS, 2005	Quality Improvement Issues	none	
MAS, 2005	Effectiveness and economic review	not data based (one statement on patients fear	

Reference	Study type	Social aspects mentioned	Remarks
		of complications)	
MSAC, 2003			Publication not publicly available anymore

Appendix 4: Results of the literature review, included studies (n=2)

Study characteristics

Reference	Study type	Setting	Patients	Radiologic Examinations	Follow-Up-Investigations	Completeness of Follow-Up	Limitations/ Remarks
Schoepf, 2003	Prospective case series	Cardiac Imaging Outpatient Clinic of University hospital; routine care	n=142 consecutive patients of the department gender: Age Inclusion criteria: Clinical suspicion of CAD or progression of CAD after PTCA or CABG because of chest pain and/or positive stress test. Exclusion criteria: Acute coronary syndrome, stented lesions, chronic congestive heart failure, renal insufficiency, hyperthyroidism, allergic reaction against contrast media, COPD	MSCT Somatom Volume Zoom 4-slice scanner (Siemens) or Somatom Sensation 16 (Siemens) Result reporting: Group I: No coronary angiography recommended Ia: no severe stenosis detected Ib: CAD excluded Group II: Coronary angiography recommended IIa: detection of stenosis IIb: insufficient image quality or calcifications prohibiting determination of lesion severity	Telephone interview after 455 ± 155 days: a) Compliance of treating physicians with MSCT results b) Results of angiography if performed c) Correspondence of angiography results with MSCT d) Patients clinical symptoms (better – equal – worse) e) Patients satisfaction with care in Cardiac Imaging Outpatient Clinic (very satisfied – satisfied – not satisfied) f) Quality of life (better – equal – worse)	136 of 142 Drop Outs: 2 deaths (carcinoma, unknown reason) 4 moved away (1 consent withdrawn)	one-arm study, no control group Instruments for follow-up investigation not specified
Schönenberger, 2007	Cross-sectional comparative study; survey of patient acceptance of invasive and non-invasive coronary angiography MSCT, MRI, Angiography	University Hospital (part of an investigator initiated study to determine accuracy of MSCT and MRI)	n=111 consecutive patients n=28 (26%) female mean age: 63 ± 8 years Inclusion criteria: suspected CAD Exclusion criteria: contraindication against MSCT, MRI or angiography	MSCT Aquilion 16 (Toshiba) MRI 1,5T MRI Scanner (Siemens) Angiography (Integris 2000, Philips)	Written questionnaires to be filled one day after completion of all tests patient acceptance of: a) preparation and information prior to tests b) degree of concern prior to test c) comfort through the test d) degree of helplessness during the tests e) overall satisfaction all: 5-point Likert scale f) maximum subjective pain level (VAS 0-100) g) preference for future examinations h) free text comments on advantages / disadvantages of examinations	111 of 111 (100%)	patients were blinded to diagnostic test results upon completion of the questionnaire

Results

Reference	MSCT results	Compliance with MSCT results	Follow-Up Diagnostic accuracy	Clinical symptoms	Quality of life	Patient satisfaction	Remarks
Schoepf, 2003	Group I Ia: n= 51 Ib: n=26 Group II IIa: n=38 IIb: n=21	Group I Ia: n= 47 (92%) Ib: n= 26 (100%) Group II IIa: n=16 (42%) IIb: n=7 (33%)	Group I: 4 angiographies performed against recommendations in 77 patients, 2 with positive results (by recommendation: false negative rate of MSCT: 2,6%) Group II: 23 out of 59 recommended angiographies performed, 7 with negative results (by recommendation: false positive rate of MSCT: 11,8%)	Group Ia: better 18 (35%) equal 33 (65%) worse 0 (0%) Group Ib: better 13 (50%) equal 13 (50%) worse 0 (0%) Group IIa better 12 (32%) equal 24 (64%) worse 2 (4%) Group IIb: better 5 (24%) equal 14 (66%) worse 2 (10%)	Group Ia: better 16 (32%) equal 35 (68%) worse 0 (0%) Group Ib: better 10 (38%) equal 16 (62%) worse 0 (0%) Group IIa better 12 (32%) equal 25 (66%) worse 1 (2%) Group IIb: better 4 (19%) equal 15 (71%) worse 2 (10%)	Group Ia: very satisfied 18 (35%) satisfied 32 (63%) not satisfied 1 (2%) Group Ib: very satisfied 11 (42%) satisfied 14 (54%) not satisfied 1 (4%) Group IIa very satisfied 7 (18%) satisfied 28 (74%) not satisfied 3 (8%) Group IIb: very satisfied 6 (29%) satisfied 14 (66%) not satisfied 1 (5%)	
Schönenberger, 2007	not given	not given	not given	Pain on VAS (mean ± SD) MSCT 0,9 ± 4,5 MRI 5,2 ± 16,6 Angio 24,6 ± 23,4 Comfort during test 5-point Likert-Scale (mean ± SD) MSCT 1,49 ± 0,64 MRI 1,75 ± 0,81 Angio 1,54 ± 0,68	Patient acceptance of Preparation and Information 5-point Likert-Scale (mean ± SD) MSCT 1,27 ± 0,52 MRI 1,35 ± 0,64 Angio 1,48 ± 0,72 Degree of concern prior to test 5-point Likert-Scale (mean ± SD) MSCT 1,51 ± 0,85 MRI 1,64 ± 0,93 Angio 2,75 ± 1,23 Degree of helplessness 5-point Likert-Scale (mean ± SD) MSCT 1,19 ± 0,48 MRI 1,39 ± 0,89 Angio 1,52 ± 0,86	Overall satisfaction 5-point Likert-Scale (mean ± SD) MSCT 1,32 ± 0,51 MRI 1,58 ± 0,89 Angio 1,46 ± 0,61 Preferred test MSCT 80 (75%) MRI 18 (16%) Angio 13 (12%) Not preferred test MSCT 31 (28%) MRI 93 (84%) Angio (98 (88%))	Open commentaries Advantages (n; %*): MSCT 104 comments by 79 patients Fast 63; 61% uncomplicated 13; 13% painless 11; 11% noninvasive 7; 7% non confinement 4; 4% noncardiac findings, low risk, outpatient setting, silent, no fear, comfortable each 1; 1% MRI 42 comments by 38 patients no radiation 13; 31 nonvasive 11; 26% painless 7; 17% uncomplicated 3; 7% fast 2; 5% noncardiac findings, low risk, outpatient setting, no contrast agent, images immediately available, active cooperation of patient each: 1; 2% Angio 65 comments given by 59 patients therapy possible 33; 51% highest accuracy 16; 25%

Reference	MSCT results	Compliance with MSCT results	Follow-Up Diagnostic accuracy	Clinical symptoms	Quality of life	Patient satisfaction	Remarks
							images during examination 8;12% faster information regarding findings 3; 5% fast 2;3% painless 2; 3% Disadvantages (n; %): MSCT 37 comments by 34 patients radiation 23; 62% contrast agent 7;19% no therapy 3;8% long breathhold 3; 8% no online images 1;3% MRI 105 comments by 73 patients long examination 43;41% confinement 34;32% noise 9;9% long and frequent breathholds 7;7% strenuous 3;3% great strain 3;3% being alone 2;2% no therapy, active cooperation, fan, felt cold each: 1;1% Angio 112 comments given by 75 patients long lying flat after procedure 35; 31% invasive 17; 15% pressure dressing 15; 13% pain 14; 13% time consuming 8; 7% possible adverse effects 8;7% inpatient setting 3; 3% radiation 2;2% groin hematoma 2;2% not possible to use restroom 2; 2% contrast agent, duration, more expensive, narrow table, sensation of catheter in the heart, psychological stress each 1;1%

* percentages relate to total number of commentaries given to the respective test

Legal Aspects

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

Introduction

Multi(64)-slice computed tomography (MSCT) was recently introduced into the market. It is proposed to be a substantial improvement in the diagnostics of cardiac diseases, when compared with traditional, invasive alternatives. Legal issues related to MSCT technology are discussed in this domain. Some are directly related to the patient and his/her basic rights, such as autonomy, informed consent, privacy and confidentiality. Introduction of MSCT in coronary angiography does not represent a major change in legal issues compared to existing computed tomography protocols; there are no specific regulations, principles or guidelines dedicated to MSCT. Therefore some issues in this domain were considered not relevant and they were not translated into research questions.

The issues that are directly linked to MSCT technology, such as authorisations, patents/licenses, price and reimbursement regulations, product safety, guarantee and liability, and European directions, do not include specific instructions for MSCT. Rather, they follow the general regulations of similar imaging technologies. Also the acquisition processes are similar to those previously applied in acquiring imaging technologies using ionizing radiation (i.e. CE certification for new technologies).

Methodology

The authors performed a comprehensive search on several issues. All sources of relevant, topic related information, from both legal and patient autonomy perspectives, were considered. The methodology of this Core HTA is based on several steps that are reported below. Each issue contains a specific methods section.

1. According to the guidelines provided by the Core Model, legal sources related to MSCT were analysed at the different levels requested.
 - 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 MSCT producers.
2. Subsequently the authors performed a search in legal databases such as EURlex and DOGIS using specific key words for each specific topic: “market”, “guarantee”, “property”, “ownership”, “liability”, “safety”, “tourism”, “privacy”, “advance directive”, “medical file”, “medical data”, “consent”, “autonomy”, “information”, “equality”, and variations of these roots. Articles on medical-legal aspects were searched in Medline with Pubmed search

engine, using a specific search strategy (see appendix 1). The results were limited to articles published in the last five years. In total 171 articles were selected from Pubmed.

3. An analogous search strategy was used in Cinahl and Emerald databases. The results of these strategies are reported in Appendices 2 and 3 respectively.
4. Finally, articles were searched also in grey literature using generic search engines (e.g. Google).

Assessment elements

Autonomy of the patient

Can future patients understand the implications of using/not using the MSCT?

Methods

Search on Eur-lex internet database was performed in order to find EC legislation on informed consent. Analysis of guidelines on appropriateness criteria for cardiac computed tomography. Examination of patient information sheets about radiological procedures with contrast injection obtained by internet search on hospitals' websites.

Results

Patient's capacity to understand the health implication of being submitted to CT scan is connected to the type of information received from the physician and the way it is transferred. The potentially harmful effects of radiation exposure should be explained to the patient. The Practice Guidelines on informed consent for image-guided procedures elaborated by American College of Radiology state: "Because of the documented low incidence of adverse events in intravenous injection of contrast media, this may be exempted from the need for informed consent, but this decision should be based on state law, institutional policy, and departmental policy"(1).

Consensus on the use of CT in the assessment of coronary artery disease is still developing. The first major document dealing with the clinical indication for a range of clinical scenarios for MSCT was recently published by American College of Cardiology (ACC) and AHA. It is clear from these reports that there are a larger number of situations where appropriateness of MSCT is uncertain. A list of appropriate indications for cardiac CT is reported below (2):

CT Coronary Angiography is appropriate in the

- Evaluation of chest pain syndrome when there is
 - intermediate pre-test probability of coronary artery disease (CAD), uninterpretable ECG and the patient is unable to exercise
 - uninterpretable or equivocal stress test (exercise, perfusion or stress echo)
- Evaluation of acute chest pain when there is
 - Intermediate pre-test probability of CAD, no ECG changes and serial enzymes negative
- Assessment of complex congenital heart disease, including anomalies of coronary circulation, great vessels and cardiac chambers and valves

- Evaluation of coronary arteries in patients with new-onset heart failure to assess aetiology
- Non-invasive coronary arterial mapping, including internal mammary artery before repeated cardiac surgical revascularisation

In emergency situations (not just in the emergency department), when immediate treatment is required to prevent more serious harm, the patient lacks decision making capacity, and no substitute decision maker (surrogate) is always available. In these circumstances law allows emergency medical treatment to be administered without consent. MSCT procedures are usually elective. Therefore, when patients are legally competent an informed consent needs to be obtained. Informed consent is a communicative process of sharing information with patients, ascertaining their understanding of the information, and asking for their cooperation and their permission to proceed. Patients legally competent to give their own consent are usually able to understand the procedure of MSCT coronary angiography and its clinical implications, if correctly explained.

Three essential elements in obtaining informed consent (3,4):

1. Determining whether the patient has decision making capacity (can understand the options, understand the risks and benefits to them of the options, and make decisions based on a stable set of values and goals). If the patient lacks decision making capacity, the surrogate decision makers should be given the same information.
2. Providing patients with sufficient information to allow them to make an informed choice.
3. Allowing patients to make their decision voluntarily and without coercion.

Are there relevant optional technologies for MSCT that future patients should be allowed to consider?

Methods

Search on Eur-lex internet database in order to find EC legislation on informed consent.
Analysis of guidelines on appropriateness criteria for cardiac computed tomography.
Examination of patient information sheets about radiological procedure with contrast injection obtained by internet search on hospitals' websites.

Results

The concept of informed consent also comprises the possibility to consider other diagnostic and therapeutic choices. The available alternatives to MSCT are invasive coronary angiography and cardiac magnetic resonance imaging. Invasive coronary angiography is currently the gold standard for assessing coronary artery stenoses. The patients' informed consent forms (found by internet search on world wide hospitals' websites) usually also inform patients on risks with injection of radiographic intravenous contrast media (3).

Is it possible to give future patients enough time to consider their MSCT related decisions?

Methods

Semi-structured interviews to a radiologist and a medico-legal clinician in staff at an Italian university hospital were performed.

Results

In an elective MSCT scan procedure it is possible to have advance meetings with the patients, so that they can receive all of the necessary information to make informed decisions on their health. If MSCT scan is performed in emergency situation the patient may not have enough time to decide whether to submit to the diagnostic procedure. Moreover, it is possible that the patient temporarily lacks decision making capacity.

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

Methods

Search on Eur-lex internet database in order to found EC legislation on advance directive. Internet research has been performed in order to find advance directives related to the MSCT scan procedure.

Results

An advance directive is a legal document that helps to ensure that patient's wishes will be respected if he becomes unable to speak or otherwise communicate. In the absence of a written document, an advance directive may sometimes be an oral communication, where patient express his wishes for care verbally to his family members or health care professional. 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 due to e.g. ventilation or feeding tubes or in the event the patient is in a terminal condition or persistent vegetative state.
- A medical power of attorney is a legal document that lets a person appoint someone (usually called a health care agent or health care proxy) to make medical treatment decisions for him/herself not only at the end of life but at any time one is unable to speak for oneself.

Convention On Human Rights And Biomedicine (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" (4). 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 one's own life, could affect, in case of life danger, advance directives' relevance.

The performed research produced no meaningful results that link advance directives with MSCT scan procedures; it has been thought that it is not necessary to obtain an advance directive on the use of this specific technology.

Privacy of the patient

Does the use of MSCT produce such information on the patient that is not directly relevant to the disease/condition that is being diagnosed or tested?

Methods

Literature review on clinical use of MSCT and semi-structured interview to a radiologist and a medico-legal clinician in staff at an Italian university hospital were performed.

Results

No evidence was found that MSCT would produce such additional information on patients that would violate their privacy. Incidental findings (e.g. pulmonary nodules) are described in the in the safety domain.

Does the use of MSCT produce information that would be relevant for relatives of the patient?

Methods

Literature review on clinical use of MSCT and semi structured interview to a radiologist and a medico legal clinician in staff at an Italian university hospital were performed.

Results

The MSCT does not produce additional information on patients relevant for their relatives.

Can the access to the patient database be secured properly?

Methods

An analysis of the sources of legislation at European level was carried out. The search was done using specific search engines. The keywords used were 'Privacy in health care', 'Patient privacy, MSCT.'

Results

The systems of data handling, regardless of nationality or residence of individuals, have to respect the freedoms and fundamental rights of people, in particular their privacy as announced by Directive 95/46/EC, October 24 1995 of the European Parliament and European Union Council (5), on the protection of individuals with regard to the processing of personal data, in Section III, Article 8, Member States prohibit the processing of personal data concerning health. This principle shall not apply where:

(Citation from art 8 point 2)

- the data subject has given his explicit consent to the processing of those data or

- processing is necessary for the purposes of carrying out the obligations and specific rights of the controller in the field of employment law in so far as it is authorized by national law providing for adequate safeguards; or
- processing 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; or
- processing is carried out in the course of its legitimate activities with appropriate guarantees by a foundation, association or any other non-profit-seeking body with a political, philosophical, religious or trade-union aim and on condition that the processing relates solely to the members of the body or to persons who have regular contact with it in connection with its purposes and that the data are not disclosed to a third party without the consent of the data subjects; or
- the processing relates to data which are manifestly made public by the data subject or is necessary for the establishment, exercise or defence of legal claims

In addition, the point 3 in Article 8 states that the general principle shall not apply: “where processing of the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data 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”

In the sequent section VIII, article 17, the Directive foresees that: “Member States shall provide that the controller must implement appropriate technical and organizational measures 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. Having regard to the state of the art and the cost of their implementation, such measures shall ensure a level of security appropriate to the risks represented by the processing and the nature of the data to be protected”.

What levels of access to which kind of patient information exist in the chain of care?

Methods

An analysis of regulatory sources was carried out on specific search engines by using a specific keyword like “privacy of patient”.

Results

Using MSCT does not imply a specific management of patients’ clinical data in order to guarantee the privacy of patients. Access to the patients’ data must be allowed to all clinical professionals involved in the health care process (referral clinicians, nurses, residents, etc). In the European context EuroSOCAP Commission, has produced a document containing standard on confidentiality and privacy in health care. The document states that: “All patients have the right to privacy and the reasonable expectation that the confidentiality of their personal information will be rigorously maintained by all healthcare professionals. Each patient’s right to privacy and the professional’s duty of confidentiality apply regardless of the form (for example, electronic, photographic, biological) in which the information is held or communicated. Not all healthcare professionals are

bound by the same legal obligations of confidence, but all are under the same ethical obligations to maintain confidentiality. Particular care is needed on the part of healthcare professionals to ensure that the right to privacy of vulnerable patients is respected and that their duty of confidentiality toward them is fulfilled”(6).

Another European committee, Cittadinanzattiva-Active Citizenship Network group, has elaborated the “European Charter of Patients' rights” identifying fourteen rights; the sixth states: “Every individual has the right to the confidentiality of personal information, including information regarding his or her state of health and potential diagnostic or therapeutic procedures, as well as the protection of his or her privacy during the performance of diagnostic exams, specialist visits, and medical/surgical treatments in general.

All the data and information relative to an individual’s state of health, and to the medical/surgical treatments to which he or she is subjected, must be considered private, and as such, adequately protected. Personal privacy must be respected, even in the course of medical/surgical treatments (diagnostic exams, specialist visits, medications, etc.), which must take place in an appropriate environment and in the presence of only those who absolutely need to be there (unless the patient has explicitly given consent or made a request)” (7).

Equality in health care

Is MSCT equally accessible to all needing members in a given society?

Methods

An analysis of regulatory sources was carried out on search engines by using specific keywords like “equality care”, “accessibility”.

Results

As provided in Article 35 of the Charter of Fundamental Rights of the European Union, every individual has the right of access to preventive health care and to obtain medical care, surgical procedures and diagnostic performance under the conditions established by national laws and practices (8). The definition and implementation of all policies and activities shall ensure a high level of protection of human health. The equality in health care is a main topic in the Convention for the Protection of the Rights and Dignity of the Human Being with regard to biology and medicine: Convention on the Rights and Biomedicine.

The introduction of MSCT may reduce the time needed to diagnose coronary artery disease. It may shorten the waiting lists for elective examinations, and give a more immediate answer to the patients more equally. However it is necessary to highlight the balance between improved access and the available resources managing the highly complex technology of MSCT, which may cause problems especially in rural areas and further away from large urban centres (9).

Is MSCT subsidized by the society?

Methods

An analysis of legal sources at International level was performed. Articles were searched from scientific journals and ad hoc searches from both generic search engines (e.g. Google) and specialized databases (e.g. Pubmed).

Results

From the legal point of view no evidence of specific subsidizing principles of MSCT was found. Cost of purchasing and maintenance of MSCT or fee for service delivered have been subsidized by health care systems.

Is there a wide variation in the acceptability of MSCT across Europe?

Methods

An analysis of legal sources at National level was performed. Articles were searched from scientific journals and ad hoc searches from both generic search engines (e.g. Google) and specialized databases (e.g. Pubmed).

Results

The performed search produced no meaningful results in terms of wide variation in the acceptability of the technology across Europe. As a consequence, since it is difficult to find differences in the comparison of the legal issues concerning the acceptability, we should deduce that the technology issues are not controversial.

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

Methods

Sources of legal information at European level were searched. Specific search engines, using keywords such as: "Cross-border health care", "Mobility, MSCT" and "Health care tourism, MSCT".

Results:

The coordination of care and diagnostic services that are provided across borders is increasingly becoming in the field of European legislation. In particular, the border areas are developing more flexible procedures for access to treatment. An analysis of these developments from the institutional / constitutional (economic) point of view suggests that a great legislative flexibility could lead to paretian improvements and, as a consequence, to an improvement in equity for migrants. This theory could be applied also to the international mobility based on access to MSCT. In this case mobility should follow the migratory flows from Eastern European nations, recently joined the European Union (Romania, Poland, Bulgaria), to countries like Italy, Spain and France (10). The bilateral agreements and the flexible procedures in the frontier areas should be encouraged to adapt the institutional arrangements to the request for "cross-border" care. This can be made possible by the judgement of the Court of Justice of the European Community that enforce to reimburse the cost

of treatment delivered in a hospital in another member state that applies to a national health service which provides such treatment free of charge. In the case of MSCT the regulations governing international mobility may be applied and these should consequently cover the problems and dynamics in general (11) .

End-users

Who is the intended end-user of MSCT?

Methods

Scientific articles on this issue were not found, therefore a semi structured interview to a radiologist and a medico legal staff clinicians was performed at an Italian university hospital.

Results

MSCT end users are:

1. Patients who need:
 - A clear, understandable and complete information on the MSCT and options in order to make a conscious decision assuming that the technology meets the safety standards established by EC or national laws.
2. Medical professionals who need:
 - Easiness of use.
 - On-going training.
 - Protection from radiation exposure.
3. Regulatory institutions who require:
 - CE marks
 - Conditions that are in line with EU's and national laws.

Is the use of MSCT limited in legislation?

Methods

Search on Eur-lex internet database in order to find EC legislation.

Results

Radiation in large doses can cause injury and death or induce cancer. Chronic exposure to lower levels of radiation may cause an increased risk of certain kinds of disease, such as cancer. The major source of radiation exposure to the public is medical and environmental. Medical exposure involves radiation-producing machine such as computed tomography. The Directive 97/43/Euratom (“Health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom”) (12) states the general principles of the radiation protection of individuals in relation to medical exposure. The use of MSCT is allowed when it guarantees two principles:

1. Justification principle;
2. Optimization principle.

The first principle means that medical exposure to MSCT shall show a sufficient net benefit, weighing the total potential diagnostic or therapeutic benefits it produces, against the individual detriment that the exposure might cause, taking into account the efficacy, benefits and risks of available alternative techniques having the same objective but involving no or less exposure to ionizing radiation. So a medical exposition through MSCT is forbidden when it is unjustified. The second principle means that radiation doses should be kept as low as reasonably achievable, still obtaining the required diagnostic information.

EU member states shall promote the establishment and the use of diagnostic reference levels for ionizing radiation. The optimization process shall include the selection of equipment, the consistent production of adequate diagnostic information or therapeutic outcome as well as the practical aspects. It includes also quality assurance and quality control, and the assessment and evaluation of patient doses, or administered activities, taking into account economic and social factors. Written protocols shall be established for each equipment and for every type of standard radiological practice. Member states shall ensure that recommendations concerning referral criteria for medical exposure, including radiation doses, are available to the prescribers of medical exposure. The Directive has been implemented in each single EU nation trough national implementing measures.

Is the health care personnel using MSCT according to the professional standards?

Methods

Searches on Eur-lex internet database in order to find EC legislation, and on “Pubmed” with the following keywords: “Ct angiography” and “training” was carried out.

Results

“Council Directive 97/43/Euratom of 30 June 1997 (12) on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom” states that (art.5) Member States shall ensure that any medical exposure is effected under the clinical responsibility of a practitioner. Clinical responsibility comprises (art.2): justification; optimization; clinical evaluation of the outcome; cooperation with other specialists and the staff, as appropriate, regarding practical aspects; obtaining information, if appropriate, of previous examinations; providing existing radiological information and/or records to other practitioners and/or prescribers, as required; giving information on the risk of ionizing radiations to patients and other individuals involved, as appropriate. In order to ensure that patients, personnel and the environment are protected, Members States shall ensure that the operators are properly trained (art. 7), and radiation equipment and facilities meet current protection standards (art. 8).

Art. 7 establishes that Member States shall ensure that practitioners and other clinical operators have adequate theoretical and practical training for the purpose of radiological practices, as well as relevant competence in radiation protection. For this purpose Member States shall ensure that appropriate curricula are established and shall recognize the corresponding diplomas, certificates or formal qualifications. Member States shall ensure that continuing education and training after qualification is provided and, in the special case of the clinical use of new techniques, they shall assure the organization of training related to these techniques and the relevant radiation protection

requirements. Member States shall encourage the introduction of a course on radiation protection in the basic curriculum of medical and dental schools.

The complex nature of imaging devices, as well as the rapidly advancing practices require the trainee to be introduced to MSCT. Scientific societies (i.e. ACC/AHA, British cardiovascular Society) have developed recommendations for attaining and maintaining the minimum experience, cognitive and technical skills necessary for competent performance of MSCT (13,14,15). A more detailed explanation is given in the organisational domain.

Authorisation & safety

Has MSCT national/EU level authorisation?

Methods

Scientific articles on this issue were not found, therefore an analysis of the database of European Lex and Directive (<http://eur-lex.europa.eu>) at European level was made. The search of the sources was conducted with the help of specific search engines and using keywords like “level authorisation” and “product safety”.

Results

At the moment there are four models of MSCT 64-slice available in the market. All the products satisfy the authorisation requirements.

Patient safety, as expressed in product safety, is one domain of health care technology assessment which clearly falls under the mandate of the European Union. It is important to consider all the various permission levels, starting with the European directive on eco-compatibility RoHS (2002/95/CE) and to identify in our case the potential exemptions, consulting Attachment 5 of the Decree, which provides exemptions for electro-medical technologies, such as the CT.

There are national regulations for the characteristic of the premises where MSCT procedures are performed: a proper room, adequate energy sources and walls designed to protect from X-ray beams are needed. Crucial is also the radiation protection equipment both for the patient and operator. For example, in Italy, the Italian National Institute of Health ensures proper management of interventional and diagnostic imaging involving ionizing radiation, and issues appropriate guidelines to guarantee the imaging units' quality control (National Assembly) (16). The guidelines emphasize the technical management and quality control equipment and optimizing examinations and dosimetry of the patient, with particular reference to the evaluation of diagnostic reference levels and the provisions of the D.Lgs. 187/2000 (17,18). Similar guidelines exist in other countries as well (19,20).

Comments

MSCT is classified, according to Directive 2007/43/CE of European Council, as a device. This directive demands an approval defined as “CE mark”. It allows marketing the device in all European countries.

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

Methods

Consultation of the directive on ionizing radiations as available on Eurolex search engine (eurolex.europa.eu)

Results

“Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom” establishes that each Member States shall ensure that (art.8) an up-to-date inventory of radiological equipment for each radiological installation must be available to the competent authorities. So, each Member State must organize its own register.

Does MSCT fulfil product/tissue safety requirements?

Methods

Consultation of the directive on ionizing radiations as available on Eurolex search engine (eurolex.europa.eu)

Results

Many novel health technologies may utilize human cells or tissue. These products must fulfil the safety requirements issued by EC Directive 2004/23/EC; MSCT does not utilize those organic samples. So the above mentioned Directive is not applicable to MSCT.

Nevertheless MSCT must fulfil other requirements for protection against ionizing radiation as it is stated by the “Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and by the repealed Directive 84/466/Euratom”. This directive is not referring specifically to MSCT but to any kind of radiological equipment.

Ownership & liability

Does MSCT infringe some intellectual property right?

Methods

Medline was searched using keywords such as “computed tomography” and “patent” or “property right” in title. Also the following databases were consulted: CINAHL Plus with Full Text, NHS Economic Evaluation Database (Trial), Health Technology Assessments (Trial), Cochrane Central Register of Controlled Trials (Trial), Cochrane Database of Systematic Reviews (Trial), Database of Abstracts of Reviews of Effects (Trial). Keywords were “msct” or “mdct” and “patent”. EPO and World Intellectual Property Organization websites were also searched.

Results

Articles from Medline were not pertinent to this issue. The search performed in CINAHL and others databases resulted in no article on the topic. We found many patents related to CT equipment, software and linked services. They did not reveal that CT would infringe any intellectual property rights.

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

Methods

Medline was searched using keywords such as “computed tomography” and “licensing fee”. Also the following databases were consulted: CINAHL Plus with Full Text, NHS Economic Evaluation Database (Trial), Health Technology Assessments (Trial), Cochrane Central Register of Controlled Trials (Trial), Cochrane Database of Systematic Reviews (Trial), Database of Abstracts of Reviews of Effects (Trial). Keywords were “msct” or “mdct” and “licensing fee”.

Results

Articles from Medline were not pertinent to this issue. The search performed in CINAHL and others databases resulted in no articles on the topic. It is not apparent that the introduction of MSCT would presume additional fees to be paid.

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

Methods

We have performed a search of the MSCT manufacturers’ websites.

Results

We focused the analysis on the 64-slice MSCT. The table below shows the features of each MSCT system and manufacturers’ guarantee. Data have been collected from rt-image website (21).

EUnetHTA WP4 - Core HTA on MSCT Coronary Angiography
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

	GE Healthcare	GE Healthcare	GE Healthcare	Philips Medical Systems	Siemens Medical Solutions	Toshiba America Medical Systems	Toshiba America Medical Systems	Toshiba America Medical Systems
Product Name	LightSpeed VCT	LightSpeed VCT XT	LightSpeed VCT standard	Brilliance CT, 64-channel configuration	SOMATOM Sensation	Aquilion 32	Aquilion 64	Aquilion 64 CFX
Web Site	www.gehealthcare.com	www.gehealthcare.com	www.gehealthcare.com	www.medical.philips.com	www.medical.siemens.com	www.medical.toshiba.com	www.medical.toshiba.com	www.medical.toshiba.com
FDA-Approved	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DICOM-Compliant	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Images								
Slice Acquisition per Rotation	64	64	64	N/A	24, 40, 64 depending on the version	32 slices, upgradeable to 64	64 slices	64 slices
Image Storage Capabilities	146 GB for 250,000 images ; 2.3 GB MOD and 9.4 DVD-R DICOM	146 GB for 250,000 images ; 2.3 GB MOD and 9.4 DVD-R DICOM	146 GB for 250,000 images ; 2.3 GB MOD and 9.4 DVD-R DICOM	292 GB	146 GB image disk (260,000 images) + 5.2GB MOD (7500 images) + 700 MB CD-R (1100 images) + 300 GB raw data disk	180 GB hard drive; 9.4 GB DVD-RAM / CD-R; additional storage available	180 GB hard drive; 9.4 GB DVD-RAM / CD-R; additional storage available	180 hard drive; 9.4 GB DVD-RAM / CD-R Additional storage available
Services								
Service/Support	InSite remote support center is available 24/7/365. Service offering can be customize to meet your unique needs, including: after-hour and weekend service, uptime performance guarantees, 24/7 remote support, expedited part delivery, asset management	After-hour and weekend service, uptime performance guarantees, 24/7 remote support, expedited part delivery, asset management tools and much more	InSite remote support center is available 24/7/365. Service offering can be customize to meet your unique needs, including: after-hour and weekend service, uptime performance guarantees, 24/7 remote support, expedited part delivery, asset management	Customer Care Center offering tier 1 (24/7) and tier 2 support for applications and/or service assistance. Remote service network (with "Look-Over-the-Shoulder" feature.)	Available	National service support, InnerVision Plus, minimize system interruptions and optimize system utilization, monitors functionality and room conditions to identify and resolve problems before your system is compromised, allows transfer of clinical images	National service support, InnerVision Plus, minimize system interruptions and optimize system utilization, monitors functionality and room conditions to identify and resolve problems before your system is compromised, allows transfer of clinical images	National service support, InnerVision Plus, minimize system interruptions and optimize system utilization, monitors functionality and room conditions to identify and resolve problems before your system is compromised, allows transfer of clinical images
Training	University style curriculum, TVA, remote training with live interactive observation and two-way interaction, classroom training with hands-on lab work, CE credits for completion of TiP programs	University-style curriculum, TVA, remote training with live interactive observation and two-way interaction, classroom training with hands-on lab work, CE credits for completion of TiP programs	University-style curriculum, TVA, remote training with live interactive observation and two way interaction, classroom training with hands-on lab work, CE credits for completion of TiP programs	Yes, on-site, off-site, computer-based CD, online	Available	1 week at International Training Academy in California 1 week onsite, 1 week follow-up onsite. A full complement of classrooms and labs, the most advanced training products, technologist training, physician training, practical hands-on training*	1 week at International Training Academy in California 1 week onsite, 1 week follow-up onsite; a full complement of classrooms and labs, the most advanced training products, technologist training, physician training, practical hands-on training*	1 week at International Training Academy in California 1 week onsite, 1 week follow-up onsite; a full complement of classrooms and labs, the most advanced training products, technologist training, physician training, practical hands-on training*
Warranty	1 year	1 year	1 year	1-year parts and labor	1 year	1 year	1 year	1 year

Is the user guide of MSCT comprehensive enough?

Methods

We have performed a search of the MSCT manufacturers' websites.

Results

Substantial changes in computed tomography (CT) protocols are essential as radiologists move from 4-slice to 16-slice and more recently towards 64-slice MSCT systems. As the number of CT applications expands with newer generations of CT systems, practicing radiologists face significant challenges. Not only must they develop and implement new protocols such as cardiac CT or peripheral angiography, but they need to revise established protocols in view of CT technical refinements (22). Given the abbreviated scan times associated with 16-slice and even more with 64-slice CT, accurately timed contrast delivery becomes critical. GE, Philips, Siemens, Toshiba Manufacturers have developed Protocols for Multidetector CT.

In particular protocols describe three features:

1. Technical Considerations”;
2. Preparing Patients for Contrast-Enhanced Exams;
3. Contrast medium Safety.

Technical Considerations refer to:

- Temporal resolution;
- Spatial resolution;
- Radiation dose;
- CM administration;
- Scan timing.

Preparing Patient refers to:

- Scheduling the exam;
- Preparing the exam;
- Planning the scan.

Contrast Medium Safety refers to:

- Patients at risk for contrast-induced nephropathy;
- Patients with immediate-type hypersensitivity to contrast;
- Other reactions to IV contrast administration;
- Treatment of reactions to IV contrast;
- Considerations when using gastrointestinal (GI) contrast.

Regulation of the market

Is MSCT subject to price control?

Methods

The European Court of Justice Database, Eurlex database was searched by using the keyword “MSCT” and “price control”. Medline, Cinhal, and Emerald were also searched using keywords

such as “MSCT” and “price control”. In addition, a grey literature search on Italian system has been performed.

Results

Search in European Court of Justice Database and Eurlex did not identify any relevant information on MSCT linked to price control. Medline, Cinhal and Emerald searches did not either identify any useful information. There seems not to be an explicit price control of the MSCT market.

Is MSCT subject to acquisition regulation?

Methods

“Directive 2004/18/Ec” was consulted to verify if it contains prescriptions that may influence MSCT acquisition

Results

“Directive 2004/18/Ec” does not contain prescriptions on MSCT acquisition. This is a general law that regulates public works, supply, and service contracts, without explicit reference to medical devices sector.

Is the marketing of MSCT to the patients restricted?

Methods

The European Court of Justice Database and Eurlex database were searched by using the keyword “MSCT” and “market\$” and “marketing”. Medline, Cinhal, and Emerald were also searched by using keywords such as “MSCT” and “market\$” and “marketing”. In addition, a grey literature research on Italian system has been performed.

Results

CE marking is a legal requirement for medical devices intended for sale in Europe. MSCT CE marking is regulated by Council Directive 2007/47/EC of 5 September 2007 concerning medical devices.

Legal regulation of novel/experimental techniques

Is MSCT so novel that existing legislation has not been designed to cover its regulation?

Methods

Semi-structured interview to a radiologist and a medico legal clinician in staff at an Italian university hospital

Results

MSCT is not a new technology from this point of view. General regulation on CT is most likely suitable also for MSCT.

How are the liability issues solved according to existing legislation?

Methods

Semi structured interview to a radiologist and a medico legal clinician in staff at an Italian university hospital

Results

There are no specific liability questions about the use of MSCT. The liability is linked to an appropriate use of medical devices and diagnostic instruments. From this point of view the question is not pertinent to MSCT.

Are new legislative measures needed?

Methods

Semi-structured interview to a radiologist and a medico-legal clinician in the staff of an Italian university hospital.

Results

MSCT does not require new specific legislation for its use.

Is the voluntary participation of patients guaranteed properly?

Methods

Semi-structured interview to a radiologist and a medico-legal clinician in the staff of an Italian university hospital

Results

The technology cannot be considered experimental, and as a consequence this question is not pertinent to MSCT. In general the use of MSCT as medical diagnostic tool go under general laws on informed consent, see the topic “Autonomy of patient”.

Discussion

The objective of legal domain was to point out questions on basic rights of patients (autonomy, informed consent, privacy and confidentiality) and legal requirements of the new technology (authorisation, guarantee, regulation of market). It was very difficult to find specific information on MSCT on legal issues, because usually the literature and the laws use the general concept of CT. As a consequence, the MSCT, from this point of view is not a completely new technology, because its use, as far as legal issues are concerned, is similar to traditional CT. The main issues are about legal requirement to guarantee the safety (health protection of individuals against the dangers of ionizing radiation).

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Assessment elements table

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT Or Comment (if regarded as a not relevant issue in this context)
I0030	Legal aspects	End-user	Who is the intended end-user of the technology?	yes	Who is the intended end-user of MSCT?
I0031	Legal aspects	End-user	Is the use of the diagnostic technology limited in legislation?	yes	Is the use of MSCT limited in legislation?
I0032	Legal aspects	End-user	Is the health care personnel using the technology according the professional standards	yes	Is the health care personnel using MSCT according to the professional standards?
I0002	Legal aspects	Autonomy of the patient	Can future patients understand the implications of using/not using the technology?	yes	Can future patients understand the implications of using/not using the MSCT?
I0003	Legal aspects	Autonomy of the patient	Are there relevant optional technologies that future patients should be allowed to consider?	yes	Are there relevant optional technologies for MSCT that future patients should be allowed to consider?
I0004	Legal aspects	Autonomy of the patient	Is it possible to give future patients enough time to consider their decisions?	yes	Is it possible to give future patients enough time to consider their MSCT related decisions?
I0005	Legal aspects	Autonomy of the patient	Is it possible to obtain an advance directive on the use of the technology?	yes	Is it possible to obtain an advance directive on the use of MSCT coronary angiography?
I0007	Legal aspects	Privacy of the patient	Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the patient?		
I0008	Legal aspects	Privacy of the patient	Does the use of the technology produce such information on the patient that is not directly relevant to the disease/condition that is being diagnosed or tested	yes	Does the use of MSCT produce such information on the patient that is not directly relevant to the disease/condition that is being diagnosed or tested?
I0033	Legal aspects	Privacy of the patient	Does the use of the technology produce information that would be relevant for the relatives of the patient	yes	Does the use of MSCT produce information that would be relevant for relatives of the patient?
I0009	Legal aspects	Privacy of the patient	Can the access to the patient data be secured properly?	yes	Can the access to the patient data be secured properly?
I0010	Legal aspects	Privacy of the patient	What levels of access to which kind of patient information exist in the chain of care?	yes	What levels of access to which kind of patient information exist in the chain of care?
I0011	Legal aspects	Equality in health care	Is the technology equally accessible to all needing members in a given society?	yes	Is MSCT equally accessible to all needing members in a given society?
I0012	Legal aspects	Equality in health care	Is the technology subsidized by the society?	yes	Is MSCT subsidized by the society?

EUnetHTA WP4 - Core HTA on MSCT Coronary Angiography
31 Dec 2008
Pilot assessment to test the HTA Core Model. Not for decision-making.

ID	Domain	Topic	Issue	Relevance in the context of MSCT Yes/No	Research question(s) in the context of MSCT Or Comment (if regarded as a not relevant issue in this context)
I0013	Legal aspects	Equality in health care	Is there a wide variation in the acceptability of the technology across Europe?	yes	Is there a wide variation in the acceptability of MSCT across Europe?
I0014	Legal aspects	Equality in health care	Is health-care tourism expected from/to other European countries?	yes	Is health-care tourism expected from/to other European countries?
I0015	Legal aspects	Authorisation & safety	Has the technology national/EU level authorisation?	yes	Has MSCT national/EU level authorisation?
I0016	Legal aspects	Authorisation & safety	Does the technology need to be listed in a national/EU register?	yes	Does MSCT need to be listed in a national/EU register?
I0017	Legal aspects	Authorisation & safety	Does the technology fulfil product safety requirements?	yes	Does MSCT fulfil product/tissue safety requirements?
I0018	Legal aspects	Authorisation & safety	Does the technology fulfil tissue safety requirements?	no	
I0019	Legal aspects	Ownership & liability	Does the technology infringe some intellectual property right?	yes	Does MSCT infringe some intellectual property right?
I0020	Legal aspects	Ownership & liability	Does the introduction of the technology presume some additional licensing fees to be paid?	yes	Does the introduction of MSCT presume some additional licensing fees to be paid?
I0021	Legal aspects	Ownership & liability	What are the width, depth and length of the manufacturers guarantee?	yes	What are the width, depth and length of the manufacturers guarantee?
I0022	Legal aspects	Ownership & liability	Is the user guide of the technology comprehensive enough?	yes	Is the user guide of MSCT comprehensive enough?
I0023	Legal aspects	Regulation of the market	Is the technology subject to price control?	yes	Is MSCT subject to price control?
I0024	Legal aspects	Regulation of the market	Is the technology subject to acquisition regulation?	yes	Is MSCT subject to acquisition regulation?
I0025	Legal aspects	Regulation of the market	Is the marketing of the technology to the patients restricted?	yes	Is the marketing of MSCT to the patients restricted?
I0026	Legal aspects	Legal regulation of novel/experimental techniques	Is the technology so novel existing legislation was not designed to cover its regulation?	yes	Is MSCT so novel existing legislation was not designed to cover its regulation?
I0027	Legal aspects	Legal regulation of novel/experimental techniques	How are the liability issues solved according to existing legislation?	yes	How are the liability issues solved according to existing legislation?
I0028	Legal aspects	Legal regulation of novel/experimental techniques	Are new legislative measures needed?	yes	Are new legislative measures needed?
I0029	Legal aspects	Legal regulation of novel/experimental techniques	Is the voluntary participation of patients guaranteed properly?	yes	Is the voluntary participation of patients guaranteed properly?

Appendix 1 Search Strategy: Pubmed

(Day of search: 16.06.2008)

Search strategy:

#1

Search coronary disease (195355)

#2

Search coronary AND disease* (392185)

#3

Search coronary AND (disease* OR vessel*) (437372)

#4

Search coronary AND (disease* OR vessel* OR arter* OR aneurysm* OR stenosis* OR restenosis* OR thrombosis* OR vasospasm) (520363)

#5

Search #4 (520363)

#6

Search coronary AND vasospasm* (3815)

#7

Search (#4) OR (#6) (520366)

#8

Search angiograph* AND tomograph* (30630)

#9

Search coronary (1007000)

#10

Search (#7) AND (#8) (5778)

#11

Search (#7) AND (#8) Limits: published in the last 5 years (2722)

#12

Search msct OR mdct Limits: published in the last 5 years (2478)

#13

Search msct OR mdct (2730)

#14

Search slice OR row (23628)

#15

Search multislice OR multirow (2749)

#16

Search multi-slice (804)

#17

Search ((#16) OR (#15)) OR (#14) (25594)

#18

Search (#11) AND (#17) (938)

#19

Search (((((((coronary AND (disease* OR vessel* OR arter* OR aneurysm* OR stenosis* OR restenosis* OR thrombosis* OR vasospasm))) OR ((coronary AND vasospasm*)))))) AND ((angiograph* AND tomograph*)) AND ("last 5 years"[PDat])) AND (((((multi-slice)) OR ((multislice OR multirow))) OR ((slice OR row)))) (938)

#20

Search autonomy (24249)

#21

Search autonomy or information* (546059)

#22
Search autonomy OR information (541259)
#23
Search consent (41774)
#24
Search consent OR informed (58551)
#25
Search (#19) AND (#24) (18)
#26
Search medical file (2895)
#27
Search medical (file OR data) (378851)
#28
Search advance directive (5300)
#29
Search (#19) AND ((#27) OR (#28)) (64)
#30
Search privacy (11001)
#31
Search (#19) AND (#30) (0)
#32
Search tourism (1205)
#33
Search touris* (2556)
#34
Search (#33) AND (#19) (0)
#35
Search safety (191984)
#36
Search (safety) AND (#19) (13)
#37
Search ownership OR liability (40361)
#38
Search ((#37)) AND (#19) (1)
#39
Search property (42504)
#40
Search (property) AND (#19) (0)
#41
Search guarantee (6449)
#42
Search (guarantee) AND (#19) (0)
#43
Search market (27402)
#44
Search (market) AND (#19) (1)
#45
Search (#19) AND ((#43) OR (#41) OR (#39) OR (#37) OR (#35) OR (#33) OR (#30) OR
(#28) OR (#27) OR (#24) OR (#21)) (171)

Appendix 2 Search Strategy: CINAHL

(Day of search: 18.06.2008)

CINAHL Plus with Full Text, NHS Economic Evaluation Database (Trial), Health Technology Assessments (Trial), Cochrane Central Register of Controlled Trials (Trial), Cochrane Database of Systematic Reviews (Trial), Database of Abstracts of Reviews of Effects (Trial)

Limiters - Published Date from: 2000/01-2008/06; Language: English; Date Abstract Published from: 2000-2008; Year of Publication - Reviews from: 2000-2008; Language: English; Date Abstract Published from: 2000-2008; Year of Publication - Reviews from: 2000-2008; Language: English; Language: English; Year of Publication -- Reviews from: 2000-2008; Year of Publication -- Protocols from: 2000-2008; Date Abstract Published from: 2000-2008; Year of Publication -- Reviews from: 2000-2008; Language: English
Expanders - Apply additional terms to query; Also search within the full text of the articles

Search strategy:

1. coronary disease (10508)
2. coronary and (disease\$ or vessel\$ or arter\$ or aneurysm\$ or stenosis\$ or restenosis\$ or thrombosis\$ or vasospasm\$) (33931)
3. coronary angiography (4467)
4. angiography\$ and tomography\$ (2476)
5. tomography X-ray Computed (11361)
6. (S3) and (S5) (377)
7. ((S4)) or (S6) (2475)
8. (S2) and (S7) (819)
9. msct or mdct (309)
10. (slice or row) and ((S2) or (S3) or (S7)) (968)
11. ((S1) and (S9)) and informed consent (1)
12. (S1) or (S9) and informed consent (10515)
13. multirow or multislice or "multi-slice" or "multi slice" or multidetect\$ or "multi detect\$" or "multi-detect\$" or multidetect\$ (515)
14. ((S13) or (S9)) and coronary disease (67)
15. S14 and informed consent (2)
16. ((S1) or (S2)) and patient autonomy (63)
17. (S16) and ((S13) or (S9)) (0)
18. S9 and patient autonomy (0)
19. (S13) and patient autonomy (0)
20. ((S13) or (S9)) and advanced directives (0)
21. ((S1)) and (S2)) and patient data (53)
22. S21 and (S9 or S13) (0)
23. (S9 or S13) and patient data (10)
24. (S9 or S13) and (equality and access) (0)
25. (S9 or S13) and equality (0)
26. (S9 or S13) and access (0)
27. (S1 or S2) and equality (213)

28. (S27) and (S9 or S13) (0)
29. (S9 or S13) and acceptability (0)
30. (S9 or S13) and tourism (0)
31. (S1 or S2) and tourism (0)
32. (S9 or S13) and authorisation (0)
33. (S1 or S2) and authorisation (0)
34. (S9 or S13) and safety (0)
35. (S1 or S2) and safety (0)
36. (S9 or S13) and property right (0)
37. (S9 or S13) and ownership (0)
38. (S9 or S13) and liability (0)
39. (S9 or S13) and patent (0)
40. (S9 or S13) and licensing fee (0)
41. (S9 or S13) and price control (0)
42. (S9 or S13) and guarantee (0)
43. (S9 or S13) and market\$ (0)
44. (S9 or S13) and experiment\$ (0)
45. (S9 or S13) and (legislation or legal rules) (0)

Appendix 3 Search Strategy: Emerald

(Day of search: 17.07.2008)

Search strategy:

1. coronary disease (765)
2. (1) AND computed tomography OR CT (35)
3. (1) AND (2) AND patient informed consent (0)
4. (1) AND (2) AND patient autonomy (2)
5. (1) AND (2) AND advances directive (0)
6. (1) AND (2) AND patient data (14)
7. (1) AND (2) AND equality OR access (6)
8. (1) AND (2) AND acceptability (0)
9. (1) AND (2) AND medical tourism (0)
10. (1) AND (2) AND authorization (0)
11. (1) AND (2) AND safety (0)
12. (1) AND (2) AND property right (0)
13. (1) AND (2) AND ownership (0)
14. (1) AND (2) AND liability (0)
15. (1) AND (2) AND patent (0)
16. (1) AND (2) AND licensing fee (0)
17. (1) AND (2) AND price control (0)
18. (1) AND (2) AND guarantee (0)
19. (1) AND (2) AND market\$ (2)
20. (1) AND (2) AND legislation (0)