Technology *Report*

Issue 59 October 2005

CT and MRI for Selected Clinical Disorders: A Systematic Review of Clinical Systematic Reviews

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CCOHTA
600-865 Carling Avenue
Ottawa ON Canada K1S 5S8
Tel. (613) 226-2553
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Email: pubs@ccohta.ca

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Cite as: Foerster V, Murtagh J, Lentle BC, Wood RJ, Reed MH, Husereau D, Mensinkai S. *CT and MRI for selected clinical disorders: A systematic review of clinical systematic reviews* [Technology report no 59]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

Production of this report is made possible by a financial contribution from Health Canada's Health Care Strategies and Policy, federal, provincial and territorial partnership grant program.

Legal Deposit - 2005
National Library of Canada
ISBN: 1-894978-88-9 (print)
ISBN: 1-894978-89-7 (online)

PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT
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Canadian Coordinating Office for Health Technology Assessment

CT AND MRI FOR SELECTED CLINICAL DISORDERS: A SYSTEMATIC REVIEW OF CLINICAL SYSTEMATIC REVIEWS

Victoria Foerster MD MSc[1]
James Murtagh MHA CHE[1]
Brian C. Lentle MD FRCP(C)[1]
Ronald J. Wood RTR[1]
Martin H. Reed MD FRCP(C)[2]
Don Husereau BScPharm MSc[3]
Shaila Mensinkai MA MLIS[3]

October 2005

[1] ProMed Associates Ltd., Coquitlam BC
[2] Children's Hospital of Winnipeg Health Sciences Centre, Winnipeg MB
[3] Canadian Coordinating Office for Health Technology Assessment, Ottawa ON

Reviewers

These individuals kindly provided comments on this report.

External Reviewers

Sandor Demeter, MD MHSc FRCP(C)
Assistant Professor of Radiology and Assistant Professor of Community Health Sciences
University of Manitoba
Winnipeg MB

John R. Mayo, MD FRCP(C)
Associate Professor
University of British Columbia
Vancouver General Hospital
Vancouver BC

Adrian Kendal Dixon, MD FRCR FRCP FRCS FMedSci
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University of Cambridge
Cambridge UK

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Montréal QC

David Hailey, MSc PhD GradRIC
Adjunct Professor
Community Health Sciences
University of Calgary
Calgary AB

Authorship

All authors planned the project, developed the protocol and the report, and revised the report in response to reviewer comments. In addition, Vicki Foerster and James Murtagh selected literature, extracted data, and wrote the draft report; and Shaila Mensinkai designed and executed the literature searches, wrote the methods section on literature searching and the associated appendix and verified the bibliographic references.

Conflicts of Interest

John Mayo has received an unrestricted grant from General Electric Medical Systems and an equipment grant from Siemens Medical Systems.

Brian Lentle has served as a paid member of the Canadian Bone Metabolism Board of Proctor and Gamble Inc., and has received speaker fees from the same company.

No other conflicts were reported.

REPORT *IN BRIEF*

October 2005

CT and MRI for Selected Clinical Disorders: A Systematic Review of Clinical Systematic Reviews

Technology

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).

Disease

This report explores 13 conditions for which the use of CT and MRI remain controversial: arteriovenous malformations carotid artery disease, cerebral aneurysms, coronary artery disease, headaches, head injuries, lung cancer screening, peripheral vascular disease, pulmonary embolism, renal artery stenosis, seizures, stroke and urolithiasis screening.

Issue

Although CT and MRI are accepted investigations for some clinical conditions, uncertainty exists as to their value for other investigations.

Methods and Results

Published literature from January 2000 to November 2004 was identified and retrieved using a defined search strategy. A total of 48 articles were included in a systematic review (SR), reporting on 49 SRs that examined CT and MRI for the investigation of 11 of the 13 specified clinical conditions. Based on studies of the diagnostic accuracy of CT and MRI as compared with traditional gold standard investigations, promising evidence was found for applications for carotid artery disease, peripheral vascular disease, pulmonary embolism, renal artery stenosis and stroke. Findings were more cautious for cerebral aneurysms, coronary artery disease and lung cancer screening, while SR evidence was sparse for use of these technologies for the investigation of headaches, head injuries and seizures. No SR evidence was found for cerebral arteriovenous malformations or urolithiasis screening.

Implications for Decision Making

- **CT and MRI technologies may not be appropriate for every clinical condition.** Evidence of effectiveness from recent systematic reviews (SRs) indicates that CT and MRI technologies can improve diagnostic certainty in some medical conditions. In other conditions, there was less compelling evidence or no evidence available. There was no evidence that CT and MRI technology has an effect on patients' health or management.
- **Decisions regarding the use of CT and MRI should be based on an updated review and revisited.** CT and MRI technology has advanced rapidly. Findings from the identified SRs may not be sufficiently contemporary to be useful for clinicians and decision makers.
- **To ensure the most effective use of CT and MRI, their influence on patient management and outcomes must be measured.** By moving beyond the diagnostic accuracy of these technologies, more relevant assessments of the benefits and harms of such technologies will be possible.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Foerster V, Murtagh J, Lentle BC, Wood RJ, Reed MH, Husereau D, Mensinkai S. *CT and MRI for selected clinical disorders: A systematic review of clinical systematic reviews.*

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
600-865 Carling Avenue, Ottawa ON Canada K1S 5S8 Tel: 613-226-2553 Fax: 613-226-5392 www.ccohta.ca

EXECUTIVE SUMMARY

The Issue

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are sophisticated medical imaging techniques used to investigate a variety of clinical disorders. They are costly to purchase and to operate. For some clinical indications, CT and MRI are accepted investigations; however, for others there is uncertainty and controversy surrounding the value of their use. For this report, radiologists on an expert guidelines committee of the Canadian Association of Radiologists, identified clinical conditions where controversy exists around the benefits of investigative uses of CT and MRI.

Objective

To summarize the evidence from systematic reviews (SRs) reporting on the clinical effectiveness of CT and MRI in the investigation of specific clinical conditions of the chest and the cardiovascular, neurological, and urological systems.

Clinical Review

Methods: Published literature from 2000 to November 2004 was identified and retrieved using a well-defined search strategy encompassing both electronic databases and grey literature. References were considered eligible for inclusion if they were SRs; covered the populations of interest (arteriovenous malformations (AVMs), carotid artery disease, cerebral aneurysms, coronary artery disease, headaches, head injuries, lung cancer screening, peripheral vascular disease, pulmonary embolism, renal artery stenosis, seizures, stroke and urolithiasis screening); and examined CT and MRI technologies for investigation of the conditions. Two authors independently applied the selection criteria in broad and selective screening. From the included references, information was extracted into evidence tables and analyzed. In addition, all included references were assessed as to their quality using two separate tools, one developed by Oxman and Guyatt and the other, examining diagnostic imaging efficacy, by Fryback and Thornbury.

Results: From the electronic database search, 31 of 947 articles were selected for inclusion, with 17 (of 145) added after review of the grey literature. The 48 articles reported on 49 SRs covering 11 clinical conditions, ranging from one SR for headaches to 12 SRs for pulmonary embolism.

Based on studies of diagnostic accuracy, the evidence was promising for five conditions: carotid artery disease, peripheral vascular disease, pulmonary embolism, renal artery stenosis and stroke. Authors were more cautious about three conditions: cerebral aneurysms, coronary artery disease and lung cancer screening. Evidence was sparse for three conditions: headaches, head injuries and seizures. No SR evidence was identified for the remaining two conditions: cerebral AVMs and screening for urolithiasis.

Quality scores for the SRs were generally low. Using the Oxman and Guyatt scale, 72% (40/49) of SRs were deemed to have substantial flaws, the remainder having minor to minimal flaws. Using the Fryback and Thornbury efficacy grading scale, 86% of SRs were deemed to be Level 2

studies (of six levels), assessing diagnostic accuracy, sensitivity and specificity, rather than impact on patient management or outcomes.

Conclusions

In this project we aimed to summarize the SR evidence reporting on CT and MRI for the investigation of 13 specific medical conditions where controversy around the use of the technologies exists. Analysis of the information obtained led to a spectrum of support for CT and MRI, from promising, to cautious, to non-existent. Most studies suggested more research would be welcome to explore the benefits of the technologies as compared with the investigations that have traditionally been used.

For CT and MRI, technology has advanced rapidly and the devices that were used to conduct the primary studies in the SRs analyzed for this report have often been upgraded or replaced. For this reason, practitioners in the field could argue that the findings of this report may not be contemporary enough to be useful for clinicians and decision makers – the ability of the report's findings to guide decisions may be seen as limited.

The case can be made that diagnostic imaging technologies may improve or expedite the identification of a disease process but cannot, a priori, change its outcome. Because an imaging investigation occurs early in the clinical timeline of the work-up of a patient's clinical disorder, it may be difficult for imaging findings to affect patient management and outcomes. However, to ensure the most effective use of the technologies, measurement of their influence on patient management and outcomes must be a goal.

ABBREVIATIONS

2D / 3D	two dimensional / three dimensional
ACR	American College of Radiology
AGREE	Appraisal of Guidelines Research and Evaluation (Collaboration)
AHRQ	Agency for Healthcare Research & Quality (US)
ANAES	Agence Nationale d'Accréditation et d'Evaluation en Santé (France)
AVM	arteriovenous malformation
CAD	coronary artery disease
CAR	Canadian Association of Radiologists
CI	95% confidence interval
CIHI	Canadian Institute for Health Information
CPG	clinical practice guideline
CT	computed tomography
CTA	CT angiography
CTFPHC	Canadian Task Force on Preventive Health Care
CXR	chest x-ray
DWI	diffusion-weighted imaging (MRI)
EBA	electron beam angiography
EBCT	electron beam computed tomography
FDA	Food and Drug Administration (US)
HTA	health technology assessment
ICES	Institute for Clinical Evaluative Sciences
ICSI	Institute for Clinical Systems Integration
MDCT	multi-row detector CT
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee (Australia)
MSCT	multi-slice CT
NCI	National Cancer Institute (US)
NHS	National Health Service (UK)
NMR	nuclear magnetic resonance
NPV	negative predictive value
OECD	Organization for Economic Co-operation and Development
OHIP	Ontario Health Insurance Plan
PE	pulmonary embolism
PI	perfusion imaging (MRI)
PPV	positive predictive value
PVD	peripheral vascular disease
RAS	renal artery stenosis
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TOF	time-of-flight (MRA)
TPD	Therapeutic Products Directorate
UK	United Kingdom
USPSTF	United States Preventive Services Task Force
VP or VQ	ventilation-perfusion scintigraphy

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Background

This report summarizes the evidence available in systematic reviews (SRs) regarding the clinical effectiveness of two sophisticated medical imaging techniques, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), as they relate to a defined set of clinical scenarios. The report is intended to help decision makers and health care workers involved in the purchase and operation of CT and MRI equipment and in patient management. Specific controversial clinical conditions were targeted for review, these being selected by expert radiologist members of the Canadian Association of Radiologists (CAR). In addition to this review of the clinical effectiveness of CT and MRI, a review of economic analyses of CT and MRI for the selected clinical conditions will be published by CCOHTA in a separate document.

CT and MRI are used to investigate a variety of clinical disorders. The technologies were introduced to Canada in 1973 (CT) and 1985 (MRI). The first CT scanners were limited by small apertures and could only be used to image the head or small children. CT scanners for the whole body became available and were in wide use in Canada by the late 1970's and early 1980's. MRI emerged from a laboratory technology, nuclear magnetic resonance (NMR) spectroscopy. At first MRI provided more detailed images of the brain than were possible using CT, particularly the structures of the posterior fossa. Further MRI developments made it possible to image parts of the body that had been hard to visualize, such as the spinal cord and musculoskeletal system.

There are a number of clinical situations where the use of CT and MRI are accepted investigations. One, the other, or both technologies are used when clear anatomic imaging is needed to show disease and its penetration to facilitate management decisions. For example, CT is the imaging procedure of choice for the detection of, staging and monitoring therapy in malignancies; investigating the chest, abdomen, and cranium to show abnormal structures or tumours; pre-operative investigation of complex masses to assess treatment possibilities; and guidance for drainage procedures, biopsies and nerve blocks. CT and MRI are felt to have equivalent abilities for some conditions, although MRI provides more information than CT for some disorders of the head and neck; and is superior for imaging of the spine and musculoskeletal system. It is also being used increasingly in oncology.[1]

Continuing advances in technology have made it possible to investigate a wider variety of medical conditions. For CT scanning, the technology has advanced from the performance of a single cross-sectional image (single slice) at a time to multiple cross-sectional images [multi-slice − concurrent capture of from four up to 64 slices (or more)]. This has allowed the diagnostic accuracy of CT to continually improve and led to its use in musculoskeletal applications; myelography (imaging the fluid space around the spinal cord); angiography (imaging blood vessels); cardiac scoring; evaluation of brain perfusion, acute chest pain and dyspnea (shortness of breath); and using computed image reconstruction tools and virtual endoscopy.[2] For MRI, recent advances include: breast and cardiac imaging, angiographic procedures and interventional techniques, as well as examination of brain function to map onto images of brain structure.[1]

The appropriate use of the MRI technology is key, as is the management of wait times. These challenges are not easy. For example, the Western Canada Waiting List (WCWL) project sought to establish a set of standardized clinical criteria to set priorities among patients waiting for MRI exams. After piloting and refining an MRI wait times tool, the WCWL developers stated "further development and testing of the tool appear warranted, although considerable question remains concerning the utility of priority criteria for MRI and other diagnostic services."[3] In other words, despite the efforts of a group of experts, it has been a challenge to design an MRI prioritization system that has works.

The evolving uses of CT and MRI have increased their utility from strictly investigative imaging technologies to therapeutic modalities such as for the guidance of biopsies and other minimally invasive therapies.

1.2 Technology Overview

1.2.1 Description of the technology

CT and MRI scanners acquire pictures of the inside of the human body. CT scanning uses x-rays and computed analysis to produce cross-sectional images of slices of the body, whereas MRI typically uses the molecular hydrogen in tissues, a large magnet, intermittent radio waves and a computer to produce 2D or 3D images. MRI scans avoid the use of ionizing radiation. Both imaging technologies (CT and MRI) allow for detailed visualization of internal organs. Contrast media or other injected agents may be used to enhance the images for both modalities.

The operation of CT and MRI scans in dedicated suites involves a number of specialized personnel. Technologists are trained to perform the examinations and obtain and process the images. Radiologists supervise the examinations, help determine the most appropriate imaging sequences for the particular clinical problem and interpret the resulting images. Nurses may be required if the patient requires contrast medium or sedation. Physicists supply technical support for image quality and radiation safety.

Imaging technology is continually changing, with newer machines that allow for more detailed images and faster scanning. Image improvements are attributable in part to the decrease in time required to capture the images, minimizing artifacts due to breathing. This is particularly significant for patients who are short of breath. With the CT scanners, a volume of the body is scanned and reconstructed as individual images, providing detailed information that can be manipulated by a technologist to produce 2D and 3D images of the body.

The increasing speed of imaging, improved detail and 3D capability also facilitate new types of imaging such as CT and MRI angiography and CT virtual endoscopy. These techniques are being investigated as alternatives to; and in some cases have replaced, more invasive techniques such as catheter angiography, colonoscopy and bronchoscopy.

With respect to CT and MRI discussed in this report, the studies use a variety of technologies:

- Helical (or spiral) CT: The CT x-ray tube rotates and scans continuously while the radiology table moves a patient along. This contrasts with earlier "step and shoot" CT technology where an individual image was captured while the patient was stationary and the patient was moved slightly with the machine off before another image was captured.
- Multi-slice CT [or multiple row detector CT (MDCT)]: Multiple slices are acquired simultaneously, thus increasing scanning speed. Initially four slices were captured, but new technology allows for the capture of at least 64 slices.
- CT and MRI angiography: Imaging of the lumen of a blood vessel is possible due to the fine detail and rapid scanning introduced with newer CT and MRI systems.
- Electron beam CT (EBCT): Referred to as a comparator in some SRs, EBCT is not a subject of this report as it is not used in Canada. EBCT is a CT imaging system which uses a focused electron beam to image the coronary arteries, including arterial calcification.

1.2.2 Regulatory status in Canada

In Canada, CT and MRI machines are approved and regulated by Health Canada's Therapeutic Products Directorate (TPD), which has a mandate to ensure that the medical devices offered for sale in Canada are safe, effective and are of high quality. For regulation of medical devices, TPD uses a four-class system modelled on a European classification scheme, with Class I being the most benign and Class IV being the least benign. Presently, CT scanners require Class III licences (devices in this class are considered potentially hazardous or could represent immediate danger if they fail); and MRI scanners are classified as Class II devices.

1.2.3 Clinical indications

The specific clinical indications for use of CT and MRI scanners are not restricted through government regulation and licensing. Rather, clinical practice guidelines (CPGs) or "referral guidelines" for diagnostic imaging have been developed in Europe, the US and a number of other countries. Evidence-based CPGs aim to limit the use of medical investigations or interventions to those supported by good research proving their clinical and cost-effectiveness.[4]

During the past decade, a myriad of CPGs have been published, created by professional groups, governments, industry, academics and others. Although facility-specific or health-region-specific guidance for CT and MRI use has been developed in a number of Canadian centres as a result of local initiatives, evidence-based CPGs do not exist on a national scale in Canada. However, during the last decade, the Canadian Association of Radiologists (CAR), has started developing CPGs for diagnostic imaging procedures, expressing a commitment to the creation of CPGs that are evidence-based. A CAR Guidelines committee has been particularly interested in the appropriate use of CT and MRI in clinical conditions where the use of these technologies was considered by them to be controversial. Of interest to the CAR experts was the evidence of effectiveness of the technologies specifically for diagnosis and guidance of therapy, unless otherwise noted.

Consensus opinion of the radiology experts on the CAR committee identified 13 clinical conditions in which investigative use of CT and MRI could be further explored: coronary artery disease (CAD), peripheral vascular disease (PVD), renal artery stenosis (RAS), lung cancer (screening), pulmonary

embolism (PE), carotid artery disease, cerebral aneurysms, headaches, head injuries, seizures/epilepsy, strokes, arteriovenous malformations (AVMs), and urinary tract calculi (screening).

1.2.4 Source of the technology

There are a number of manufacturers of CT and MRI equipment worldwide. For CT, some of the principal manufacturers include: GE Medical Systems (US), Phillips (the Netherlands), Siemens (Germany), Shimadzu (Japan) and Toshiba (Japan). For MRI, principal manufacturers include: GE Medical Systems; Hitachi (Japan); ISOL Technology (Korea); Phillips, Siemens, Shimadzu and Toshiba. Machines are generally purchased as new installations with various features and attachments, but there is also a market for used equipment.[5] In some cases, health regions may move their scanners from tertiary sites to community hospitals as the newest technology is acquired for the large teaching centres. Industrialized countries may sell or donate equipment to less-developed countries.

1.2.5 Unit cost

Purchase costs for CT and MRI machines depend on the level of sophistication required and the number of additional features installed. A 2000 CAR report estimated the average purchase cost of a CT machine at $1,400,000 and MRI at $2,500,000.[6] A suitable space in a facility must also be identified and renovated; or constructed. Yearly operating costs are considerable, as are maintenance contracts. Operating and maintenance costs may render the purchase and installation of these technologies impractical in some Canadian jurisdictions. The dollars required to purchase a CT or MRI may be obtained through local fundraising, but operating costs may not be forthcoming from government funders.

As advancements in CT and MRI technologies continue, devices which are up-to-date at the time of purchase and installation are considered obsolete within a few years since they are unable to accomplish the latest refinements and advances. Radiology staff may request upgrades of software and hardware annually that incur additional costs.

In Canada, radiologist fees to provide CT and MRI scan interpretation are set provincially and vary among jurisdictions. For example, the Ontario Health Insurance Plan (OHIP) 2003 Schedule of Benefits lists 25 separate fee codes, depending on the part of the body scanned (nine areas listed), the type of scan performed and the use or absence of intravenous contrast media. Of the 25 fees established, compensation ranges from $34.60 for reviewing CT images used to guide a biopsy to $109.35 for CT of the spine, abdomen or pelvis, with and without contrast media. Fees for MRI are similar, ranging from $31.75 to $109.85 (10 areas of the body; 23 fee codes).[7] For some examinations, several areas of the body may be scanned and numbers of sequences may vary; in some of these cases, the total professional fee paid will be the sum of the individual fee items. Overall, the fee structure is complex and evolving.

Like other technologies, CT and MRI machines have limited lifecycles. According to the CAR, outdated diagnostic imaging equipment is undesirable for a number of reasons: older machines may produce poorer quality images, there is a higher rate of failure which disrupt(s) imaging services and may be dangerous for patients and staff, parts may be difficult to obtain, repairs may be costly, and the machines may be difficult or impossible to update or augment.[6]

The lifecycle of diagnostic imaging equipment varies. There is no universally accepted standard. In 2000, the CAR published lifecycles for a number of diagnostic imaging technologies, stating it should be eight years for CT and six years for MRI.[6] In March 2003, the European Coordination Committee of the Radiological, Electromedical and Medical IT Industries established general standards for electromedical equipment in Europe: 60% should be <five years; ≤30% should be between six and 10 years; and ≤10% should be older then 10 years.[8] In Canada, in January 2004, the Canadian Institute for Health Information (CIHI) reported that the proportion of machines newer than five years old was 64% for CT and 71% for MRI.[9]

1.2.6 Utilization and expenditure patterns

In 1991, there were 200 CT scanners and 22 MRI scanners in Canada (counts include publicly funded machines only). Since then, the growth in acquisition of this technology has been dramatic. In 2004, 12 years later, installations had expanded to 338 CT machines and 151 MRI machines in Canada (counts include both publicly and privately funded machines). This represents a growth rate of 70% for CT and almost 700% for MRI.[9] The number of units per million people varies across jurisdictions (Table 1).

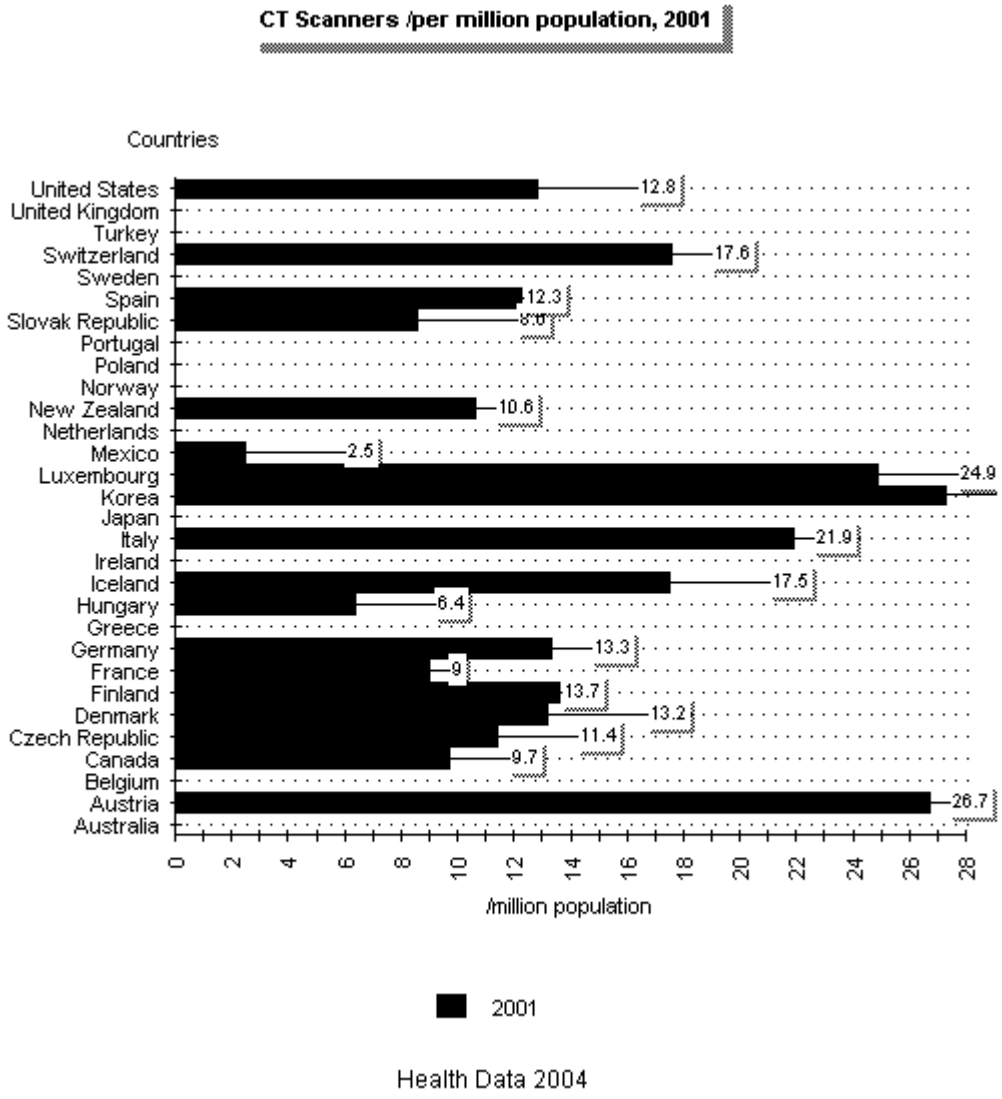
The number of CT and MRI machines, as a rate per unit of population, are often compared between provinces, but also between countries. For example, the number and rate of CT and MRI scanners are indicators tracked by the Organization for Economic Co-operation and Development (OECD); the variation in installations among countries is significant (Figures 1 and 2). However, installation numbers do not correlate directly with the degree of technology utilization, access or health outcomes for the population.[10]

Table 1: Numbers of CT and MRI machines installed per million people (rate) for Canadian jurisdictions (January 2004 data)

Province or Territory	CT	MRI
BC	10.6	4.6
AB	9.5	7.3
SK	11.1	3.0
MB	14.6	2.6
ON	8.1	4.2
QC	13.0	5.3
NB	12.0	6.7
NS	16.0	4.3
PE	21.7	7.2
NL	19.2	1.9
NU	--	--
NT	23.6	--
YK	31.8	--
Canada	**10.6**	**4.8**

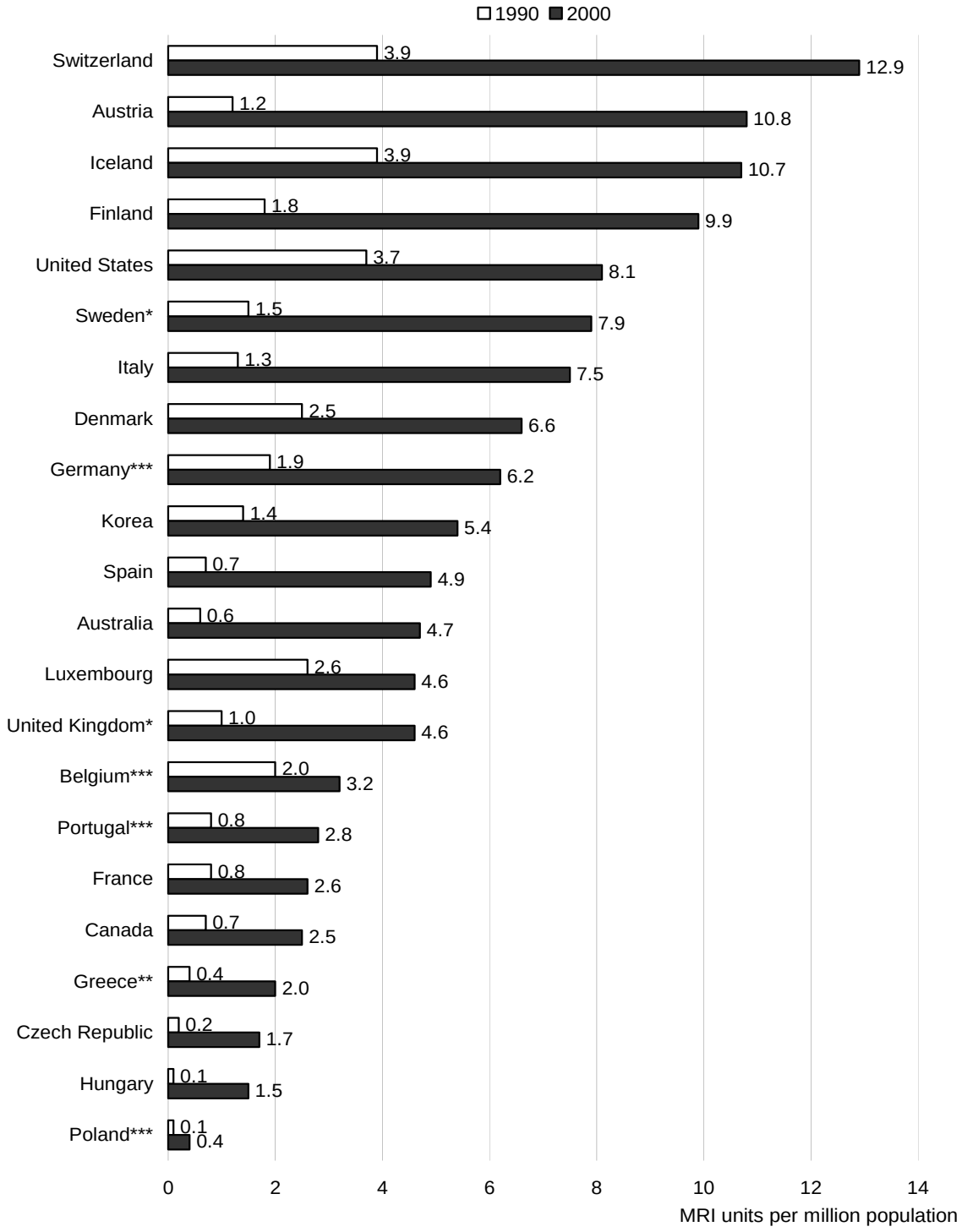
Source: Canadian Institute for Health Information, Medical Imaging in Canada, 2004 (Ottawa: CIHI, 2004)[9]

Figure 1: Diffusion of CT scanners in 30 countries



Data adapted from *OECD Health Data 2004: A Comparative Analysis of 30 Countries: 2004 Edition ; Eco-Santé OCDE 2004 : Analyse comparative de 30 pays: Edition 2004*,

Figure 2: Diffusion of MRI scanners in 30 countries



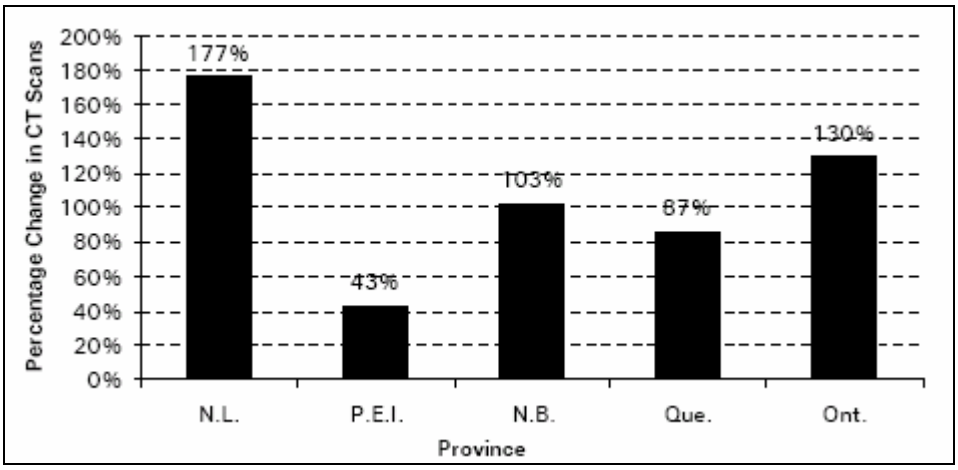
* 1999. ** 1998. *** 1997. **** 2001.

Chart 3. Diffusion of MRI units, 1990 to 2000, Health at a Glance: OECD Indicators 2003, © OECD 2003 All rights reserved.

In Canada, tracking the number of CT and MRI scans performed is complex and has not been accomplished nationally. Procedures are performed on an inpatient and outpatient basis, in hospital and in non-hospital settings; and in publicly funded and privately funded facilities. Fee codes vary, depending on the body site scanned and the method of counting scans. This differs from province to province. In some jurisdictions, such as the US, standard codes have been set nationally by the Centers for Medicare & Medicaid; these codes may be used by insurance companies and others to determine reimbursement. No single database collects these data; some are collected provincially and some nationally. Standardization of coding systems is a goal of interprovincial and federal efforts.

For the 2004 CIHI report "Medical Imaging in Canada," radiologist fee-for-service CT billings were obtained and compared for five provinces (NB, NL, ON, PE, QC), for the years 1994 and 2001. CIHI accessed several data sources to obtain the scan numbers. Provincial data were sought from three ministries of health (NB, NL and QC) and from the CIHI National Physician Database for two (ON and PE). Rates of change in the number of CT scans performed in 1994 versus 2001 were presented in the report, rather than raw numbers. As can be seen in Figure 3, growth in the number of scans ranged during the seven years from 1994 to 2001, from 43% (PE) to 177% (NL).[9] This growth can theoretically be due to the increasing number of installed machines and/or the increasing utilization of existing machines. Data show that the number of installed machines is increasing, but the growth attributable to these new machines versus increased utilization is unclear.

Figure 3: Growth in number of CT scans in Canada, 1994 to 2001



Source: Canadian Institute for Health Information, Medical Imaging in Canada, 2004 (Ottawa: CIHI, 2004)[9]

An illustration of the increase in the number of MRI scans performed is available in a recent Institute for Clinical Evaluative Sciences (ICES) report on MRI in Ontario. This report found that between 1992 and 2001, the number of MRI scans performed in Ontario increased nearly six times to 145,801 in 2001, from 25,406 scans in 1992. During this time the cost to OHIP increased almost 10 times, to more than $26 million in 2001, from about $3 million in 1992. MRI scans for seven body areas were reported: abdomen, extremities, head, neck, pelvis, spine and thorax. The head was the most common area scanned [39% of all scans in 2001 (57,106 of 145,810)], but the increase in abdominal scans was the greatest at 1,233% (1992=394; 2001=4,858).[11]

2 THE ISSUE

CT and MRI machines are costly to purchase, operate and replace. Their findings may also generate additional investigations with their own cost consequences. Demand generated by patients and physicians outpaces supply, leading to issues of access. In parts of the country where there has been significant limitation in access to CT and MRI, pent-up demand exists. This means that even when access is increased through the purchase of new machines or extensions in operating hours, wait times may not shrink as the queue is managed. In addition to those already waiting for a CT or MRI scan, there are likely further new patient referrals that may have been considered borderline for requiring the scan, before access was increased.

Ideally CT and MRI would be employed only for the investigation of those clinical cases where compelling evidence from medical literature has shown that the results of the test will influence or expedite the management of the patient's treatment positively or change the patient's health outcome.

3 OBJECTIVE

The objective of this report is to summarize the evidence available in SRs, which report on the clinical effectiveness of CT and MRI in the investigation of 13 clinical conditions:

Cardiovascular system
- CAD
- PVD
- RAS

Chest
- lung cancer (screening)
- PE

Neurological system
- carotid artery disease
- cerebral aneurysms
- headaches
- head injuries
- seizures and epilepsy
- strokes
- AVMs

Urological system
- urinary tract calculi (screening)

This objective is accomplished by addressing the following question: What is the evidence of clinical effectiveness from SRs that examine CT and MRI for the investigation of the clinical conditions considered?

SRs are regarded as the least biased and most rational method to summarize research evidence.[12] Therefore our project aimed to explore scientific literature to find SRs that were relevant to the clinical conditions of interest; and to summarize their results and assess their quality. The report is intended to help decision makers who are involved in the purchase and operation of CT and MRI equipment and those involved in the investigation of patients who might be candidates for use of the technology.

The results of an SR of economic analyses of CT and MRI for the 13 clinical conditions will be discussed in a subsequent CCOHTA report.

4 CLINICAL REVIEW

4.1 Methods

A protocol for this project was written *a priori* and was followed throughout (Appendix 1). The protocol covers both a review of clinical studies and a review of economic studies. At the outset, the plan was to combine these into one report. As the project progressed, it became apparent that the two topics would best be handled by splitting the material into two projects, the economic report following the clinical report and including studies based on the selected clinical conditions reported.

4.1.1 Literature search strategy

Published literature was retrieved using a well-defined search strategy (Appendix 2). On the DIALOG® system, the MEDLINE®, EMBASE®, INSPEC®, BIOSIS Previews® and PASCAL databases were cross-searched using the duplicate removal feature. The search strategy focused on the objective of the project and included descriptors and keywords for CT and MRI technologies in the chest and the cardiovascular, neurological and urological systems.

The search was limited to the year 2000 onward to retrieve literature on contemporary technologies. It was understood that this date limit meant the possible elimination of relevant literature from pre-2000 literature. A language limit was not applied. A clinical filter was used to limit the retrieval to SRs. Regular database alerts were established on MEDLINE®, BIOSIS Previews®, EMBASE® and INSPEC® databases to capture new publications until November 2004.

Parallel searches were performed and updated on LILACS, the Cochrane Library and PubMed databases to capture additional studies. The last PubMed update was performed in November 2004. Grey literature was retrieved by searching the web sites of health technology assessment (HTA) and related agencies. Search results from all the databases were downloaded into a Reference Manager database and undetected duplicates were removed.

4.1.2 Selection criteria and method

a) Selection criteria

Inclusion criteria

- Study design: references determined to be SRs. Some reviews were not titled "systematic reviews," but based on the presence of documented literature search strategies and tabular listings of the included trials, they were considered to have been conducted systematically.
- Population groups: cardiovascular (CAD, PVD, RAS); chest (lung cancer screening, PE); neurological (seizures, headaches, head injuries, stroke, carotid artery disease, cerebral aneurysms, AVMs); and urological (screening for urinary tract calculi)
- Interventions: any investigative application of CT and MRI technologies, including CT angiography (CTA) and MR angiography (MRA). Articles were excluded that reported exclusively on electron beam CT (EBCT), a related technology, which is not in use in Canada and is experiencing decreased use elsewhere.

b) Selection method

From the broad search of citations and abstracts (where available), two authors (VF and JM) independently applied the selection criteria. A pilot selection test of the first 30 citations or abstracts was carried out and revealed 100% agreement. The two authors then proceeded to develop independent subsets of potentially relevant citations.

The two independent subsets were compared. Where both authors agreed on relevance, citations were accepted and where both reviewers agreed on lack of relevance, citations were eliminated. Where there was initial disagreement, relevance was determined by consensus. When an abstract was not available, but the material in the citation suggested potential relevance, this citation was included. A short-list of potentially relevant citations was therefore developed. These citations were requested in full text.

The full text articles were independently reviewed (VF and JM) against the inclusion criteria. The two sets of included articles were compared and refined to a single list, with the reviewers reaching agreement by consensus. The level of agreement was calculated using a kappa statistic.

The grey literature was organized and reviewed independently, with inclusion and exclusion categorization compared between authors. Due to the complexity of tracking and organizing the grey literature, the final selection of included articles from the grey literature was carried out by consensus.

The final collection of included articles was assembled, composed of the relevant articles from the electronic search and the grey literature.

4.1.3 Data extraction strategy

A template for summary evidence tables was developed. The final list of information categories in the evidence tables included:

- authors and affiliation; publication and date; purpose of the review; and research funders
- literature sources and dates
- inclusion and exclusion criteria; included studies
- results
- conclusions; limitations as per authors
- quality scores; efficacy grade; comments

From each included SR, data considered important for capture in the tables included (where available and space allowed):

- purpose of the SR
- funder of the SR research
- literature sources, including search strategy and limitations, e.g., date and language limitations
- selection (inclusion and exclusion) criteria for studies
- number of studies included
- authors, publication dates and sizes of enrolled populations
- types of technology and types of studies
- outcomes as reported in SR results sections, such as measures of test performance
- conclusions as per the SR authors
- SR limitations as identified by the SR authors

In a SR, to reduce possible bias in reporting and interpretation, it is ideal to have two reviewers involved in the analysis of each included study, with collaboration in data extraction and interpretation. However, due to time constraints in the production of this report, the data were extracted from each article and assembled into the evidence tables by one author (VF).

4.1.4 Quality assessment strategy

a) Oxman and Guyatt scoring

Scientific reviews of higher quality are believed to draw more reliable conclusions. For this report, a modified version of a tool originally developed and validated by Oxman and Guyatt for assessing the quality of analysis articles served as the basis for quality assessment.[13-15] The version used in this report most closely resembles that presented by Egger.[16]

This tool was adapted to suit the project. The principal adaptations were minor modifications to the interpretation guidelines evident in the Egger version as well as minor modifications to a version developed earlier by CCOHTA researchers. An example of a modification made for this project was the addition of a requirement that a comprehensive search strategy must examine unpublished (grey) literature. The final version of the Quality Assessment Tool as adapted for the project is attached as Appendix 3.

The tool was piloted by VF and JM through several iterations to ensure consistency in interpretation. When the level of agreement between reviews was determined to be high, due to time constraints in completing the analysis, the final quality scoring was carried out by one author (JM).

b) Fryback and Thornbury grading

A hierarchy for assessment of the efficacy of diagnostic imaging was published in 1991 by Fryback and Thornbury.[17] While this tool was not identified a priori in the protocol, it was subsequently determined to be a useful method for classifying studies. The hierarchy of the tool assesses how the technology being examined contributes to patient management. The hierarchy consists of six levels.

- Level 1: Technical quality of the images
- Level 2: Diagnostic accuracy, sensitivity and specificity of the images
- Level 3: Degree to which results influence physicians' diagnostic thinking
- Level 4: Degree to which imaging results affect patient management
- Level 5: Efficacy studies measure the degree of effect on patient management
- Level 6: Analyses of societal costs and benefits of a diagnostic imaging technology

The Fryback & Thornbury quality hierarchy of efficacy was applied to each article by one author (JM).

c) Funding source

Empirical research with pharmaceuticals has found that conclusions are associated with bias in favour of a product when its manufacturer has funded the research. This trend may result from choice of an inappropriate comparator or publication bias. However, the quality of trials sponsored by industry versus others was found to be equal.[18]

4.2 Results

4.2.1 Quantity of research available

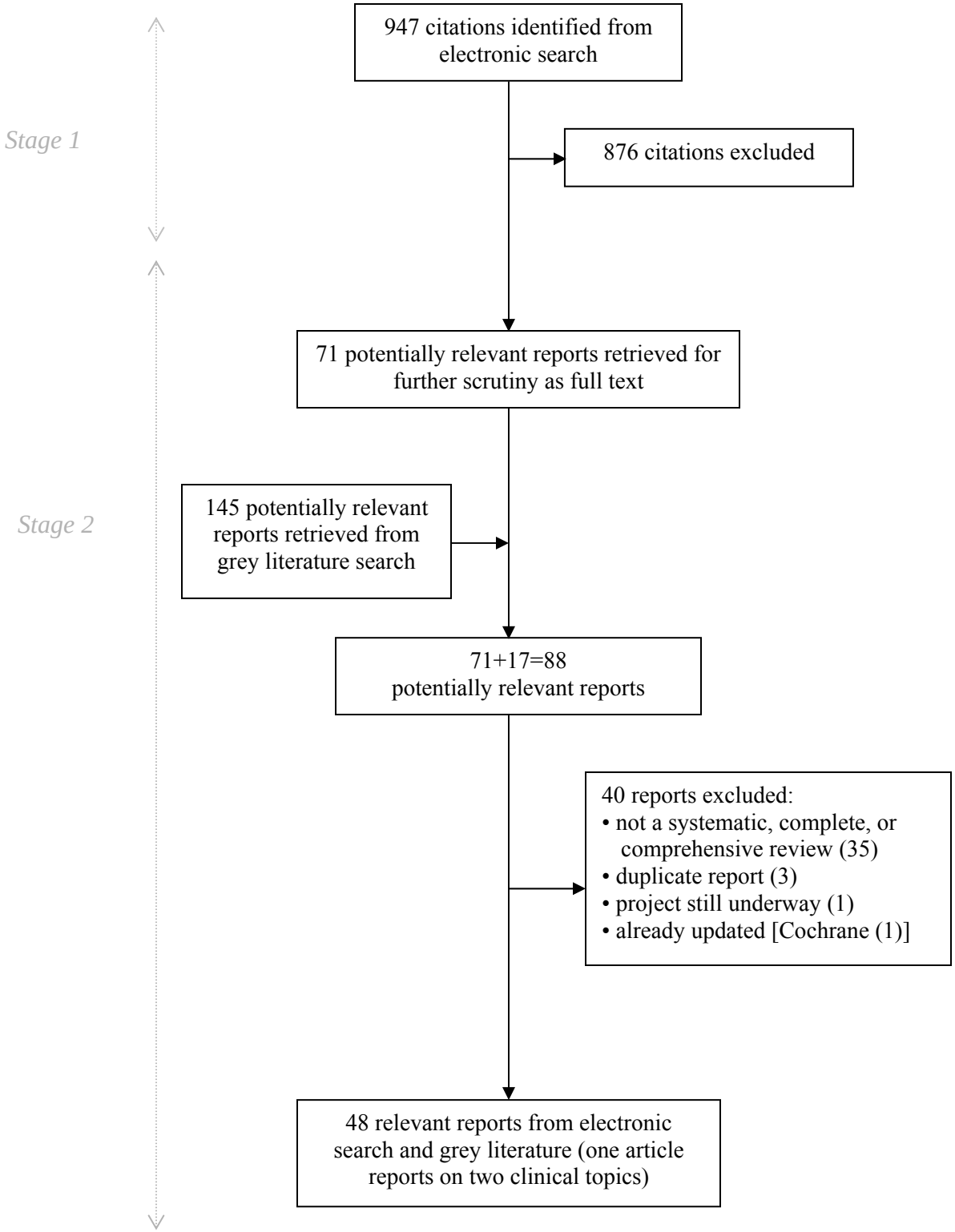
a) Electronic search

The electronic search yielded 947 possibly relevant citations. Independent screening using the selection criteria was carried out by two researchers (VF & JM) using the citations and abstracts (when abstracts were available) and resulted in the selection of 71 articles. These were requested in full text and then independently reviewed by the same researchers. A short-list of 31 articles (3%) resulted when the selection criteria were once again applied. The second round of review excluded 40 of 71 articles, primarily as they did not meet the inclusion criterion requiring them to be systematic or comprehensive reviews of the literature (Figure 4; Appendix 4). One reviewer selected 36 relevant articles, the other selected the same 36, plus four more. Of the four additional articles, the reviewers agreed to include one and reject the other three. A kappa score of 0.89 was calculated to measure the agreement between the two reviewers in the final selection of the articles. This high kappa score indicates excellent agreement.

b) Grey literature search

Search of the grey literature resulted in the identification of 145 electronic documents. These were independently reviewed for relevance (VF and JM), through application of the selection criteria. Seventeen articles (12%) were selected as relevant, through discussion and consensus. The higher yield from grey literature selection versus electronic literature selection (12% versus 3%) could arise from the fact that grey literature is sought in a more selective fashion. A number of relevant sources are directly tapped whereas an electronic search is much more broad-based and less selective at the outset.

Figure 4: Flow of document selection



c) Clinical categories and numbers of studies

Combining the articles selected through the electronic search (31) with those selected from the grey literature search (17) resulted in a total of 48 articles. One of these[19] reported on two of the included conditions and was therefore counted twice when the included SRs were summed.

Information on the use of CT or MRI for the investigation of the 13 clinical conditions had been sought, but SRs meeting the inclusion criteria were located for only 11 conditions; no SRs were found for cerebral AVMs or screening for urinary tract stones (Table 2).

Table 2: Selected clinical conditions and the number of SRs

Clinical Condition	Numbers of Included SRs
Cardiovascular conditions	
CAD	5
PVD	5
RAS	2
Chest conditions	
Lung cancer screening	8
PE	12
Neurological conditions	
Carotid artery disease	6
Cerebral aneurysms	3
Headaches	1
Head injuries	4
Seizures and epilepsy	1
Stroke	2
AVMs	0
Urological system	
Urinary tract calculi screening	0
TOTAL	**49***

* Number of included articles was 48: one reported on two conditions.

4.2.2 Quality of research available

a) Oxman and Guyatt scoring

Table 3 presents the questions contained in the adapted Oxman and Guyatt tool as well as the distribution of answers generated by applying the tool to the 49 SRs reviewed for this project. Generally, "YES" answers generated the best score, 7. One or more "CAN'T TELL" reduced the quality score to between 4 and 5, indicating minor flaws at best and possibly major flaws. A "NO" answer to questions 2, 4, 6 or 8 suggested major flaws and generated a quality score of three or less.

When the tool was applied, in terms of answer frequency, just over 50% of the questions earned "YES" responses. "NO" responses were particularly common for questions 2, 3 and 5; and questions 4 and 6 generated a large number of "CAN'T TELL." As suggested by these results, deficiencies related to search strategies, management of bias and validity issues were common.

Table 3: The number of studies achieving various scores on questions 1 to 9 [13-15]

Question	Yes	Partially or Can't Tell	No
Were the search methods stated?	39	4	6
Was the search fairly comprehensive?	26	8	15
Were the inclusion criteria stated?	32	7	10
Was bias avoided?	15	33	1
Were the criteria for validity stated?	16	10	23
Was validity assessed appropriately?	19	29	1
Were the methods used to combine the findings of studies reported?	40	6	3
Were findings combined appropriately?	31	11	7
Were the SR authors' conclusions supported by the data and/or analysis reported?	28	21	0

In terms of the distribution of overall quality scores, 72% (40/49) of the included reviews had scores of four or less (i.e., they possibly had major flaws or worse, while the balance had minor to minimal flaws (Table 4).

Table 4: The numbers of studies achieving various overall scores

Quality Score	0	1	2	3	4	5	6	7
Numbers of studies (n=49)	0	8	6	17	9	4	2	3

b) Fryback and Thornbury grading

While seven papers (14%) did not lend themselves to grading using the Fryback and Thornbury scale, the balance (86%) were all deemed to be Level 2 studies out of a possible 6 grading levels. Level 2 studies are defined as assessing the diagnostic accuracy, sensitivity and specificity of the images, in this case, often against the standard. The articles did not examine the impact of the technologies on patient management or outcomes, relationships necessary to earn a Level 4 to Level 6 study designation.

c) Funding source

No industry funding was reported for any of the included SRs (Table 5). Of the 49 reviews reported, 40% (20 out of 49) were funded by a government agency, such as the Agency for Healthcare Research & Quality (AHRQ) in the US and the National Health Service (NHS) in the UK. Non-profit agencies in the US − the Institute for Clinical Systems Integration (ICSI) and ECRI − conducted 8% (4 out of 49) reviews. No source of funding was reported for 42% (21 out of 49); this appeared to relate to whether the journal required authors to reveal their funding source(s).

Table 5: Sources of funding of included reviews (n=49)

Funding Source	Number of Reviews
Government agency	20
Non-profit agency	4
Professional or disease group	3
Not funded and explicitly stated	1
Not reported	21

4.2.3 Review characteristics for included reviews

a) General comments

Although all languages were considered and the English citations and abstracts of non-English (primarily German or French) reports were examined during the first step of the literature selection process, only English-language reviews met the inclusion criteria. The reviews were variable in scope, length, rigor and quality, ranging from several pages (e.g. Safriel & Zinn, 2002)[20] to hundreds of pages (e.g. Wardlaw *et al.*, 2004).[21] They were conducted by teams varying from one person (e.g. Gor, 2004)[22] to collaborations of dozens of people with several oversight committees (e.g. Teasdale *et al.* for SIGN, 2000).[23] In general, the reviews obtained through the electronic search were shorter and more focused whereas the grey literature pool included some extensive reviews of a number of competitive technologies and clinical conditions.

b) Country of origin

Nearly half of the reviews were led by investigators in the US (23 out of 49). The UK was a strong contributor, as were the Netherlands and Australia. A number of the reviews were conducted by teams of investigators and some were collaborations across several countries (Table 6).

Table 6: Country of lead investigator (n=49)

Country	Number of Reviews
Australia	4
Canada	1
Denmark	1
France	1
Netherlands	6
Sweden	1
UK	12
US	23

4.2.4 Data analysis and synthesis

In total, 49 SRs in 11 clinical categories met the inclusion criteria and the information from these 49 SRs was abstracted into 11 evidence tables (Appendix 5).

Based on studies of diagnostic accuracy, the evidence was promising for five conditions: carotid artery disease, peripheral vascular disease, pulmonary embolism, renal artery stenosis and stroke. Authors were more cautious about three conditions: cerebral aneurysms, coronary artery disease and lung cancer screening. Evidence was sparse for three conditions: headaches, head injuries and seizures. No SR evidence was identified for the remaining two conditions: cerebral AVMs and screening for urolithiasis.

a) Cardiovascular: CAD

Five reviews met the inclusion criteria for CAD,[22,24-27] the lead investigators being from the US (3), Australia and the UK (Appendix 5, Table 1). Several technologies were examined, including helical and spiral CT, MDCT and MRA.[a] Various reference standards were employed.

Budoff *et al.*[24] compared MRA, MDCT and electron beam angiography (according to the investigators, the three most promising non-invasive methods to visualize obstructions in the coronary tree) to invasive angiography. For MDCT, eight studies were analyzed and for MRA, five studies. For MDCT, the range for sensitivities was 37% to 85% and the summary value 59%; for MRA the range for sensitivities was 40% to 90% (no summary value was provided). With respect to specificities, for MDCT, the range was 76% to 99% and the summary value 89%; for MRA the range was 89% to 97% (no summary value was provided). The investigators felt these were rapidly developing techniques and displayed many advantages, but were not, at present, alternatives to conventional angiography.

Devang Gor,[22] a chief resident in diagnostic radiology in New Jersey, performed a meta-analysis of nine English language studies published between 1996 and 2003, enrolling from 11 to 109 patients (total n=317), and comparing MRA to invasive angiography. Study sensitivities ranged from 45% to 88% (overall 83%); specificities ranged from 58% to 95% (overall 82%). The investigator commented that MRA holds promise in being fast, safe and efficient, but technical advances and further studies are required.

Lillehie *et al.*[25] authored an HTA document for the ICSI in Minnesota, updating a 2000 report on EBCT. Helical CT was mentioned in one small section of the report and one trial was discussed – the MUNICH trial of 2,030 patients. The study was assigned a grade of "D" by the investigators, the grade awarded for the least rigorous trials. Coronary calcium was the outcome of interest and the investigators acknowledge that this outcome is not well researched for helical CT.

In Australia, the government-funded HTA Medical Services Advisory Committee (MSAC) produced a horizon scanning brief to advise policy makers about diagnostic and therapeutic procedures for CAD.[26] MDCT and MRA were discussed, as were several other technologies. For MDCT, 19 studies met inclusion criteria as did 10 studies for MRA; most studies were case series. Only overall summaries of findings were presented. For CT, MDCT angiography was found to have sensitivities and specificities which were quite high, but a number of arteries could not be evaluated using this technology. Two types of MRA were explored, both 2D and 3D techniques. Although published sensitivities and specificities varied widely, 2D MRA was felt to be inferior to invasive angiography. It was also stated that motion artifacts must be reduced and spatial resolution and contrast improved before 3D MRA can replace conventional angiography. The investigators caution that timelines were short for this horizon scanning brief and all steps for a full HTA were not carried out.

[a] There are several different MRA techniques, each one replacing the previous as technology advances: Time of Flight (TOF) MRA has been around longer, is quick and easy to do but has a relatively poor format and lots of artifact; phase contrast MRA can be 2D or 3D, can use single slabs or a wider field of view, but can also display unacceptable artifact and gaps in vessels; contrast enhanced studies can produce excellent images yet be inferior to CTA with respect to resolution of fine vessels.

The fifth and final SR originated in the UK; conducted by Morgan-Grant *et al*.[27] This 2002 publication aimed to review the technical advances and early trial data for MDCT and coronary artery imaging. No specific literature search or inclusion criteria were described. Only four studies were analyzed. Reported sensitivities, as compared with invasive angiography, ranged from 78% to 91% and specificities from 76% to 98%. The investigators stated, "there is currently certainly no place in clinical practice for routine MSCT coronary angiography. The images are not yet as reliable [as invasive angiography] and the radiation doses may be higher." The investigators acknowledged that there are some specific clinical situations where MDCT may be useful as an alternative or in addition to invasive techniques.

All papers referenced in this section earned very low quality scores (1 to 2). Most of the papers demonstrated serious deficiencies related to the comprehensiveness of the literature search, definition of criteria for including articles and steps taken to manage bias in the selection of articles. Overall, for this clinical indication, SRs were small in number and poor in quality.

b) Cardiovascular: PVD

PVD was addressed in five SRs[19,28-31] (Appendix 5, Table 2). All investigated MRA and all used invasive angiography as a reference standard; one[28] also permitted studies using intra-arterial pressure measurement (10% of the included studies) and another[19] also permitted cut-film angiography.

A number of primary studies have been published on this topic. The investigators included between nine and 34 studies in their reviews, with enrolled study populations of 11 to 155 patients (Table 7). Included studies covered several different MRA techniques: 2D, 2D phase contrast and 3D gadolinium-enhanced. Some investigators considered several categories of degree of stenosis, (e.g., 0% to 49% and 50% to 100%; or 50% to 99% and occlusion). Some investigators also divided the disease by arterial tract of the lower extremity (e.g., aortoiliac versus femoropopliteal versus infrapopliteal).

Table 7: SRs on MRA for PVD

Author	Country	Publication Year	Studies Included (#)	Sample Sizes of Included Studies	Studies with Contrast-enhanced MRA	Sensitivities and Specificities
Berry *et al.*[19]	UK	2002	20	12 to 155	8	Used SROC* curves
Eiberg *et al.*[28]	Denmark	2001	28	12 to 155	15	TOF-MRA: 93%; 88% CE-MRA: 96%; 96%
Koelemay *et al.*[29]	Netherlands	2001	34	13 to 115	20	40 possibilities: sensitivities ranged from 81% to 100%; specificities ranged from 23% to 100%
Nelemans *et al.*[30]	Netherlands	2000	23	12 to 45	8	Sensitivities ranged from 64% to 100%; specificities ranged from 68% to 96%
Visser & Hunink [31]	Netherlands /US	2000	9	11 to 30	9	Pooled data: sensitivity 97.5%; specificity: 96.2%

* SROC=Summary receiver operating characteristic

In general, investigators were enthusiastic about the performance of MRA and its potential to replace invasive angiography. Also, those investigating several MRA technologies found the newer technology, gadolinium-enhanced 3D MRA, to be superior to 2D in terms of examination time and accuracy. Limitations in primary studies were identified by several investigators. The limitations included small heterogeneous studies, incomplete clinical data, aggregate data, patient enrollment irregularities, arbitrary subdivision of arterial tracts, delays between tests and the possibility of publication bias.

Quality scores for the papers referenced in this section ranged from low to high (2 to 7). Eiberg *et al.*[28] and Visser and Hunink[31] earned scores of 2 and 3 respectively while Koelemay *et al.*[29] and Nelemans *et al.*[30] each received a score of 4. The paper by Berry *et al.*,[19] (referenced in section 6; Neurological: carotid artery disease) was one of two papers to earn a 7. The deficiencies evident in lower quality papers again related primarily to the comprehensiveness of the literature search, definition of inclusion criteria, steps to avoid bias.

c) Cardiovascular: RAS

Two SRs explored the use of CTA and MRA for the diagnosis of RAS: Tan *et al.* (2002) from the UK and the Netherlands[32] and Vasbinder *et al.* (2001),[33] also from the Netherlands (Appendix 5, Table 3). Invasive angiography was the reference standard in both cases – either catheter angiography or digital subtraction angiography (DSA).

Tan *et al.*[32] selected 25 studies for a meta-analysis, including 998 patients and 1,993 renal arteries. Publication dates for the studies ranged from 1991 to 1999. The studies were separated into those using gadolinium (12) and those without (15) (two studies included both). For each study, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The investigators concluded that "MRA is highly sensitive and specific for the diagnosis of RAS and that MRA with gadolinium enhancement is superior to non-enhanced MRA." They also acknowledged significant limitations to their analysis.

The publication of Vasbinder *et al.* from Maastricht[33] examined five technologies for patients suspected of having renovascular hypertension; two of them being CTA (five studies included) and MRA (14 studies included). Performance was measured using summary receiver-operator curves and linear regression compared the performance of tests to one another. The investigators found that CTA and MRA (particularly gadolinium-enhanced MRA) have better diagnostic accuracy than the other three tests studied (ultrasound, captopril renal scintigraphy or the captopril test) for the detection of RAS, but they felt patients must be carefully selected to ensure cost-effectiveness of investigations.

The paper by Tan *et al.*[32] earned a quality score of 3. The major deficiency related to the comprehensiveness of the literature search (i.e., only MEDLINE® and bibliographies were searched), and the lack of clarity regarding the steps taken to avoid bias. Vasbinder *et al.*[33] earned a quality score of 4. As was typical of most papers earning scores of 4 to 5, the paper by Vasbinder *et al.* suffered from a lack of clarity on one or two of the Oxman and Guyatt questions.

d) Chest: Lung cancer screening

CT was the only imaging modality of interest for lung cancer screening in the eight SRs identified[34-41] (Appendix 5, Table 4). These reviews were all conducted within a four-year time period, but there was considerable variation in the studies chosen by each group of investigators. None of the investigators pooled the data for the studies they analyzed, most reported each study separately.

Table 8: SRs on CT for lung cancer screening

Author	Country	Publication Year	Studies Included (#)	Publication Years of Studies Included	Total "N" of Studies Included
Bepler *et al.*[34]	US	2003	8	1995 to 2002	19,107
ECRI[35]	US	2002	3	1999 to 2001	7,852
Harmon *et al.* (ICSI) [36]	US	2001	4	1996 to 1999	8,082
Humphrey *et al.* (USPSTF)[37]	US	2004	6	1999 to 2003	18,387
Manser *et al.* (Cochrane Collaboration)[38]	Australia	2004	0*	N/A	N/A
Marcus *et al.* (NCI)[39]	US	2002	4	1996 to 2002	9,372
Minnesota HTA[40]	US	2000	4	1996 to 1999	9,295
Paulda *et al.* (CTFPHC)[41]	Canada	2003	3	1999 to 2001	7,188

* Manser *et al.*[38] for the Cochrane Collaboration examined lung cancer screening using sputum cytology, CXR and CT. Included studies were limited to RCTs and none existed for CT. Manser *et al.* is therefore excluded henceforth. N=combined patient populations of all studies included in SR.

All investigators commented that their included studies showed CT was capable of detecting small lung tumours at a stage earlier than what was achievable by other means. At the same time, all investigators were unable to recommend the use of CT for lung cancer screening because:

- evidence is insufficient
- no studies have shown reductions in mortality (i.e., there is no direct evidence linking CT screening with improved survival)
- PPVs are low (Bepler *et al.*[34] report PPVs of 0.08 for age ≥60; 0.04 for 50 to 59; 0.00 for <50)
- cost-effectiveness is unknown and in particular, the cost of follow-up of the high number of false positives is unknown
- there is high morbidity associated with post-CT follow-up procedures
- overall it is unclear whether the benefits of CT screening for lung cancer outweigh the harms.

The papers referenced in this section earned quality scores ranging from 1 to 6. As with the papers in previous sections, low quality scores were frequently associated with significant deficiencies related to the search for and selection of articles, while mid-range scores were associated with lack of clarity (frequently with regard to validity assessment) as opposed to clear deficiencies.

e) Chest: PE

For the investigation of PE, 12 SRs were included (Appendix 5, Table 5). Ten SRs investigated the performance of CT or CTA.[14,20,42-49] Segal and colleagues from Johns' Hopkins University in Baltimore explored both CTA and MRA in one section of a large report for AHRQ.[50] Stein *et al.* (2003) explored the use of MRA to determine whether it could be included among diagnostic alternatives for this indication.[51]

Table 9: SRs on CT or MRA for PE

Technology	Author	Number of Studies Included	Publication Years of Studies Included	Comparator Technology
CT or CTA	Berry *et al.*[42]	4	1992 to 1996	VQ and others
CT or CTA	Cueto *et al.*[43]	7	1992 to 1998	PA
CT or CTA	Harvey *et al.*[44]	11	1992 to 1998	PA
CT or CTA	Kelmenson *et al.* (ICSI)[45]	10	1992 to 2001	NR
CT or CTA	Kruip *et al.*[46]	3	1997 to 2001	NR
CT or CTA	Mullins *et al.*[47]	11	1992 to 1998	VQ or PA
CT or CTA	Rathbun *et al.*[48]	15	1992 to 1999	VQ or PA
CT or CTA	Safriel and Zinn[20]	12	1992 to 1999	VQ or PA
CT or CTA	van Beek *et al.*[49]	12	1994 to 1999	PA
CT or CTA	Villaneuva *et al.*[14]	6	1992 to 1998	PA
CTA and MRA	Segal *et al.* (ARHQ)[50]	CT: 8 studies plus 6 SRs MRI or MRA: 7	CT studies: 1994 to 2001 CT SRs: 2000 to 2002 MRI or MRA: 1993 to 2001	VQ or PA
MRA	Stein *et al.*[51]	3	1997 to 2002	PA

NR=not reported; PA=pulmonary angiography; VQ=ventilation-perfusion scintigraphy.

All reviews sought to determine the performance of CT (or MRI) in detection of PE as an alternative to the traditional investigations, primarily pulmonary angiography (PA) and ventilation-perfusion (VQ) scintigraphy. Investigators were generally interested in the sensitivities and specificities of the technologies being examined as compared with the identified reference standard(s).

The 10 included reviews examining CT and CTA were published between 1999 and 2003 and included from four to 15 studies. In all cases, the objective was to explore whether CT, as a rapid and non-invasive investigative technology, could replace the more time-consuming and invasive alternatives, especially since patients being worked up for PE can be very ill. Four compared CT to PA only,[14,43,44,49] while the others also allowed studies comparing CT with VQ scintigraphy; or the inclusion criteria were not stated.

In some cases the findings of included studies were reported individually whereas other reviews presented pooled calculations. Also, some reviews considered the data for emboli in the central pulmonary arteries apart from data for the peripheral pulmonary arteries (Appendix 5, Table 5). Investigators seem to vary in their enthusiasm for CT as the sole investigation, with many commenting that it may have a place among other tests, particularly early in the work-up of a patient.

The AHRQ report[50] is extensive, addressing nine research questions related to deep vein thrombosis and PE. Only one of these questions is relevant to this report: "What are the test characteristics of helical CT, MRI and MRA, relative to PA or VQ scanning, for the diagnosis of PE?" Both existing SRs and primary studies were analyzed for CT; only primary studies existed for MRA. Overall for CT, the sensitivities reported ranged from 45% to 100%; for the primary studies only, sensitivity was calculated at 86% (95% CI: 80%; 90%). Specificities overall ranged from 78% to 100% and for primary studies, was calculated as 92% (95% CI: 88%; 95%). The investigators listed a number of cautions about the results but concluded that moderate evidence exists to support a role for helical CT or MRA for the diagnosis of PE.

Stein and colleagues from five centres in the US and Canada were interested in the role of gadolinium-enhanced MRA for the detection of acute PE.[51] The three studies that met their inclusion criteria were case series (36 to 141 patients; published 1997 to 2002); and used PA as a reference standard. In these three studies, sensitivities ranged from 77% to 100% and specificities from 95% to 98%. The investigators concluded MRA may be a useful alternative for some patients, particularly if they have risk factors limiting other investigative technologies. They also commented that results may improve with today's advanced MRI technology and new contrast agents.

The papers referenced in this section earned quality scores ranging from 1 to 5. The papers by Berry *et al.;*[42] and Segal *et al.*;[50] had minimal flaws while the remaining papers had major to extensive flaws. Major flaws tended to be associated with lack of clarity, while extensive flaws were frequently associated with the literature search and selection.

f) Neurological: Carotid artery disease

Six SRs were located for this clinical category (Appendix 5, Table 6).

- One for CTA: Hollingworth *et al.* (2003),[52] from Seattle, Washington.
- One for both CTA and MRA: Long *et al.* (2002) from Marseilles, France, for the French government-funded HTA agency, ANAES.[53]
- Four for MRA: Berry *et al.* (2002) from Leeds in the UK, for the NHS;[19] Meenen *et al.* (2002) from Portland, Oregon, for the US agency AHRQ;[54] Nederkoorn *et al.* (2003) from the Netherlands;[55] and Westwood *et al.* (2002),[56] also from Leeds in the UK[56] (Berry and Westwood may cross-over somewhat).

Note: There are several MRA technologies, however not all the SRs specified the type of MRA used in their included studies, even though the performance of various types of MRA differ.

Table 10: SRs on CT or MRA for carotid artery disease

Technology	Author	Country	Publication Year	Studies Included (#)	Publication Years of Studies Included
CTA	Hollingworth *et al.*[52]	US	2003	43	1992 to 2002
CTA and MRA	Long *et al.* (ANAES)[53]	France	2002	30	NR
MRA	Berry *et al.*[19]	UK	2002	10	1993 to 1999
MRA	Meenen *et al.* AHRQ)[54]	US	2002	6	NR*
MRA	Nederkoorn *et al.*[55]	Netherlands	2003	21	NR
MRA	Westwood *et al.*[56*]	UK	2002	8	1993 to 1999

NR=not reported; *Westwood and Berry include the same eight primary studies with Berry having two additional. Both research groups are from the same centre in the UK.

Hollingworth *et al.*[52] examined CTA for carotid lesions, which required included studies to employ DSA or surgical findings as a reference standard. Beyond atherosclerosis, they also explored the use of CTA for blunt and penetrating carotid arteries injuries (13 out of 43 studies included in the review). Of the 30 atherosclerosis studies selected, data were pooled for the 15 highest quality studies: calculated were sensitivity of 95% (95% CI: 91%; 97%) for stenosis >70% (severe stenosis) and specificity of 98% (95% CI: 96%; 99%). Moderate stenosis (>30%) was also examined; and sensitivity calculated again at 95% (95% CI: 93%; 97%) with a slightly lower specificity at 92% (95% CI: 88%; 94%). The investigators concluded that "CTA is both a sensitive and specific imaging technique for identifying severe atherosclerotic stenosis and occlusion of the carotid arteries."

Both CTA and MRA (along with Doppler ultrasound) were assessed in an HTA performed by Long *et al.* in France,[53] both were compared with DSA as a reference standard. For CTA and MRA sensitivity and specificity in particular, 30 studies met inclusion criteria [CTA (19); MRA (11)]. The investigators reported the number of studies which obtained sensitivities ≥80% and specificities for ≥90% for both CTA and MRA, for both arterial stenosis ≥70% and arterial occlusion (Table 11).

Table 11: CTA and MRA sensitivities and specificities as reported by Long *et al.* (2002)

	CTA Sensitivity ≥80%	**CTA Specificity ≥90%**	**MRA Sensitivity ≥80%**	**MRA Specificity ≥90%**
Stenosis ≥70%	8 out of 9 studies	9 out of 9 studies	6 out of 6 studies	5 out of 6 studies
Occlusion	8 out of 9 studies	9 out of 9 studies	4 out of 4 studies	4 out of 4 studies

The investigators concluded that CTA and MRA "appear suitable for measuring stenosis of the proximal internal carotid when compared to DSA."

The four remaining SRs focussed on MRA:

- Berry *et al.*[19] and Westwood *et al.*,[56] from Leeds, UK, both published in 2002. Both used similar comprehensive literature search strategies, although Westwood included eight studies and Berry included 10 (Westwood's plus two). Both compared the performance of contrast-enhanced MRA to DSA or cut-film angiography to assess patients with carotid stenosis being considered for carotid endarterectomy. Westwood performed a meta-analysis, calculating values of maximal joint sensitivity and specificity: for 70% to 99% stenosis, 99% (95% CI: 98%; 100%); for 50% to 99% stenosis, 90% (95% CI: 81%; 99%). Westwood *et al.* concluded MRA is accurate for the pre-operative selection of patients with 70% to 99% stenosis, but not for patients with 50% to 99% stenosis, and they comment that the evidence is not robust. Berry *et al.* came to similar conclusions, supporting the use of MRA for 70% to 99% stenosis, but not for 50% to 99% stenosis.

- Meenan *et al.* from Oregon,[54] funded by AHRQ, produced an extensive report (320 pages) examining five technologies, including MRA, for the assessment and management of new stroke patients. Fifteen research questions were posed at the outset; one was directly relevant to this report: "What are the operating characteristics of available tests for measuring carotid

artery stenosis?" To address this question, six studies on MRA were included and pooled accuracy calculated for stenoses ≥50% and ≥70%. The results obtained were compared with calculations from a 1995 SR performed by Blakeley *et al.* and were generally lower. The investigators observed that studies assessing MRA accuracy for detecting severe stenosis (≥70%) demonstrated high sensitivities and specificities when 3D TOF imaging was used, but that these may be optimistic estimates as the study quality was poor and investigators in the included studies likely possessed skill and experience that were greater than average.

- From the Netherlands, the 2003 study by Nederkoorn *et al.* compared MRA (including contrast-enhanced MRA) and Doppler ultrasound with DSA in the determination of carotid stenosis severity.[55] For MRA, 21 studies were selected and analyzed according to the degree of arterial stenosis: <70%, 70% to 99%, and occlusion. Pooled results for 70% to 99% stenosis were: sensitivity 95% (95% CI: 92%; 97%), specificity 90% (95% CI: 86%; 93%), whereas pooled results for occlusion were: sensitivity 98% (95% CI: 94%; 100%), specificity 100% (95% CI: 99%; 100%). The investigators concluded that MRA is a sensitive and specific test for the evaluation of carotid artery stenosis and occlusion, but before it should be disseminated into practice, costs and effectiveness must be examined further.

The quality scores for these papers ranged from 3 to 7. This group of papers had the highest average score (5) of any of the clinical conditions addressed in this CCOHTA report. The lower-scoring papers in this group lacked clarity, particularly in relation to questions 4 and 6 of the Oxman and Guyatt tool.

There are several MRA technologies, however not all the SRs specified the type of MRA used in their included studies even though the performance of various types of MRA differ.

g) Neurological: Cerebral aneurysms

For this clinical condition, imaging can be used to work up a patient who presents with an acute event such as a subarachnoid hemorrhage. Cerebral aneurysms may also be diagnosed as a chance finding when imaging is carried out for other reasons. Screening is advocated by some in specific circumstances when there is a high index of suspicion, such as a positive family history or secondary risk factors.

Three SRs met the inclusion criteria: Chappell *et al.* (2003),[57] Van Gelder *et al.* (2003)[49] and White *et al.* (2000);[58] from the US, Australia and the UK respectively (Appendix 5, Table 7). All reported on use of the technology for diagnosis of cerebral aneurysms, although Van Gelder *et al.* and White *et al.* also mention screening. The SRs investigated the use of CTA but White *et al.* also investigated MRA and Doppler ultrasound. All used DSA as a reference standard, although Van Gelder *et al.* also allowed surgical findings to serve as the reference.

The number of included studies in the SRs varied considerably: 21, nine and 38 (the latter, White *et al*., examined three imaging modalities). Sensitivities and specificities were the outcomes of interest in two, Chappell *et al.* reporting calculations (weighted for sample size) of 92.7%; 77.2%; and Van Gelder *et al.* reporting ranges of 66% to 98%; 77% to 100%. White *et al.* reported accuracy per aneurysm: CT 89% (95% CI: 87%; 91%) and MRI 90% (95% CI: 87%; 92%); and noted that the test performed better when aneurysms were >3 mm. All investigators stated that CTA and MRA performed well, although not as well as the reference standard.

The paper by White *et al.* had only minor flaws but relied on older data. The remaining papers had major flaws driven by lack of clarity and/or issues related to validity.

h) Neurological: Headaches

Only one SR from the US,[59] met the inclusion criteria (Appendix 5, Table 8). This review focussed on children (ages three to 18) and was conducted for the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Included studies investigated the etiology of various types of headaches and were required to have 25 or more enrollees. Although 1,275 children were enrolled in the six included studies, only 605 (47%) had neuroimaging using CT or MRI.

The investigators combined the 605 patients and examined how many had imaging abnormalities (97/605; 16%) and of these, how many abnormalities were deemed to be incidental findings (79/97; 82%). Of the remaining 18 patients (3% of the total), 14 required surgery (10 tumours) and 4 required medical treatment. All of the 14 surgical patients had had abnormal neurological examinations. The investigators concluded that children with recurrent headaches do not benefit from CT or MRI if their neurological examinations are normal, although they provide some clinical scenarios that may be exceptions.

This paper earned a quality score of 3 which suggests major flaws. Inclusion criteria and issues related to process and validity assessment were unclear.

i) Neurological: Head injuries

For the investigation of head injuries, four SRs, from Sweden (1), the US (2) and Scotland (1) met the inclusion criteria[23,60-62] (Appendix 5, Table 9). The clinical conditions varied, with the first three limiting their reviews to mild head injuries, one of these being in children only.[62] The objective of the fourth document, developed by the Scottish Intercollegiate Guidelines Network (SIGN),[23] was to make recommendations on the initial management of head and neck injuries.

Af Geijerstam and Briton[60] calculated how often a CT performed on a patient with a mild head injury revealed pathological findings (15 studies reported use of CT; N=13,311; pathological findings in 7.8%). Eng and Chanmugam[61] also sought to identify the incidence of injury-related abnormalities on CT and analyzed 10 studies (N=9,362), finding an incidence of abnormal CT in 3% to 14% (weighted mean 7.5%).

Only one of these reviews sought to compare CT and MRI to other imaging modalities. The work of Homer *et al.*[62] evaluated the pediatric literature to synthesize evidence for an American Academy of Pediatrics CPG on head injury. Although 108 articles were analyzed in this document, only five reported on imaging modalities: skull x-rays, CTs and MRIs; CT served as the reference standard. The data showed that skull x-rays displayed sensitivity and specificity rates inferior to CT and that although MRI performed well, it offered no clinical advantage compared with CT.

In Scotland, the SIGN group produced an extensive report on head injury, with imaging (CT) forming one piece.[23] The investigators stated "criteria for use of CT in less severe head injuries was the most controversial part of the guidelines development process." The report presents a number of clinical scenarios where CT may be considered appropriate.

With respect to the use of skull x-rays, three of the four included SRs suggested that this technology is increasingly falling out of favour.[23,60,62] Af Geijerstam and Briton[60] suggested that routine use of skull x-rays to triage patients with mild head injury costs roughly the same as CT but provides results of less diagnostic value. Homer *et al.*[62] stated the test does not have sufficiently high sensitivity and specificity to be clinically useful in most cases; and the SIGN report[23] commented about the progressive move away from skull x-rays in favour of CT for provision of a definitive answer.

The papers referenced in this section were characterized by extensive to major flaws (scores of 1 to 3). Deficiencies were largely related to elements of the literature search and validity assessment.

j) Neurological: Seizures and epilepsy

The only SR to meet the inclusion criteria was a report from SIGN in Scotland (Appendix 5, Table 10).[63] The focus of the SIGN report was to provide recommendations for the diagnosis and treatment of epilepsy and the imaging section was short. Although an extensive literature review was conducted, few details were provided such as study selection criteria, included studies and specific results. Conclusions were reached as to the roles of CT and MRI, for example that MRI is the standard of reference in investigation of patients with epilepsy and that CT has a role in urgent assessment or when MRI is contraindicated. Imaging for seizures primarily aims to rule out underlying pathology such as tumours, malformations and stroke.

This SIGN paper earned a quality score of 3 which suggests major flaws. Problems relating to potential selection bias and the assessment of validity were evident, as well as the lack of identification of inclusion criteria.

k) Neurological: Strokes

Two SRs reported on the use of CT and MRI in the assessment of patients with stroke; both are from Scotland (Appendix 5, Table 11).[21,64] One SR was published in the journal *Stroke* and the second is an extensive HTA report from the NHS.

The first SR[64] looked at two advanced types of MRI for stroke: diffusion-weighted imaging (DWI) and perfusion imaging (PI). The SR included 84 studies of 3,235 patients examined using DWI or PI alone, combined, or combined with other advanced imaging modalities. In the analysis, the investigators stated that DWI found more lesions than conventional MRI or CT and could distinguish new lesions from old. However they felt there was insufficient information to enable firm conclusions about the superiority of DWI or PI compared with conventional MRI or CT. They suggested that further studies of DWI and PI as compared with routine imaging techniques such as CT should be done, allowing an assessment of added clinical value.

The HTA report produced by Wardlaw *et al.* in 2004 [21] covered many topics related to stroke; one chapter discussed imaging. The emphasis of the report was cost-effectiveness, with the clinical material being presented at the outset to establish clinical effectiveness. The investigators sought to determine from the literature what the sensitivity and specificity of CT and MRI were in the distinction of infarction versus hemorrhage for patients with stroke. They included 130 studies in their review (publication years 1976 to 2000; sample sizes 5 to 1,191).

As inadequate information was available from the literature, particularly comparing CT to MRI, they launched two prospective observational studies. However, they did draw several relevant conclusions from their analysis: knowledge of scan results made a difference to clinical management in 17% of cases following CT and 12% following MRI; rapid access to CT (<8 days) should be considered for patients suspected of having suffered a stroke to ensure diagnosis and management are appropriate; in patients with mild stroke, CT and MRI positively identify a similar proportion of recent infarcts; and more data are needed to determine a) the sensitivity and specificity of MRI for hemorrhage early after stroke and b) how to improve the detection of hyperacute infarcts on CT.

Both of the papers referenced in this section lacked clarity on points related to management of bias and validity assessment, resulting in quality scores of 4.

5 ECONOMIC ANALYSIS

In addition to this review of the clinical effectiveness of CT and MRI, a review of economic analyses of CT and MRI for the selected clinical conditions will be published by CCOHTA in a separate document.

6 HEALTH SERVICES IMPACT

CT and MRI are expensive to purchase and to operate. In addition, results of CT and MRI scans can lead to the requirement of further investigations, consuming additional resources from the health care system and patients (travel, inconvenience, time off work, etc.). This report is intended to help decision makers who are involved in the purchase and operation of CT and MRI equipment and those involved in the management of patients who might be candidates for use of the technology, to ensure that an evidence base for decision making exists. A more extensive examination of the health services implications of CT and MRI technologies, in light of the clinical and economic evidence underlying their use in these conditions, will be published by CCOHTA in a separate document.

7 DISCUSSION

7.1 Principal Findings

A complex search strategy was developed and resources combed, through both electronic databases and grey literature. Two researchers used selection criteria to distil nearly 1,100 citations down to 48 articles of interest, covering 49 relevant SRs. Of these, 31 were derived from electronic databases of published literature and 17 from grey literature. There were no relevant reviews located for two of the 13 clinical conditions initially identified (cerebral AVMs

and screening for urolithiasis). The number of included reviews per clinical condition varied from one (headaches, seizures) to 12 PE, with a median of four.

Findings for each of the 11 individual clinical conditions can be summarized as follows:

- CAD (five reviews): The selected reviews examined both CT and MRI, comparing them with invasive angiography. Overall, investigators concluded that these modalities are promising, but are not yet superior to catheter angiography.
- PVD (five reviews): All selected reviews examined MRA, comparing it with catheter angiography in most cases. Investigators were generally positive about MRA, particularly the newer gadolinium-enhanced 3D technology, which performed well in comparison with the traditional alternative [e.g., sensitivity and specificity: 96% and 96% reported by Eiberg *et al.* (2001)].
- RAS (two reviews): Although only two SRs were located for this clinical condition, both sets of investigators were impressed with the performance of gadolinium-enhanced MRA in particular. However, both reviews also identified limitations to the analyses they had performed and one expressed caution with respect to cost-effectiveness.
- Lung cancer screening (eight reviews): There is an increasing push to identify appropriate methods of screening for lung cancer and CT is foremost among these. All eight included SRs noted that CT is superior to other means for the detection of small lung tumours; however, there has thus far been no link between the detection of these tumours and reductions in mortality. Also, the false-positive rate is high and post-CT procedures can be invasive. It is unknown whether benefits outweigh harms, yet this balance is essential for all worthwhile screening maneuvres.
- PE (12 reviews): CT or CTA were investigated in 10 SRs and MRA in two, all being compared with PA or VQ scintigraphy. Overall, investigators were cautious about the role of CT or MRI, believing these technologies may well have a role in the work-up of patients suspected of having PE, although not all investigators were willing to exclude the use of traditional investigations as well. For MRA in particular, Stein and colleagues felt the newest MRA technology may benefit patients with contraindications for other noninvasive technologies and may also produce improved performance results compared with those reported in earlier studies.
- Carotid artery disease (six reviews): Four SRs examined MRA alone; one examined CTA alone; and one examined both. DSA and/or surgical results were used as the reference standard. Results generally supported these technologies when the most severe stenoses were investigated (≥70%). However, investigators remained cautious with respect to costs and effectiveness.
- Cerebral aneurysms (three reviews): All three SRs investigated the use of CTA although one also included MRA. It appeared performance of the technologies was good but insufficient to replace traditional catheter angiography.
- Headaches (one review): The only review located for this condition was restricted to pediatric cases and the perspective was to determine how worthwhile CT or MRI were as investigative technologies in children with recurrent headaches. The investigators found that all children with significant pathology on imaging also had abnormal neurological examinations and therefore concluded that CT and MRI are not beneficial for children with normal physical examinations.

- Head injuries (four reviews): The SRs differed significantly from each other: two were mainly interested in documenting the incidence of abnormal CT findings for patients with mild head injuries (which is approximately 8%); one compared skull x-rays to CT and MRI in children with mild head injuries and found the performance of CT and MRI to be similar to each other and superior to that of skull x-rays; and the fourth reported that use of CT is controversial but presented clinical scenarios where it may be appropriate.
- Seizures (one review): The single SR located was primarily interested in the role of CT and MRI in the diagnosis and treatment of epilepsy and concluded that MRI appears to be the current standard of reference, with CT being reserved for urgent assessments and when MRI is contraindicated.
- Stroke (two reviews): One review found DWI and PI, two specific forms of MRI imaging, promising, although in need of further research, but the review did not examine the applicability of CT and MRI overall as investigative tools for stroke. The second extensive SR supported the use of CT and MRI for investigation of stroke although found data lacking in some areas.[21]

The comprehensiveness of SRs was a continuum. Some investigators reported their processes in a very detailed and transparent fashion, while some provided little or no detail. Some used multiple information sources and performed exhaustive searches, some used a single literature source, and some provided little detail on their information sources. Some investigators were clear and comprehensive with respect to inclusion criteria, but in other cases it was not possible to determine what exact criteria were used to include or exclude studies. This variation is reflected in the quality scores assigned to each SR.

Assessment of the quality of the SRs was deemed to be important and tools were sought to allow quality to be measured and expressed in a quantitative fashion. The importance of quality in clinical trials of diagnostic imaging technologies has been acknowledged by Arrivé *et al.*,[65] but quality tools specifically for SRs in radiology were not identified. It is clear from our findings that the quality of the SRs was low and the SRs explored only Level 2 (of 6 possible levels) of the Fryback and Thornbury hierarchy of evidence, therefore not addressing impact on patient management or outcomes.

Several other observations can be made.
- Most of the reviews reported on case series trials, although occasionally case control studies and case reports were included.
- Most reviews (but not all) required the technology in question to have been compared with a reference or gold standard, generally catheter angiography. Increasingly, CT and MRI are considered the gold standard, therefore it will prove difficult to carry out comparative studies using older technologies as reference standards.
- In some reviews (but not all) the radiologist interpreters of images were blinded.
- Most investigators commented on the marked variation among their included trials, making synthesis of information difficult or impractical.
- Due to the small number of trials, many investigators used research that was more than five or even 10 years old, yet the technology has advanced significantly since that research was conducted.
- In reviews of the same topic during the same time period, lists of included primary research studies varied significantly.

Overall it was clear that assessment of diagnostic imaging technologies is challenging as it remains difficult to find good quality work extending much beyond technical reports and appraisal of diagnostic accuracy. This shortcoming appears to be accepted (though perhaps reluctantly) by many in the field. One factor contributing to the lack of published evidence on imaging is the lack of research funding in this area.

7.2 Strengths and Weaknesses

This report collected information from SRs on 11 clinical areas which radiology experts determined to be controversial with respect to investigation using CT and MRI technologies.[b] It appears that this approach may be unique. Only one similar body of work was located in the literature, an "ultra rapid review" of Positron Emission Tomography (PET) imaging in cancer management by Facey *et al.* in the UK (2004).[66] This review, commissioned and funded by the UK National Health Service HTA Program, is also a summary of SRs and HTAs and it examines the clinical effectiveness of PET in eight specific cancers.

A strength of our study is that we performed a rigorous SR of the literature. Accepted tools were used to assess the quality of study reporting and the level of efficacy. We also worked with diagnostic imaging experts to determine the conditions of interest. In addition, our review was initially requested to meet the needs of guideline developers, suggesting an immediate application for the work. In order to meet the timelines set for the guideline developers, the initial analysis and report drafts were completed during a short period of time.

However, there are a number of weaknesses.

- The limitation of the material to SRs dated the primary research under analysis, an important issue in this field where technology is improving and advancing rapidly – it could be argued that this disconnect between the literature reviewed and the currently used technology weakened the relevance of the conclusions drawn based on the SRs available.
- Since the literature capture was limited to the year 2000 forward, to try and align the research with current technology, some older (pre-2000) work was necessarily eliminated, thus also shrinking the pool of available research in certain clinical areas.
- The timeframe of the project did not allow for the exploration of the bibliographies of included references or contact with investigators for missing information.
- The clinical conditions that were identified as controversial were determined by consensus of a small group of experts, therefore other relevant conditions were likely overlooked.
- Due to the large number of conditions assessed, there were limited resources and a short timeline available to explore each condition in detail.
- Few SRs have been performed for a number of the clinical conditions, in some cases, only one or two; and in two cases (AVMs and screening for urinary tract calculi) no SRs were located.

[b] It is acknowledged that CT and MRI are employed in a large number of clinical conditions therefore other clinical conditions are worthy of study, beyond the subset examined in this report.

- Even within clinical categories, the types of patients included in the selected studies varied significantly, meaning that pre-test probabilities of disease or abnormalities could not be determined.
- The quality of the included reports was generally poor.
- Due to time constraints in the production of this report, data extraction for the population of the evidence tables and the quality assessment of the included reports were each conducted by only one CCOHTA author, possibly leading to bias in reporting and interpretation.

7.3 Meaning of the Study

In general, the clinical community would like to see rapid, noninvasive modalities such as CT and MRI, or minimally invasive modalities such as CTA and MRA, replace invasive and time-consuming investigations such as catheter angiography. Often, the patients being investigated are very ill and would benefit from testing that only takes several minutes with few potential complications. However, the new proposed modalities must perform as well as the modalities they are replacing, serving as more than add-ons, without additional benefits. On the other hand, use of a new technology as an add-on investigation may be justified if there are substantial gains to diagnostic certainty and consequent benefits to patient management, or if the investigations can replace several less sensitive procedures. These investigations may also free up hospital beds if they replace invasive technologies that traditionally required hospital admission or delays in hospital discharge.

A diagnostic imaging investigation occurs early in the clinical timeline of a patient, therefore there is a great deal of room for confounding; a number of treatment steps will occur between the diagnostic imaging test and the ultimate patient outcome. Radiologists do not manage patients beyond the diagnostic test and may therefore seldom design their research studies to include clinical outcomes from which they are temporally and physically removed. As a result, the studies reviewed for this report did not examine whether CT and MRI can positively influence the management or clinical outcomes of patients. However, this lack of reporting does not necessarily imply lack of clinical benefit.

Policy makers, clinicians and patients should be aware that the decision to use these technologies may be based solely on demonstrated diagnostic performance or clinical opinion. The level of evidence available for CT and MRI in these applications is limited; on the other hand, clinical opinion and experience may provide insights that are not reflected in the SR literature. Additionally, clinicians developing CPGs should be aware that many of the included SRs are of low quality and therefore could be of questionable accuracy.

7.4 Unanswered Questions and Future Research

The assessment of SR quality in this project employed a tool that examined the quality of the reporting of each of the included SRs, not the quality of their design and process. It is possible that the quality of reporting may not fully reflect the quality of the review itself; that is poor reporting may not reflect poor execution of an SR. Factors such as restrictions on the length of a

publication could theoretically lower the score of a well-conducted SR because its reporting was necessarily too spartan.

Of ultimate interest in HTA is the contribution that technology can make to patient management and outcomes. Reviews generally examined the accuracy of CT and MRI as compared with alternative technologies, not going beyond these outcome measures. It is entirely possible that in certain clinical scenarios, evidence of similar or improved diagnostic accuracy equates with clinical advantage, whereas in other clinical scenarios, it does not. Also, there may be advantages that are hard to quantitate, for example the use of CT and MRI as investigative tools may increase the confidence of clinicians and due to their noninvasive nature, may be preferred by patients.

This report examined only a subset of the many clinical conditions that CT and MRI are used to investigate. Further research could examine the evidence for the use of CT and MRI for the investigation of other clinical conditions as well as focusing on various specialized investigative uses of these technologies such as CTA and MRA and therapeutic uses. A significant limitation to research in the future, however, will be the use of comparative technologies: many of the traditional investigations are already being replaced by CT and MRI and it may be increasingly difficult to obtain ethical approval or to enroll patients in a study which employs the older standard investigations as comparators.

Restriction of this project to the analysis of SRs limited the review of recent literature, thus also limiting the use of studies which have been performed on the latest equipment. Updating of this report could consider analysis of only the most contemporary primary studies to try and target the use of technologies directly applicable to clinical practice. Such an exercise may be essential to ensure an impact for clinical and administrative decision makers. Also, early review, analysis and reporting of individual primary trials may allow the highlighting of weaknesses in this research, thus encouraging modifications in subsequent yet still timely trials. It should be noted, however, that the lack of SR evidence of the influence of CT and MRI investigations on patient management and outcomes could continue to be a shortcoming of more recent primary research.

Ongoing research in some areas may shed light on current controversies. For example, with respect to CT screening for lung cancer, an RCT of 50,000 individuals who are at high risk of developing lung cancer is underway at 20 sites in the US to determine whether CT screening reduces lung cancer-specific mortality. The effect of screening on quality of life and costs will also be assessed.[67]

8 CONCLUSIONS

In this project we aimed to summarize the SR evidence reporting on CT and MRI for the investigation of 13 specific medical conditions where controversy exists. Analysis of the information obtained led to a spectrum of support for CT and MRI, from promising to cautious to non-existent. Most studies suggested more research would be welcome to investigate the benefits of the technologies as compared with the techniques that are traditionally used.

For CT and MRI, technology has advanced rapidly and the devices which were used to conduct the primary studies in SRs analyzed for this report have often been upgraded or replaced. For this reason, practitioners in the field could argue that the findings of this report may not be contemporary enough to be useful for clinicians and decision makers as the ability of the report's findings to guide decisions may be seen as limited.

The case can be made that diagnostic imaging technologies may improve or expedite the identification of a disease process but cannot, a priori, change its outcome. Because an imaging investigation occurs early in the clinical timeline of the work-up of a patient's clinical disorder, some feel it may be difficult for imaging findings to affect patient management and outcomes. However, to ensure the most effective use of the technologies, measurement of their influence on patient management and outcomes must be a goal.

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APPENDIX 1: Project Protocol

Protocol for Two Reviews: Clinical and Economic Reviews of CT and MRI for Specific Disorders of the Cardiovascular, Thoracic, Neurological and Urological Systems

Background

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are high-end medical imaging technologies used for the investigation of a number of clinical disorders. The list of indications is constantly expanding, due in part to the increasingly detailed images possible with newer rapid multi-slice machines. These are expensive machines to purchase, operate and replace. Demand outpaces supply and probably always will.

One strategy developed to limit the use of CT and MRI scanners to investigations supported by evidence is clinical practice guidelines (CPGs). The Canadian Association of Radiologists (CAR) has an initiative underway to investigate CPGs for CT and MRI and the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) has offered assistance with the goal of producing evidence-based guidelines for decision makers.

The CAR is particularly interested in the use of CT and MRI in areas they have determined to be controversial:

- cardiovascular: coronary artery disease (both investigation and screening), peripheral vascular disease and renal artery disease
- thoracic: screening for lung cancer, diagnosis of pulmonary embolism
- neurological: primary investigation of seizures, headaches, head injuries, stroke, carotid artery disease, cerebral aneurysms (both investigation and screening); and arteriovenous malformations (both investigation and screening)
- urological: screening for urinary tract calculi.

CCOHTA has offered to carry out two different projects: two systematic reviews (SRs) on the use of CT and MRI for the clinical conditions listed above. One project will consist of an SR of clinical SRs published on these topics; and the other project will be an SR of economic evaluations (EEs) published on these topics.

The projects will each be conducted in two stages, first to respond to the timelines of the CAR and its Guidelines Committee and then to produce a final CCOHTA report.

Objective

The objective of the two projects is to investigate and report on the existing literature; and to determine what SR and EE evidence exists related to CT and MRI for the clinical conditions listed above.

Research questions

SR of clinical SRs

- In the available literature, what SRs have been produced?
- For these SRs, what clinical questions did they ask and what did they find?
- What are the strengths and weaknesses of each SR?
- What limitations exist and what is unknown?
- What other reviews (narrative, general) exist that are not SRs?

SR of EEs

- In the available literature, what EEs have been produced?
- For cost-effectiveness analyses (CEAs) in particular, what were the criteria, models or types of prospective analysis; and outcomes employed?
- What other relevant EE studies exist that are not CEAs?
- What are the strengths and weaknesses of each CEA (possibly for other types of EEs as well, depending on the number and type of studies)?
- What limitations exist and what is unknown?

Methods

SR of clinical SRs

a) Literature search: Published literature will be retrieved by using a well-defined search strategy. On the DIALOG® system, MEDLINE®, EMBASE®, INSPEC®, BIOSIS Previews® and PASCAL will be cross-searched. The search strategy will focus on the objectives of the review and will include search terms for CT and MRI technologies in the cardiovascular, thoracic, neurological and urological clinical areas determined to be controversial by CAR.

A clinical filter will be used to retrieve systematic reviews for the clinical review. An economic filter will be used to create a sub set of EEs for the economic review. In addition to databases searched for clinical review, NHS EED and the Health Economics Evaluations Database (HEED) will be searched.

Regular database alerts will be will be established on MEDLINE®, BIOSIS Previews®, EMBASE® and INSPEC® databases to capture new publications. Parallel searches will be performed and updated on LILACS, the Cochrane library and PubMed databases to capture additional studies.

The search will be limited to the year 2000 onward to retrieve literature on contemporary technologies. There will be no language limit applied.

Grey literature will be retrieved by searching web sites of major radiological, cardiovascular, thoracic, neurological and urological associations, as well as health technology assessment and related agencies. These searches will be supplemented by hand searching selected bibliographies (references obtained may be pre-2000). In addition, subject experts may be contacted for related information useful for both of the reviews.

b) Selection of potentially relevant articles: two reviewers (VF and JM) will independently review citations and abstracts and apply the following inclusion criteria:
- included will be self-identified reviews that are complete, comprehensive or systematic reviews of the medical literature describing the use of CT or MRI to assess the clinical conditions listed
- SRs in a language other than English will be assessed and included if feasible
- if there are few SRs, general and narrative reviews involving the clinical conditions listed, they will be included in an appendix, but will not be assessed in detail.

c) Selection of relevant studies: the full reports of articles identified in the broad screening will be acquired and two reviewers (VF and JM) will independently apply agreed inclusion criteria to make the final selection of relevant articles.

d) VF and JM will apply the validated Oxman and Guyatt tool to assess the included references; assessments will be qualitative.

e) Collaborating with the CAR, ProMed researchers will develop a set of tables displaying and commenting on existing SRs in a format useful to the CAR. Through this collaboration additional text to be added (e.g., introduction, methods, bibliography, etc.) will be determined. It is possible that appendices will include references to useful SRs written in languages other than English; and general or narrative reviews which are not SRs but are deemed noteworthy.

f) ProMed will deliver the documents to CCOHTA and the CAR according to the timelines, processes and format established.

SR of EEs

a) Literature search: the search developed for the clinical report will be run concurrently for economics references.

b) Selection of potentially relevant articles: two reviewers (JM and RW) will independently review citations and abstracts and apply the following inclusion criteria:
- included will be EEs of the use of CT or MRI to assess the clinical conditions listed. Priority will be given to cost-effectiveness analyses (CEAs)
- EEs in a language other than English will be assessed and included if feasible
- if there are few CEAs, other types of EEs of the clinical conditions listed will be included in an appendix, but will not be assessed in detail.

c) Selection of relevant studies: the full reports of articles identified in the broad screening will be acquired and two reviewers (JM and RW) will independently apply agreed inclusion criteria to make final selection of relevant articles. This collection of selected citations will be reviewed for clinical relevance before articles are requested (BL or VF).

d) Where possible, studies will be rated by the McMaster University Centre for Evidence-based Medicine criteria: Levels of Evidence and Grades of Recommendation.

e) Collaborating with the CAR, ProMed researchers will develop a set of tables displaying and commenting on existing EEs in a format useful to the CAR; and through this collaboration will determine additional text to be added (e.g., introduction, methods, bibliography, etc.). It is possible that appendices will include references to useful CEAs written in languages other than English; and other types of EEs that are not CEAs, but are deemed noteworthy.

f) ProMed will deliver the documents to CCOHTA and the CAR according to the timelines, processes and format established.

Deliverables

Phase I

Two reports will be submitted (one clinical, one economic) composed primarily of tables of information.

Phase II

Following delivery of the documents described in Phase I; and review and comments by CAR and CCOHTA, the material will be integrated into a report suitable for publication by CCOHTA.

APPENDIX 2: Literature Search Strategy

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
DIALOG One Search® MEDLINE® EMBASE® BIOSIS Previews® INSPEC® PASCAL	Human 2000 -	(Magnetic resonance imaging! OR magnetic resonance spectroscopy!)/MAJ [MEDLINE] OR (Magnetic resonance imaging OR magnetic resonance spectroscopy OR electron spin resonance OR electron tomography OR electron-beam computed tomography OR NMR spectroscopy OR NMR)/de [BIOSIS] OR (Nuclear magnetic resonance imaging!)/MAJ [EMBASE] OR (MRI OR MR()imag? OR NMR OR MR spectroscop? OR nuclear()magnetic()resonance OR magnetic()resonance()imag? OR magnetic()resonance()spectroscopy? OR OR MR()tomograph? OR FMRI OR chemical()shift()imaging OR zeugmatography)/ti,ab OR (Tomography, x-ray computed!)/MAJ [MEDLINE] OR (computed tomography OR computed tomography scan OR computerized tomography OR computerized image analysis OR spiral computed tomography OR helical computed tomography) /de [BIOSIS] OR (Computer assisted tomography!)/MAJ [EMBASE] OR (ct OR cat()scan? OR cts OR comput?()tomograph? OR multi-slice OR multi()slice OR multisection OR multidetector OR multi-detector OR multi()row OR multi-row OR 4()slice OR 8()slice OR four()slice OR 16()slice OR sixteen()slice)/ti,ab OR ((spiral OR helical OR volumetric) (3N) (scan OR scanner OR CT OR compute? OR tomograph? OR CTs))/ti,ab ***AND*** (Seizures! OR headache disorders! OR cerebrovascular disorders! OR craniocerebral trauma!)/de [MEDLINE] OR (Seizure OR headache OR head injury OR stroke OR carotid artery disease OR cerebral aneurysm OR cerebral arteriovenous malformation)/de [BIOSIS] OR (Seizure, epilepsy and convulsions! OR headache OR headache and facial pain! OR stroke OR cerebrovascular disease! OR carotid artery disease! OR aneurysm! OR arteriovenous malformation!)/de [EMBASE] OR

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		(Brain artery aneurysm OR intracranial arteriovenous malformation)/de OR ((cerebral OR cerebellar OR cerebro? OR brainstem or brain()stem OR vertebrobasilar) (2N) (infarct? OR isch?emi? or thrombo? or embol?))/ti,ab OR ((carotid? OR cerebral OR cerebellar OR cerebro? OR infratentorial OR supratentorial OR subarachnoid OR brain OR intraventricular OR brainstem OR brain()stem) (2N) (haemorrhag? OR hemorrhag? OR haematoma? OR hematoma? OR bleed? OR aneurysm?))/ti,ab OR (AVM OR arteriovenous()malformation?)/ti,ab OR (Transient()isch?emic()attack? OR TIA OR reversible()isch?emic()neurologic?()deficit?)/ti,ab OR [(Lung neoplasms! OR urinary calculi! OR pulmonary embolism)/de [MEDLINE] OR (Lung cancer OR lung carcinoma OR lung tumor OR lung tumors OR pulmonary adenocarcinoma OR pulmonary embolus OR pulmonary embolism OR ureteral calculi OR ureteral stone OR ureteral stones)/de [BIOSIS] OR (Lung cancer! OR lung tumor!)/de [EMBASE] OR ((lung? OR pulmonary OR bronchogenic OR bronchial OR pancost?)(2N)(syndrome? OR cancer? OR tumo?r? OR carcino? OR adenocarcinoma OR small()cell OR squamous()cell OR neoplasm? OR blastoma OR coin()lesion? OR embolus OR emboli?))/ti,ab OR (Urinary OR bladder OR kidney OR matrix OR ureteral OR cystine OR decubitus OR encysted OR fibrin OR hemp()seed OR mulberry OR oxalate OR struvite OR urosteality OR xanthic)(1N)(calculi OR calculus OR stone OR stones))/ti,ab AND (screening OR mass()screening OR screen?)/de,ti,ab] OR (Coronary arteriosclerosis OR peripheral vascular diseases)/de [MEDLINE] OR (coronary()artery()disease?)/de,ti,ab OR coronary heart disease/de [BIOSIS] OR (Peripheral vascular diseases! OR Coronary artery disease)/de [EMBASE]

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
		OR (peripheral (2N) (angiopathy OR angiopathies OR vascular()disease?))/ti,ab OR (Renal artery obstruction)/de [MEDLINE] OR (Renal artery stenosis)/de [MEDLINE, BIOSIS] OR ((renal()arter? (1N) (stenosis OR stenoses OR obstruction))/ti,ab OR ((heart OR myocardial OR chest OR coronary)(1N)(attack? OR isch?emia OR pain))/ti,ab ***AND*** dt=(meta-analysis OR review OR review academic OR review literature) [MEDLINE] OR dt=review [EMBASE] OR Review literature!/de [MEDLINE] OR (Meta analysis OR review)/de [EMBASE] OR Reviews/de [INSPEC] OR (review OR review articles OR literature review OR meta-analysis)/de [BIOSIS] OR (meta()analy? OR metaanaly? OR meta()analy? OR metanaly? OR meta()regression OR metaregression OR mega()regression? OR pool?()analy? OR data()synthes? OR pool?()effect? OR data()extraction? OR data()abstraction? OR mantel()haenszel OR peto OR dersimonian OR der()simonian OR fixed()effect?)/ti,ab OR ((systematic? OR quantitative? OR methodologic? OR collaborative? OR integrative OR integration) (2N)(review? OR overview? OR synthes?s OR research))/ti,ab ***NOT*** DT=(letter OR review of reported cases OR historical article OR review multicase) OR (letter? OR editorial? OR historical()article? OR review()of()reported()cases)/ti,ab *Search performed on 23 08 2004* *Dialog alerts set up on same databases until November 30,2004*

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
The Cochrane Library, Issue 3, 4, 2004	2000 – Human	Same MeSH headings and keywords as DIALOG Medline search excluding clinical filter and excluding numbers from search terms (not supported).
PubMed	2000 – Human	Same MeSH headings and keywords as DIALOG Medline search. “In Process” and “Publisher” filters were included to retrieve pre-MEDLINE records. Last PubMed update November 25, 2004
Websites of HTA & related agencies; trial registries; other databases; Professional Associations		NICE; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD; RSNA, American College of Cardiology, American College of Radiology, American Thoracic Society etc.

APPENDIX 3: Quality Assessment Tool*

Study being assessed: _____

1. Were the search methods used to find evidence (original research) on the primary question(s) stated?

   ☐ yes ☐ partially ☐ no

   Yes for studies reporting specific sources, search terms and years searched.

2. Was the search for evidence reasonably comprehensive?

   ☐ yes ☐ can't tell ☐ no

   Yes if at least three source categories are reported, one electronic and one which must potentially identify unpublished material

3. Were the criteria used for deciding which studies to include in the overview reported?

   ☐ yes ☐ partially ☐ no

   Yes, if population, intervention and outcomes are addressed.

4. Was bias in the selection of studies avoided?

   ☐ yes ☐ can't tell ☐ no

   Yes if at least two reviewers independently assessed for inclusion; method of reaching consensus is discussed; and extent of agreement recorded (qualitative or quantitative).

5. Were the criteria used for assessing the validity of the included studies reported?

   ☐ yes ☐ partially ☐ no

   Yes if the study reports "a priori" methods of validity assessment

6. Was validity assessed appropriately?

   ☐ yes ☐ can't tell ☐ no

   Yes is given if there is a description of any criteria (either internal or external) used either for inclusion, or for analysis (e.g., sensitivity analysis).

7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?

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* Adapted from *Systematic Reviews in Health Care: Meta-analysis in Context. Ed: Egger M, Smith GD, Altman DG. BMJ Books. London. 2001*

☐ yes ☐ partially ☐ no

8. Were the findings of the relevant studies combined appropriately, relative to the primary question the overview addresses?

   ☐ yes ☐ can't tell ☐ no

   If no attempt was made to combine findings; and no statement is made regarding the inappropriateness of combining findings, check "no". If a summary (general) estimate is given anywhere in the abstract, the discussion or the summary section of the paper and it is not reported how the estimate was derived, mark "no" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt mark "can't tell".

9. Were the conclusions made by the author(s) supported by the data or analysis reported in the overview?

   ☐ yes ☐ partially ☐ no

   For an overview to be scored as "yes", data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses.

10. How would you rate the scientific quality of the overview?

Extensive Flaws		Major Flaws		Minor Flaws		Minimal Flaws
1	2	3	4	5	6	7

    The overall scientific quality should be based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score. If the "can't tell" option is used one or more times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (i.e. a score of 4 or lower). It the "no" option is used on question 2, 4, 6 or 8, the review is likely to have major flaws (i.e. a score of 3 or less, depending on the number and degree of the flaws).

APPENDIX 4: Excluded Articles

Not a systematic, complete, or comprehensive review (34)

American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected pulmonary embolism. *Ann Emerg Med* 2003;41(2):257-70.

Biffl WL. Diagnosis of blunt cerebrovascular injuries. *Curr Opin Crit Care* 2003;9(6):530-4.

Collins J. CT screening for lung cancer: Are we ready yet? *Wis Med J* 2002;101(2):31-4.

Cost-effectiveness of CT in stroke: a systematic review of the available evidence, detailed costings and decision modelling analysis. *Health Technol Assess* 2004;8(1):11-20.

Cost-effectiveness of CT in stroke: a systematic review of the available evidence, detailed costings and decision modelling analysis. *Health Technol Assess* 2004;8(1):71-100.

Datortomografi eller övervakning på sjukhus vid hjärnskakning? Samlade slutsatser i ny SBU-rapport [Computer tomography or hospital monitoring in brain concussion? Current conclusions in a new SBU-report]. *Lakartidningen* 2000;97(47):5493-6.

Ertl-Wagner B, Hoffmann RT, Bruning R, Reiser MF. Wertigkeit der CT-Angiographie in der Diagnostik intrakranieller Aneurysmen: Übersicht über die Literatur und erste Erfahrungen mit 4- und 16-Zeilen-Multidetektor-Computertomographen [CT-angiographic evaluation of intracranial aneurysms - a review of the literature and first experiences with 4- and 16-slice multi detector CT scanners]. *Radiologe* 2002;42(11):892-7.

Fayad ZA, Choudhury RP, Fuster V. Magnetic resonance imaging of coronary atherosclerosis. *Curr Atheroscler Rep* 2003;5(5):411-7.

Friberg L, Sandrini G, Jänig W, Jensen R, Russell D, Sanchez del Rio M, *et al.* Instrumental investigations in primary headache. An updated review and new perspectives. *Funct Neurol* 2003;18(3):127-44.

Girard N, Chaumoitre K, Millet V, Gire C, Boubred F, Lacroze V, *et al.* Imagerie des désordres neurologiques néonataux [Imaging of neonatal brain disorders]. *J Radiol* 2003;84(5):547-78.

Glauser J. Head injury: Which patients need imaging? Which test is best? *Cleve Clin J Med* 2004;71(4):353-7.

Hatabu H, Uematsu H, Nguyen B, Miller WT, Hasegawa I, Gefter WB. CT and MR in pulmonary embolism: a changing role for nuclear medicine in diagnostic strategy. *Semin Nucl Med* 2002;32(3):183-92.

Henschke CI, Yankelevitz DF, Kostis WJ. CT screening for lung cancer. *Semin Ultrasound CT MR* 2003;24(1):23-32.

Hiorns MP, Mayo JR. Spiral computed tomography for acute pulmonary embolism. *Can Assoc Radiol J* 2002;53(5):258-68.

Hsia AW, Tong DC. New magnetic resonance imaging and computed tomography techniques for imaging of acute stroke. *Curr Atheroscler Rep* 2003;5(4):252-9.

Hutter A, Kedan I, Srokowski TP, Zheng J, Gropler RJ, Woodard PK. Coronary magnetic resonance angiography. *Semin Roentgenol* 2003;38(4):330-41.

Jacobson FL. Multidetector-row CT of lung cancer screening. *Semin Roentgenol* 2003;38(2):168-75.

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APPENDIX 5: Evidence Tables

List of Tables

Table Number	Clinical Category	Clinical Condition	Clinical Manoeuvre(s)
1	Cardiovascular	Coronary artery disease	Screening and diagnosis
2	Cardiovascular	Peripheral vascular disease	Diagnosis
3	Cardiovascular	Renal artery stenosis	Diagnosis
4	Chest	Lung cancer	Screening
5	Chest	Pulmonary embolism	Diagnosis
6	Neurological	Carotid artery disease	Diagnosis
7	Neurological	Cerebral aneurysms	Screening and diagnosis
8	Neurological	Headaches	Diagnosis
9	Neurological	Head injuries	Diagnosis
10	Neurological	Seizures or epilepsy	Diagnosis
11	Neurological	Strokes	Diagnosis

Table 1: Coronary artery disease − CT and MRA

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Budoff MJ *et al.*, 2003;[24] UCLA Medical Center Research & Education Institute, Torrance, CA; University of Erlangen-Nuremberg, Erlangen, Germany; University of Texas Southwestern Medical Center, Dallas TX Journal of the American College of Cardiology, 2003. To provide a comprehensive review of the literature relating to EBA, MRA and MDCT; currently the three most promising non-invasive methods to visualize obstructions in the coronary tree. Funder: NR	The abstract states MEDLINE searches were performed but there is no mention of a literature search in the text. No further detail is provided.	Articles were sought reporting on noninvasive angiography utilizing MRI, MDCT or electron beam tomography. There is no mention of specific inclusion or exclusion criteria and it appears articles were selected if deemed relevant. Tables display lists of studies providing accuracy data for CT and MRA versus invasive coronary angiography. Listed studies: MDCT versus invasive angiography: Achenbach *et al*., 2001, n=64 Giesler *et al.*, 2001, n=83 Giesler *et al.*, 2002, n=100 Hong *et al.*, 2000, n=25 Knez *et al.*, 2000, n=44 Kuettner *et al.*, 2003, n=66 Nieman *et al.*, 2002, n=53 Nieman *et al.*, 2002, n=78 MRA versus invasive angiography: Duerinckx *et al.*, 1994, n=21 Manning *et al.*, 1993, n=39 Mohiaddin *et al.*, 1996, n=16 Pennell *et al.*, 1996, n=39 Post *et al.*, 1997, n=35	Sensitivities and specificities are reported for the included trials. Sensitivity MDCT 37% to 85%, with a summary value of 59%; MRA 40% to 90% (no summary value given); specificity MDCT 76% to 99%, with a summary value of 89%; MRA 89% to 97% (no summary value given). Contrast-enhanced EBCT was also reported (10 trials comparing EBCT to invasive coronary angiography; total n=583). Sensitivities 74% to 92%, with a summary value of 87%; specificities 82% to 100%, with a summary value of 91%. Concerns were expressed about radiation dose for pt(s) for CT and limitations for MRI (e.g., metal artifacts, calcifications, long study times and pericardial fluid).	"Noninvasive coronary angiography is a rapidly developing technique and currently not an alternative to conventional coronary angiography in all cases." "All 3 methods [EBA, MDCT, and MRA] are currently used clinically in certain centres. Selective use might prove cost-effective and provide a safer, less invasive method for patients. These non-invasive techniques have potential capabilities of assessing perfusion and coronary flow in addition to coronary anatomy, and thus may provide a comprehensive cardiac evaluation." "Successful development of a noninvasive angiogram with consistently high sensitivity and specificity for obstructive CAD would greatly reduce the cost and also the morbidity and mortality currently associated with conventional coronary arteriography."	1 2 The literature search is not detailed and there is no evidence that studies were selected in a predetermined or rigorous fashion.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Gor DM, 2004;[22] Chief resident in Diagnostic Radiology, New Jersey Medical School, Newark NJ Supplement to Applied Radiology, 2004. To present a meta-analysis of the efficacy of MRA compared with catheter angiography in the detection of significant (>50%) coronary stenosis. This is one small part of a larger document discussing technical aspects and clinical applications of CTA and MRA. Funder: NR	MEDLINE 1993 to 2003 English language studies	Inclusion criteria: compared 3D MRA or echo-planar imaging to catheter angiography; prospective study; consecutive pt(s) enrolled; ≥10 patients; no selection bias; double-blind technique; no IV contrast; breath-hold or some method of respiratory motion correction; ≥70% of MRAs of diagnostic quality; and maximum time between MRA and catheter angiography=1 month. 20 studies identified; 9 met inclusion criteria Included studies: Bogaert *et al.*, 2003 (n=19) Kim *et al.*, 2001 (n=109) Lethimonnier *et al.*, 1999 (n=17) Muller, 1997 (n=30) Plein *et al.*, 2003 (n=40) Post *et al.*, 1996 (n=20) Sardanelli *et al.*, 2000 (n=39) Van Guens *et al.*, 1999 (n=32) Weber *et al.*, 2002 (n=11) Range of the number of coronary segments assessed=62 to 636; mean=189; and median value=151.	Findings from the MA of MRA versus catheter angiography: sensitivities 45% to 88%; specificities 58% to 95%; PPVs 54% to 87%; and NPVs 80% to 96%. Overall sensitivity of MRA=83% Overall specificity=82%	"MRA holds promise to be a safe non-invasive, and efficient test in evaluating the coronary arteries. Technical advances such as faster imaging sequences and prospective double-blinded studies are needed to evaluate the full extent of its clinical usefulness." Limitations (as per author): Only 2 variables could be evaluated in the MA (sensitivity and specificity) due to the small number of studies that met the inclusion criteria. He would also have liked to examine the effect of sample size on sensitivity and specificity. Also, there was a high level of inter-observer variability for the determination of sensitivity of coronary MRA for significant stenosis.	2 2 Very limited literature search, including only one keyword phrase used in search.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Lillehie *et al.*, 2000;[25] Institute for Clinical Systems Improvement (ICSI), Bloomington MN ICSI Technology Assessment Report, 2004 To update a 2000 ICSI report on CT for CAD, as "CT is increasingly being used as an adjunct to CV risk factors in identifying patients at high risk of developing CAD and future cardiac events." The report was primarily concerned with EBCT, but had a small section on helical CT. Funder: ICSI is an independent not-for-profit organization funded by 6 Minnesota health plans.	Literature sources, dates and strategy not provided	Inclusion and exclusion criteria were NR Process for selection of literature was NR Evidence was graded according to a classification developed by ICSI (conclusions are graded as well) Included study: The only study used was Schmermund A, Erbel R, Silber S. Age and gender distribution of coronary artery calcium measured by four-slice computed tomography in 2,030 persons with no symptoms of coronary artery disease. Am J Cardiol 2002;90:168-73. According to ICSI, the study evaluated 2,030 pt(s) from the Multislice Normal Incidence of Coronary Health Registry (MUNICH). Included pt(s) had no previous Hx or Sx of CAD; had an average age of 56 years and 75% were men. Risk factors for CAD were assessed, four-slice CT scans performed and calcium scores calculated.	In this review (and the one CT study included), calcium scores were the outcome of interest. The included study found that all risk factors (age, gender, BMI, risk factors for systemic hypertension, diabetes, smoking, family Hx of CAD and hypercholesteremia) were independent of calcium scores ($p<0.05$ for all). Calcium scores significantly increased with an increasing number of risk factors ($p<0.001$). The study was graded as a Class D report, according to an ICSI "Class of Research Report" grading scheme. The scoring assigns primary reports a score of A (most rigorous) to D (least rigorous). Class D is applied for cross-sectional studies, case series and case reports.	Conclusions in the 2004 report pertain to the measurement of coronary artery calcium (CAC). Those relevant to helical CT: • no study has reported on the use of CAC measurement to reduce MI or death • helical CT is a safe procedure but there is a potential for inappropriate and invasive follow-up • caution prevails when comparing calcium scoring from helical CT versus EBCT. The use of helical CT to assess CAC is not as well documented as is EBCT. There are insufficient data on the predictive value of a calcium score calculated from a helical CT scan • although there are no prognostic data comparing the results of helical CT or EBCT studies, there are differences between the procedures that would suggest that findings from EBCT studies cannot be applied to helical CT studies.	1 2 Literature search and findings were not discussed, nor were inclusion criteria or the process of study selection. It is unclear why only 1 study was included and no comments were made about this study aside from its classification as class D evidence.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Medical Services Advisory Committee (MSAC), Australia, 2003.[26] MSAC Horizon Scanning Briefing, 2003. To provide advice for health planners and policy makers on the introduction and use of diagnostic and therapeutic procedures for CAD in Australia. The current and future role, in comparison with current diagnostic and treatment practices; MRA, MDCT, EBCT and coated stents, was dicussed. Funder: The report was conducted at the request of the Australian Health Minister's Advisory Council by staff at the NHMRC Clinical Trials Centre, University of Sydney. The funder is possibly MSAC (not explicitly stated).	MEDLINE, PREMEDLINE, EMBASE and all EBM Reviews Internet sites of the HTA groups and other specified information sources Search dates: NR Limited to articles in English or with English abstracts The TrialsCentral portal was searched for clinical trial registers relating to CAD, including the Cardiosource Clinical Trials Registry and Cardialysis Clinical Research Management.	Inclusion and exclusion criteria: NR Literature selection process: NR Included studies: MRA 10 studies Davis *et al.*, 1996 (n=34) Duerinckx *et al.*, 1994 (n=21) Engelmann *et al.*, 2000 (n=40) Kim *et al.*, 2001 (n=109) Manning *et al.*, 1993 (n=39) Mohiaddin *et al.*, 1996 (n=16) Taylor *et al.*, 2000 (n=25) Watanuki *et al.*, 2000 (n=123) Wittinger *et al.*, 2002 (n=25) Yoshino *et al.*, 1997 (n=36) MDCT 19 studies Achenback *et al.*, 2001 (n=64) Fallenberg *et al.*, 2002 (n=1) Giesler *et al.*, 2002 (n=100) Hong *et al.*, 2002 (n=50) Horiguchi *et al.*, 2001 (n=20/60) Knez *et al.*, 2001 (n=44) Knez *et al.*, 2002 (n=99) Koop *et al.*, 2001 (n=6) Leter *et al.*, 2002 (n=8) Nieman *et al.*, 2001 (n=35); 2002a (n=59); 2002b (n=53); 2002c (n=78) Ohnesorge *et al.*, 2002 (n=50) Schroeder *et al.*, 2001a (n=15); 2001b (n=6); 2001c (n=15); 2001d (n=15); 2002 (n=14) Study type: case series (26), case control (1) and case study (1) Used a comparator: MRA (1=CT); MDCT (10=EBCT, IVUS)	Overall summaries of clinical effectiveness were presented. MRA • Most research has been with 2D techniques and sensitivities; and specificities have varied widely; however, it has been observed that 2D MRA has poorer spatial resolution and is inferior to conventional angiography. • Studies investigating 3D MRA have also shown wide ranges of sensitivities & specificities but for some arteries, 3D MRA has been shown superior to conventional angiography. • Motion artifacts must be further reduced and spatial resolution and contrast improved. MDCT • In general, MDCT angiography has been found to have high sensitivity and specificity for detecting high grade coronary artery stenosis (>70% occlusion), equivalent to EBCT angiography, however, the proportion of non-evaluable arteries is generally higher for MDCT angiography than EBCT. • Research investigating the effectiveness of MDCT is preliminary, being restricted to case series and case study reports.	"MRA: 2D MRA has poorer spatial resolution than, and is generally considered inferior to, conventional CA, and improvements to the technology are required before MRA should be used routinely in clinical practice; motion artifacts must be reduced and spatial resolution and contrast improved before 3D MRA can replace conventional CA; MRA is considered to be a safe, non-invasive imaging modality." "MDCT: neither 4-slice nor 16-slice MDCT have been shown to be comparable with conventional CA in terms of diagnostic accuracy in detecting stenosis, but in the absence of a full SR it is difficult to draw definitive conclusions from the literature; it is considered to be a safe, non-invasive procedure, but a reduction in the dose of redundant radiation is considered to be warranted." Limitations (as per SR authors): as this is a "horizon scanning" exercise, the emphasis is in getting material out for decision makers, this means all of the steps involved in a full HTA are not feasible.	1 N/A Inclusion criteria, methods of selecting included studies; and any quantitative or statistical findings in the included studies were unreported. Studies are not discussed in any detail but rather collectively used to support the report's findings.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Morgan-Hughes GJ *et al*., 2002;[27] South West Cardiothoracic Centre, Plymouth NHS Trust, Plymouth, UK Clinical Radiology, 2002. To review the technical advances and early clinical trial data for MSCT for imaging of coronary arteries. Funder: One author was supported by a "pump priming" grant from the Royal College of Radiologists; no other funding reported.	No literature search reported	Inclusion and exclusion criteria: NR Included studies: Neiman *et al.*, 2001 (n=31) Achenbach *et al.*, 2001 (n=64) Ropers *et al.*, 2001 (n=NR) Knez *et al.*, 2001 (n=44) Study summary: Total >200 patients Males 75% to 86% Clinically diverse patient population, including patients before and after revascularization; assessability of CT angiograms 8% to 94%; percent stenosis: 3 out of 4 studies used <50%; 1 out of 4 study used >70%.	Accuracy reported from the 4 included trials: sensitivity 78% to 91%; specificity 76% to 98%; PPV (only 2 trials reported) 59% and 84%; and NPV (only 2 trials reported) 98% and 96%.	"There is currently certainly no place in clinical practice for routine MSCT coronary angiography. The images are not yet as reliable [as invasive angiography] and the radiation doses may be higher. There are however, specific clinical situations where MSCT coronary angiography may provide either additional information or an alternative to invasive techniques. These include imaging of anomalous coronary arteries and acquired abnormalities such as coronary artery aneurysms. These should probably be considered on an individual basis and according to local familiarity with the required techniques. It is too early to define precise clinical indications."	1 2 Literature search and findings were not discussed, nor were inclusion criteria. It is unclear how studies were chosen. Also, there was no interpretation of the trials attempted.

BMI=body mass index; CAC=coronary artery calcium; CAD=coronary artery disease; CCA=conventional coronary angiography; CT=computerized tomography; CV=cardiovascular; EBA=electron beam angiography; EBCT=electron beam CT; F/T=Fryback & Thornbury (quality score); HTA=health technology assessment; Hx=history; IV=intravenous; IVUS=intravascular ultrasound; MA=meta-analysis; MDCT=multi-row detector spiral CT; MI=myocardial infarction; MSCT=multi-slice CT; N/A=not applicable; NPV=negative predictive value; NR=not reported; O/G=Oxman & Guyatt (quality score); PPV=positive predictive value; t(s)=patient(s); R&D=research & development; SR=systematic review; Sx=symptoms.

Table 2: Peripheral vascular disease – MRA

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Berry E *et al.*, 2002;[19] University of Leeds, Leeds General Infirmary; and St. James's Hospital, Leeds; University of Manchester; University of York, UK Health Technology Assessment, NHS R&D HTA Programme, 2002. (Also published in part as Westwood *et al.*, BMJ 2002) For PVD, to identify literature on MRA for pre-surgical assessment and to synthesize evidence about the diagnostic performance of MRA compared with DSA, at surgical decision thresholds (report is also about carotid artery disease). Funder: The UK NHS R&D HTA Programme.	MEDLINE, EMBASE, Health STAR, Science Citation Index, Index to Scientific or Technical Proceedings, the Cochrane Library, Inside (British Library), Online Computer Library Centre, EconoLIT, HTA databases, HEED, NHS EED 1990 to March 2000 Internet (limited) Hand search of 10 key journals and Department of Health databases Reference lists No language restrictions	Inclusion criteria: MRA versus DSA or cut-film angiography; sufficient data for a 2x2 table; clearly specified all pt(s) were symptomatic; conventional angiography technique described; tests within one month of each other; and not a duplicate study (if a duplicate, the study with largest number was used) 20 articles satisfied inclusion criteria. Summary of studies: 8 out of 20 used contrast-enhanced MRA; pt numbers, 12 to 155 (mean 34); proportion of males, 43% to 100% (mean 71%); ages, 22 to 97 years (mean 42 to 83); 13 out of 20 reported pt Sx; f/u was rare; and 11 out of 20 reported how many of the segments included in the analysis were normal.	"Both 2D TOF and contrast-enhanced MRA are highly accurate for distinguishing 0-49% from 50-100% stenoses. The contrast-enhanced techniques show a non-significant trend for improved performance over with 2D TOF MRA."	"In PVD, the evidence supports the use of 2D TOF and contrast-enhanced, MRA techniques for identifying occlusions and 50-100% stenoses."	7 2 This large HTA document is primarily to determine cost-effectiveness, with clinical as a prelude

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Eiberg JP *et al.*, 2001;[28] University of Copenhagen and University of Aarhus, Denmark European Journal of Vascular & Endovascular Surgery, 2001 To review the current status of lower limb MRA Funder: Grants from the Danish Medical Research Council and 3 memorial foundations	MEDLINE Jan. 1991 to Oct. 2000 English language Bibliographies of original articles	Inclusion criteria: articles reporting on the diagnostic accuracy of MRA in peripheral occlusive arterial disease of the lower limb; original and prospective studies; native arteries only; a clearly defined gold standard [contrast arteriography (CA), intra-operative arteriography, or intra-arterial pressure measurement]; 50% to 99% stenosis or occlusion; report sensitivity and specificity or data allowing their calculation; if results from >1 observer were reported, results from the first observer were used; results regarding a complete lower limb arterial segment were preferred; if not available, results from the segment with the worst result were used. 57 articles retrieved, 28 met inclusion criteria: non-enhanced MRA (13); gadolinium-enhanced MRA (14); both (1). Sample sizes, 12 to 155; publication year, 1991 to 2000; 90% used CA as gold standard.	TOF-MRA versus CA sensitivity 93% (range 64% to 100%); specificity 88% (range 57% to 100%). CE-MRA versus CA sensitivity=96% (range 71% to 100%); specificity=96% (range 63% to 100%).	"CE-MRA is accurate compared to conventional arteriography, has the potential to increase limb salvage rate for selected pt(s), is non-invasive and is well tolerated." "CE-MRA is currently the 'state of the art' MRA technique, overcoming the troublesome aorto-iliac region, reducing examination time, and increasing accuracy compared to the previous TOF-MRA technique."	2 2 Search strategy was limited and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Koelemay MJW *et al.*, 2001;[29] Academic Medical Centre, Amsterdam, the Netherlands JAMA, 2001. To obtain the best available estimates of the diagnostic performance of MRA in pt(s) with lower extremity arterial disease. Funder: NR	MEDLINE (from 1985), EMBASE (from 1988) and Current Contents Literature search ended May 2000 Languages: English, French and German	Inclusion criteria: compared MRA with CA or DSA as the reference standard; pt(s) had claudication or critical limb ischemia; aimed to detect stenosis >50% or occlusion; and presented 2x2 contingency tables or data allowing their construction. Exclusion criteria: f/u studies after PTA or surgery; and duplicate publications. Quality assessment of studies was carried out using a four-point scale. Lower extremity arteries were divided into 3 defined arterial tracts: aortoiliac tract from infrarenal artery to common femoral; femoropopliteal tract from common femoral to trifurcation; and infrapopliteal arteries from trifurcation to pedal arteries. 3,583 articles on MRA; 157 articles on MRA and PVD; 46 comparing MRA with arteriography; and 34 included. Study summary: 20 studies using contrast (17 gadolinium and 3 phase contrast); study sizes ranged from 13 to 115 (mean study n=25); total n=1,090; 72% men; and mean age 65 years.	The 34 studies were divided according to the section of lower arterial tract studied (some studied several tracts): aortoiliac tract from infrarenal artery to common femoral (19); femoropopliteal tract from common femoral to trifurcation (10); and infrapopliteal arteries from trifurcation to pedal arteries (24). For each of the 53 possibilities listed above, sensitivity, specificity and diagnostic OR were calculated. Q-points were calculated (the points at which sensitivity and specificity are equal): 3D CE-MRA 94%; 2D MRA 90%. The authors state "the clinical significance of a 4% difference in Q-points remains to be established."	"MRA is highly accurate for evaluation of the entire lower extremity arterial disease. 3D gadolinium-enhanced MRA improves diagnostic performance compared with 2D MRA." Limitations (as per authors): Inter-observer agreement on rating study quality was fair; in small studies defined arterial tracts were often subdivided into arbitrary segments which may over-estimate diagnostic accuracy; some studies presented data as aggregate results so interpretation of MRA for specific arterial segments is impossible; publication bias was a possibility as unpublished material was not sought.	4 2 Inclusion criteria and assessment process unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Nelemans PJ *et al.*, 2000;[30] University of Maastricht, the Netherlands and the Cochrane Methods Group on Systematic Review of Screening & Diagnostic Tests Radiology, 2000. To summarize the overall diagnostic performance of MRA in the evaluation of peripheral arteriosclerotic occlusive disease and to identify the most important sources of variation in diagnostic accuracy between studies. Funder: NR	MEDLINE Jan. 1991 to June 1999 English language Additional articles were obtained by citation tracking of review articles and original articles.	Inclusion criteria: reported on diagnostic accuracy of MRA in the evaluation of PAD; conventional arteriography was the standard of reference; a hemodynamically significant lesion was defined as either a stenosis of 50% to 99% or occlusion; and the absolute numbers of TP, FP, TN and FN observations were available or derivable from the data presented. 51 articles retrieved in 21 articles included (reporting on 23 studies). Study summary, technology evaluated: 2D TOF MRA (11); 3D gadolinium-enhanced MRA (8); both (2); total n=597; publication year, 1991 to 1999; sample size 12 to 45; mean age range, 50 to 69; % male range, 43% to 100%; clinical indication claudication, 4% to 100%; clinical indication critical ischemia, 0% to 96%; 13 out of 23 studies reported type of pt enrollment system and 9 out of 13 had consecutive enrollment; in most studies, the readers of MRA and conventional angiographic images were blinded to the results of the other imaging technique.	For the 23 included studies (in 21 articles), TP, FN, TN and FP were obtained or calculated. This allowed for the calculation of 23 pairs of sensitivity and specificity. Overall: sensitivity 64% to 100% for various authors and various arterial sites; and specificity 68% to 99% for various authors and various arterial sites. For 2D TOF MRA: sensitivity 64% to 100%; specificity 68% to 96%; and prevalence of stenosed segments 13% to 73%. For 3D MRA: sensitivity 92% to 100%; specificity 91% to 99%; and prevalence of stenosed segments 13% to 36%.	"The diagnostic accuracy of 3D gadolinium-enhanced MRA is superior to that of 2D TOF MRA. Also, the review of transverse source images or use of additional post-processing techniques, such as multi-planar reformation, results in significantly better diagnostic performance." "There was much heterogeneity among study results, which could not be explained as differences in the threshold for a positive result. About half of the variation was due to the type of MRA examination and the extent of image evaluation." Limitations (as per authors): a meta-analysis of site-specific results was not possible as only 13 out of 23 studies reported useful arterial site-specific data; information on clinical indications was missing in 7 out of 23 studies; only 13 out of 23 studies used consecutive pt enrollment; due to study heterogeneity, multiple regression analysis was used with 9 covariates which could overestimate statistical significance.	3 2 Limited search strategy and weak selection process.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Visser K & Hunink MG, *2000*;[31] Erasmus Medical Centre, Rotterdam, the Netherlands; and Harvard School of Public Health, Boston MA Radiology, 2000. To summarize and compare the published data on gadolinium-enhanced MRA and colour-guided duplex ultrasound for the PAD work-up. Funder: NR	MEDLINE For MRA: Jan. 1990 to Nov. 1998 For ultrasound: used a published MA for 1984 to 1994; updated search to Nov. 1998 Bibliographies of reviews and original articles Contact with experts No language restrictions	Inclusion criteria: gadolinium-enhanced MRA, colour-guided duplex ultrasound (or both), performed to demonstrate stenosis and occlusions of the arteries in the lower extremities. Conventional angiography was the reference standard. Absolute numbers of TP, FN, TN and FP were available or could be derived for a defined cut-off criterion in arterial diameter of >50%. 706 references: 92 obtained in full text; 31 met inclusion criteria and included in sensitivity analysis; 27 included in the baseline analysis [MRA (9); duplex ultrasound (18)]. Study summary (n=31): publiccation year 1989 to 1998; location: NA (13), Europe (15), Australia (2) and Asia (1); sample size: MRA n=11 to 30, ultrasound n=17 to 167; mean age: MRA=58 to 67, ultrasound=44 to 72; clinical indication (for the majority of pt(s) in a study): MRA: claudication 4 out of 9 studies, critical ischemia 3, NR 2; and ultrasound: claudication 8 out of 18 studies, critical ischemia 3, NR 7.	With a random effects model, pooled sensitivity: MRA 97.5% (95% CI: 95.7%; 99.3%), ultrasound 87.6% (95% CI: 84.4%; 90.8%); and pooled specificity: MRA 96.2% (95% CI: 94.4%; 97.9%), ultrasound 94.7% (95% CI: 93.2%; 96.2%). Summary receiver operating characteristic (ROC) analysis is a MA method used to summarize and combine the TP and FP rates for different diagnostic studies to compare diagnostic accuracies. In this report the summary ROC demonstrated better discriminatory power for MRA than for duplex ultrasound, although the regression coefficient calculated (1.67 with CI-.023 to 3.56) only approached significance.	"Gadolinium-enhanced MRA has better discriminatory power than does colour-guided duplex US (ultrasound) and is a highly sensitive and specific method, as compared with conventional angiography, for the work-up for PAD." Limitations (as per authors): the MA was limited by ambiguities in the original reported data; publication bias may have been present (particularly due to the limited number of MRA trials, all being small); delays between tests on the same pt(s) (for ultrasound, mean time delay of 17 days; for MRA, mean time delay of 5 days); ideally tests should be carried out on the same day; concerns as to whether conventional angiography is the best reference standard to use.	3 2 Inclusion process and validity assessment unclear.

CA=contrast arteriography; CE-MRA=contrast-enhanced MRA; CI=95% confidence interval; CTA=CT angiography; DSA=digital subtraction angiography; Dx=diagnosis; FN=false-negative; FP=false-positive; f/u=follow-up; F/T=Fryback & Thornbury (quality score); HTA=health technology assessment; MA=meta-analysis; MRA=MR angiography; NA=North America; NR=not reported; O/G=Oxman & Guyatt (quality score); OR=odds ratio; pt(s)=patient(s); PAD=peripheral arterial disease; PTA=percutaneous transluminal angioplasty; PVD= peripheral vascular disease; ROC=receiver operating characteristic; Rx=treatment; Sx=symptoms; TN=true negative; TOF=time of flight; TP=true positive.

Table 3: Renal artery stenosis – MRA or CTA and MRA

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Tan KT *et al.*, 2002;[32] University of Sheffield, Vascular Institute, Sheffield & Academic Medical Centre, Amsterdam Clinical Radiology, 2002. To review the published literature comparing the diagnostic accuracy of MRA as compared with catheter angiography in diagnosing RAS; and to compare the accuracy of non-enhanced and gadolinium-enhanced MRA techniques. Funder: NR	PubMed and MEDLINE English language 1985 to April 2001 Bibliographies of all articles	Inclusion criteria: comparison of catheter angiography with MRA for the Dx of RAS; blinded comparison with arteriography which used intra-aortic injection with >2 projections; indication for arteriography stated; imaging techniques described; interval between MRA and arteriography <3 months; and full, peer-reviewed articles. Exclusion criterion: abstracts or unpublished data 39 articles identified; 25 included Summary of included articles: 998 pt(s) and 1,993 main arteries; publication dates 1991 to 1999; divided into non-enhanced MRA (15 studies) and gadolinium-enhanced MRA (12 studies) groups. Two of the 25 studies included both types of pt(s).	• For each study, TP, TN, FP and FN were calculated, as were sensitivity, specificity, PPV and NPV • Cut-off values used: ≤50% stenosis versus >50% stenosis • Standard of reference for MRA was generally catheter arteriography (exceptions: IV digital subtraction in 21; surgical findings in 4) • Totals were calculated for each group (non-enhanced and gadolinium-enhanced): non-enhanced MRA: n=990 main arteries; TP 238, TN 628, FP 108, FN 16; sensitivity 94%, specificity 85%, PPV 69%, NPV 98%. Gadolinium-enhanced MRA: n=993 main arteries; TP 308, TN 627, FP 48, FN 10; sensitivity 97%, specificity 93%, PPV 87%, NPV 98%. Complications: NR	This meta-analysis shows MRA is highly sensitive and specific for the Dx of RAS and that MRA with gadolinium enhancement is superior to non-enhanced MRA. The authors recommend gadolinium-enhanced MRA for the investigation of pt(s) with suspected renovascular disease, followed by catheter angiography. Limitations (as per the authors): 47 pt(s) (4%) could not undergo MRA due to metal implants, etc.; accuracy may be an over-estimate as studies came from academic centres with specialist MR radiologists (i.e., results may not extrapolate to all settings); pt(s) were highly selected as likely candidates for RAS (resistant hypertension and decreased renal function.	3 2 Search strategy limited; inclusion process and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Vasbinder GBC, *et al.*, 2001;[33] University Hospital of Maastricht, the Netherlands Annals of Internal Medicine, 2001. To summarize and compare the validity of CTA, MRA, ultrasound, captopril renal scintigraphy (CRS) and the captopril test for pt(s) suspected of having renovascular hypertension. Funder: Dutch Health Care Insurance Board (government)	MEDLINE, EMBASE and Cochrane databases Inception to Aug. 1, 2000 Included languages were English, French and German Bibliographies of selected articles	Inclusion criteria: intra-arterial angiography was the gold standard; referral was due to suspicion of renovascular hypertension; criteria and cut-off values for a positive test result were defined; and TP, TN, FP and FN results were available or could be calculated. Exclusion criteria: studies of pt(s) with renal transplants; possibility of verification bias [positive result on index test referred to the gold standard more often than pt(s) with negative result on index test]. For the 5 modalities under review, 1,307 articles were identified and 55 were included: CTA (5); MRA (16); ultrasound (24); CRS (14); Captopril test (4) (several studies examined >1 type of test).	A meta-analysis was carried out using summary receiver-operating characteristic (ROC) curves. Areas under the curves were used as measures of the diagnostic performance of the tests. Linear regression analyses were used to compare tests with each other. Statistics were performed using SPSS software. Summary results: CTA and MRA have significantly better diagnostic accuracy than ultrasound which in turn is superior to the captopril test; CTA and gadolinium-enhanced MRA are significantly better than the other tests studied ($p<0.05$); CTA and gadolinium-enhanced MRA had similar Dx performance to each other; and non-enhanced MRA, followed by CRS and ultrasound had similar results, followed by the captopril test.	CTA and MRA (particularly gadolinium-enhanced MRA) have better Dx accuracy than ultrasound, CRS or the captopril test for the detection of RAS. To achieve cost-effectiveness, pt(s) with renovascular hypertension must be carefully selected as test candidates, based on clinical evaluation. Limitations (as per the authors): there was high heterogeneity among studies; standard criteria to define a positive test result were lacking among studies; anatomic tests were compared with functional tests; most CTA and MRA studies used arteries as the unit of analysis versus CRS studies which used pt(s).	4 2 Validity assessment unclear and no reference standard appears to have been used.

Captopril renal scintigraphy=CRS; CI=95% confidence intervals; CTA=CT angiography, Dx=diagnosis, FN=false negative; FP=false positive; F/T=Fryback & Thornbury (quality score); IV=intravenous; MRA=magnetic resonance angiography, NPV=negative predictive value; NR=not reported; O/G=Oxman & Guyatt (quality score); PPV=positive predictive value; pt(s)=patient(s); RAS=renal artery stenosis; TN=true negative; TP=true positive.

Table 4: Lung cancer screening – CT

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality score Efficacy Grade Comments
Bepler G *et al.*, 2003;[34] University of South Florida, Tampa FL Cancer Control, 2003. Efficacy in detection of early-stage lung CA; reduction in lung CA mortality; rate of Dx of cancer and other suspicious lesions; screening-related morbidity. Funder: NR, but conflicts of interest were denied with companies and organizations referenced in the article.	MEDLINE and CancerLit, with no language restrictions 1988 to Aug. 2002 Bibliographies of selected references searched	Inclusion criteria: RCTs and observational studies; CT versus no screening; allowed screening alone or followed by treatment. 208 citations; 8 included studies; Matsumoto excluded from analysis (small pilot study, limited study info available) Studies: all prospective cohort studies; 6 out of 8 included only smokers; none had control groups; 2 out of 8 also screened with CXR (Henschke & Sobue) Diederich *et al.*, 2002 (n=817) Henschke *et al.*, 1999, 2001 (n=1,000) Matsumoto *et al.*, 1995 (n=118) Nawa *et al.*, 2002 (n=7,956) Sone *et al.*, 2001 (n=5,483) Sobue *et al.*, 2002 (n=1,611) Swensen *et al.*, 2002 (n=1,520) Tiitola *et al.*, 2002 (n=602)	• Studies were not pooled • Total n=19,107 • Prevalence rate of lung cancer 0.4% to 13.6%, depending on age and smoking Hx • CT versus CXR (2 studies): 3x detection rate and 5x rate of resectable cancers (stage I and II) • Incomplete data on mortality and morbidity from cancer (short f/u, not RCTs, study populations may not be representative) and from screening • Disproportionate rate of adenocarcinoma detection (80% versus normal of 35%) – CT maybe not as useful for detecting squamous and small cell CA? • Sensitivity and specificity impossible to calculate as true negatives are unknown • PPV 0.08 for age >60; 0.04 for 50 to 59; 0.00 for <50	CT detects earlier-stage and smaller lung cancers than other screening methods. No studies have shown reductions in mortality. CT screening should be an investigative tool until mortality trials are complete.	3 2 Review did not access grey literature, inclusion process and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality score Efficacy Grade Comments
ECRI, 2002;[35] Philadelphia PA ECRI "Windows on Medical Technology" report, 2002 Investigating the use of helical CT for screening, detection and diagnosis of lung cancer. Funder: US-based nonprofit health services research agency with stringent conflict-of-interest regulations	PUBMED and EMBASE 1988 to Dec. 2001 Cochrane databases Multiple electronic and grey literature sources All searches updated to December, 2001	Included studies: helical CT for lung cancer screening or diagnosis of primary lung cancer; must have reported diagnostic data from clinical trials; >10 patients; and must have reported detectability of actual lung nodules rather than simulated nodules. Study selection process NR 10 articles were included, but these articles reported on only 3 studies (all uncontrolled); overall n=7,852: Henschke *et al.* (ELCAP project), 1999, 2000 and 2001 (n=1,000) Kaneko *et al.* (ALCA project), 1996 and 2000 (n=1,369) Sone *et al.* (Nagano project), 1998, 2000 and 2001 (n=5,483)	Each of the 3 studies were summarized separately. For example Henschke *et al.*: Cancer (by Bx): 12% (27 out of 233) of all positive CT scans; 10% (7 out of 68) of all positive CXR=>20 pt(s) (2% of screened population) had cancer Dx by CT and not CXR; none of the cancers detected by CXR were missed on CT; PPV of CT 12%; PPV of CXR 10%; sensitivity and specificity: CT 100%, 79%; CXR 26%, 94% (may be an overestimate as it does not factor in cancers missed by both tests).	CT detects more cases of lung cancer than chest x-rays do. This implies that CT sensitivity is better, which might improve mortality, but only if treatment is effective. There is insufficient evidence to support the use of any CT for lung cancer screening outside the trials now underway. The PPV of both helical CT and CXR are low.	3 2 Inclusion process and validity assessment unclear. Primarily a summary of published literature.
Harmon K *et al.*, 2001;[36] Institute for Clinical Systems Improvement (ICSI), Bloomington, MN ICSI Technology Assessment Report, 2001 Purpose of the review not well stated. Funder: ICSI is an independent not-for-profit organization funded by 6 Minnesota health plans	MEDLINE and PREMEDLINE Search dates and terms not given Hand search of bibliographies of included articles Key references supplied by Working Group members Evidence is graded according to a classification developed by ICSI	Inclusion criteria NR Study selection process NR Included studies (4); overall n=8,082: Henschke *et al.*, (ELCAP), 1999 (n=1,000) Kaneko *et al.*, (ALCA project), 1996 (n=1,369) Mori *et al.*, 1997 (n=230) Sone *et al.*, 1998 (n=5,483)	Each of the 4 studies was summarized separately: • Henschke *et al.* • Kaneko *et al.;* abnormalities found CT versus CXR 10% (331 pt(s)) versus 3% (113); 229 out of 331 referred for thin-section CT; 19 out of 229 (8%) referred for Bx; 10 out of 19 (53%) positive for lung cancer • Mori *et al.* did CT to f/u abnormalities when screening with CXR • Sone *et al.;* rate of lung cancer Dx was 0.48% (19 out of 3,967). Rate for smokers 0.52%; for non-smokers 0.46% Limitations: Search details NR; inclusion criteria NR. One study (Mori) appeared to be f/u rather than screening.	Routine CT screening for lung cancer cannot be recommended due to: the unknown cost of f/u of the high number of false positives, the lack of long-term survival data and the high morbidity associated with f/u procedures post-CT. Although CT detects cancer earlier and early-stage cancer has a better prognosis, there is no direct evidence linking CT screening with improved survival. LDCT is a safe procedure; the risks are related to false-positive and false-negative diagnoses.	1 2 Limited search, search terms not defined, inclusion and validity assessment unclear. Primarily a summary of published material.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality score Efficacy Grade Comments
Humphrey LL et al., 2004;[37] Oregon Health & Science University, Portland OR AHRQ Systematic Evidence Review #31 Also in Annals of Internal Medicine, 2004 To examine the evidence evaluating screening for lung cancer with CXR, sputum cytology and LDCT, to aid the USPSTF in updating its recommendation on lung cancer screening. Funder: US Agency for Healthcare Research & Quality (US Department of Health & Human Resources)	MEDLINE and Cochrane Inception to Jan. 2003 Bibliographies of reviews, editorials, book chapters, letters; and a recent Cochrane review and analysis	Inclusion criterion: studies that evaluated mass-screening programs for lung cancer involving CXR, CT, or sputum cytology; general and high risk populations; and RCTs and observational studies. 809 citations: 149 full-text papers; 6 cohort studies for LDCT (uncontrolled). Studies (6); overall n=18,387 Diederich *et al.*, 2002 (n=817) Henschke *et al.*, 1999 and 2001 (n=1,000) Nawa *et al.*, 2002 (n=7,956) Sone *et al.*, 2001 (n=5,483) Sobue *et al.*, 2002 (n=1,611) Swensen *et al.*, 2002 and 2003 (n=1,520)	Each of the 6 studies was summarized separately. • Referral for biopsy: 4.8% to 14.5% of pt(s) after high-resolution CT • Cancer Dx: 63% to 90% of those biopsied • Stage 1 disease: 58% to 100% • False positive rates: 5% to 50% in prevalence studies, 3% to 12% in incidence studies; most abnormalities resolved with high-resolution CT • False negative rates: NR Overall results summary: • CT is more sensitive than CXR for lung cancer • CT identifies more small, low-stage, resectable lung cancers than CXR • High rates of false positives mean many pt(s) undergo invasive procedures Complications: NR (as related to biopsy or thoracotomy)	Cancer can be diagnosed at an earlier stage with CT than with other methods in use; unknown whether this will decrease mortality. Cost-effectiveness unknown. RCT of screening CT is underway with National Lung Screening Trial (n=100,000; high risk pt(s); CXR versus CT; pt ages 55 to 74; no non-screened control groups).	5 2 No control groups or inclusion criteria; and process unclear. Primarily a summary of published material.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality score Efficacy Grade Comments
Manser RL *et al.*, 2004;[38] Royal Melbourne Hospital, Victoria Australia The Cochrane Library, 2004 To determine whether screening for lung cancer using CXR, CT or sputum examination reduces lung cancer mortality. Funder: NR although all authors deny conflict-of-interest with respect to the primary studies included in the review.	MEDLINE, PREMEDLINE and EMBASE, Cochrane Central Register of Controlled Trials 1966 to July 2000; MEDLINE search updated in 2003 Hand searching of the journal Lung Cancer 1985 to Dec 2000. Bibliographies of identified studies and narrative reviews were searched. Authors of primary studies and experts in the field were surveyed.	Inclusion criterion: RCTs or controlled clinical trials examining screening for lung cancer using CXR, CT or sputum cytology. Exclusion criteria: non-controlled trials; lung cancer mortality not reported as an outcome; f/u <5 years. 1,869 citations: 119 full-text papers; and 6 studies. One additional study found through bibliography search (no additional studies were found in the 2003 MEDLINE update search). The 7 studies all examined use of CXR, not CT.	Although the inclusion criteria allowed for trials screening with CT as well as CXR and sputum cytology, the restriction to controlled trials eliminated all studies examining use of CT.	With respect to screening with CXR, the evidence does not support its benefit. No studies examining use of CT were included as none were controlled. At least one RCT is underway to examine CT screening for lung cancer.	7 N/A Not directly about CT for lung cancer screening.
Marcus PM *et al.*, 2002;[39] US National Cancer Institute and National Institutes of Health Clinical Pulmonary Medicine, 2002 Usefulness of LDCT as a screening tool for lung cancer. Funder: NR	Literature search NR	Inclusion criteria: examined LDCT as a screening modality for lung cancer. Study selection process: NR Studies: located 8, but only 4 complete and published (n=9,372). Henschke *et al.* (ELCAP project), 1999 and 2001 (n=1,000); Kaneko *et al.*, (ALCA project) 1996, 1999 and 2002 (n=1,369); Sone *et al.*, 2001 (n=5,483); and Swensen *et al.* (Mayo Clinic), 2002 (n=1,520).	Studies are individually reviewed, but no summary results presented, For example, Henschke *et al.* (ELCAP) examined LDCT versus CXR in smokers 60; non-calcified nodules; CT:CXR= 23%; 7%; lung cancer detection CT:CXR=2.7%: 0.7%; and of the cancers found on CT, 85% were stage 1. For example, Kaneko *et al.* (ALCA) 1996 found the detection of abnormalities CT:CXR=47%, 8%; lung cancer detection CT:CXR=1.1%, 0.3%; and of the cancers found on CT, 93% were stage 1.	Data from non-RCTs indicate LDCT can detect asymptomatic lung cancers not visible on CXR. Unknown whether there is a mortality advantage or whether benefits of screening outweigh harms. Several RCTs are underway.	1 N/A Literature search and study selection not described.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality score Efficacy Grade Comments
Minnesota HTA, 2000;[40] Department of Health, St. Paul MN Health Technology Advisory Committee Evaluation, 2000. Does CT screening produce a health benefit through increasing survival, improved QOL, or reduced lung cancer-related mortality? Funder: State department of health	MEDLINE, EMBASE, HealthSTAR and Current Contents databases 1985 to Oct. 2000 Information was also obtained from the National Cancer Institute and the Radiological Society of North America. Articles in Japanese were located but not translated.	Inclusion and exclusion criteria: NR Study selection process: NR Included studies (4); n=9,295: Henschke *et al.*, 1999 (n=1,000) Kaneko *et al.*, 1996 (n=1,369) Kakinuma *et al.* 1999 (n=1,443) Sone *et al.*, 1998 (n=5,483)	Most of the published material is from studies set in Japan and the Minnesota HTA authors express concern that the study populations may not be representative of populations in the US (e.g. high smoking rates, little emphasis on smoking cessation, >90% of smokers are male).	CT scans may detect nodules at an earlier stage, but there is no RCT evidence that CT screening for lung cancer increases survival time or reduces lung cancer related mortality. Due to the high false-positive rate, CT screening for lung cancer may lead to un-necessary care and secondary testing.	2 2 Inclusion criteria, process and validity assessment unclear. Primarily a summary of published material.
Palda VA and Spall HGC, 2003;[41] St. Michael's Hospital and University of Toronto, Toronto, Canada CTFPHC, London ON, 2003. Effect of screening with CXR and CT on lung cancer mortality. Funder: CTFPHC funded by Health Canada	MEDLINE and Cochrane databases Published in English 1990 to July 2002	Inclusion criteria: controlled trials or diagnostic studies related to lung cancer screening or diagnosis, using CXR or CT Exclusion criteria: review articles, case-cohort studies, retrospective autopsy-based studies, cost effectiveness analyses, radiological studies for purposes other than screening for or diagnosing lung cancer and studies that investigated the technical aspects of CT Study selection process NR in detail. Studies were selected for both CXR (7) and CT (3) Included studies for CT (3); n=7,188: Diederich *et al.*, 2000 (n=>700) Henschke *et al.*, 1999, 2001 (n=1,000) Sone *et al.*, 2001 (n=5,483)	Radiologic interpretation of screen scans was excellent (kappa 0.91); more non-calcified lung nodules were detected by CT scan than CXR; more cancers were detected overall by CT; overall cancer detection rate was 0.40%. In the absence of any report about the population, significance of the detection rates is unclear. False-positives and false-negatives are an issue.	The CTFPHC concludes that there is insufficient evidence (in quantity and quality) to make a recommendation as to whether spiral CT scanning should be used for screening asymptomatic people for lung cancer; however other factors may influence decision making. Recommendation Grade for Specific Clinical Preventive Actions = I (insufficient evidence)	4 N/A Search strategy limited and inclusion criteria unclear. Primarily a summary of published material.

Bx=biopsy; CA=cancer; CXR=chest x-ray; Dx=diagnosis or diagnosed; F/T=Fryback & Thornbury (quality score); f/u=follow-up; Hx=history; LDCT=low-dose computed tomography; NR=not reported; O/G=Oxman & Guyatt (quality score); PPV=positive predictive value; pt(s)=patient(s); RCT(s)=randomized controlled trial(s); SR=systematic review.

Table 5: Pulmonary embolism – Primarily CT and CTA; one study reports on MRA

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Berry E *et al.*, 1999;[42] University of Leeds, Leeds General Infirmary; MEDTAP International, London; Wessex Institute of Health R&D, Southampton University; UK HTA report, NHS R&D HTA Programme, 1999. To identify publications on the use of spiral CT and EBCT to draw conclusions about the latest generation of CT devices; specific clinical uses were selected, including the investigation of PE. This report also covers the investigation of liver lesions; and coronary artery disease, in reference to EBCT only (report is 128 pages) Funder: The UK NHS R&D HTA Programme	MEDLINE, EMBASE, BIDS-ISI (Bath Information & Data Services) Health STAR, the Cochrane Library, Inside Information Plus (British Library) and FirstSearch Online Computer Library Centre 1981 to Dec. 1996 with update Oct. 1997 Bibliographies Contact with CT manufacturers Ongoing studies details requested Search of the British Library grey literature database	Study selection involved a 3-stage process, which was independently carried out for 5 streams: health economics; patient outcomes; therapeutic impact; diagnostic impact; and diagnostic performance. Initial screening retained: human studies in English; studies of >10 pt(s); not an abstract, review article, case report, editorial or letter. For diagnostic performance only, inclusion criteria for the studies on CT and PE aimed to determine detection accuracy of acute PE by CT: as a replacement for VQ; as well as VQ; as well as other modalities. Studies (n=4): Goodman *et al.*, 1995 (n=20) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) van Rossum *et al.*, 1996 (n=56) All compared CT with gold standard (PA) results.	The 4 included studies reported the following data on accuracy. Sensitivity and specificity: Goodman central vessels: 86% and 92%; all vessels 63% and 89%; Remy-Jardin (1992) central vessels: 100% and 96%; Remy-Jardin (1996) central vessels: 91% and 78%; van Rossum all vessels: 80%; 67% and 100% (results from 2 observers). Because there were so few studies, there was no attempt to synthesize the data quantitatively.	"Although there is uncertainty about the true sensitivity and specificity achievable, the future use of CT in this clinical application depends upon the determination of the clinical importance of subsegmental PE. An SR of the literature on this topic is recommended. It is unlikely that clinical trials are the optimum means of determining the best diagnostic work-up for PE… further research using decision analytic modelling should follow the review of subsegmental PE, comparing a variety of diagnostic strategies including VQ, CT, MRI and PA."	5 2 Covered a number of topics so it was difficult to tease out the material relevant to CT and PE; inclusion criteria were unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Cueto SM *et al.*, 2001;[43] York Hospital, Pennsylvania State University, Hershey, York PA The Journal of Emergency Medicine, 2001. To compare the sensitivity and specificity of CT scan and VQ scan in detecting PE with PA as the reference standard. Funder: NR	PubMED English language Jan. 1980 to June 2000 Bibliographies of retrieved articles Ongoing monitoring of the literature	Inclusion criteria: prospective studies; spiral and helical CT; both positive and negative CT results considered; reference standard=PA; sensitivity and specificity reported or derivable; test readers blinded to results of comparison tests; CT technology described; use of contrast material. Exclusion criteria: abstracts 18 articles reviewed in full text; narrowed to 7 Studies (n=7): Blum *et al.*, 1994 (n=10) Drucker *et al.*, 1998 (n=47) Garg *et al.*, 1998 (n=24) Goodman *et al.*, 1995 (n=20) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=65) Teigen *et al.*, 1995 (n=60) EBCT was the technology used in this study. Study summary: Type of data: central PE (3); central plus peripheral (3); both (1). Average pt age 34 to 63 years Males 40% to 96% Sensitivities 53% to 100% Specificities 81% to 100%	CT composite data were calculated for 3 groups (gp): group 1 central PE data; group 2 combined central plus peripheral PE data; both groups. These data were compared with the previously published results of a 1990 multi-centre study (PIOPED) which had examined VQ scintigraphy versus PA for both high probability VQ scans and high and intermediate probability VQ scans. Calculations (Group 1; Group 2; Both; PIOPED high; PIOPED high; intermediate): sensitivity (%)=77, 81, 80, 41, 83; (95% CI: 67%; 88%, 72%; 90%, 73%; 86%, 35%; 47%, 78%; 87%); specificity (%)=91, 98, 94, 97, 52; (95% CI: 86%; 97%, 95%; 100%, 91%; 98%, 96%; 99%, 47%; 56%) accuracy (%)=86, 90, 88, 78, 62; (95% CI: 81%; 91%, 85%; 94%, 85%; 92%, 75%; 81%, 59%; 66%).	"Considering that only a small proportion of pt(s) with a suspected PE yield high-probability VQ scan results (which are usually indicative of PE), while as many as 1/2 of pt(s) may yield intermediate probability results (which are commonly not useful in PE Dx), our results suggest the CT scan may be an appropriate study for use by emergency physicians in the clinical evaluation of suspected PE…either as a first-line study or for pt(s) with non-diagnostic VQ scans." Limitations: few available studies used PA as a reference standard for most pt(s), rather only for those with a negative CT, introducing selection bias; few studies blinded radiologists; some studies used surrogate reference standards, introducing a confounder.	3 2 Unclear how the narrowing to full text articles occurred; literature search quite limited; some studies are older; ER perspective may not extrapolate.

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Harvey RT *et al.*, 2000;[44] The Hospital of the University of Pennsylvania, University of Pennsylvania Medical Center, Philadelphia PA and eDict Systems, Mt. Laurel NJ Academic Radiology, 2000. To estimate, using published data, the sensitivity and specificity of CTA (and EBCT) in the evaluation of suspected PE Funder: NR	MEDLINE Jan. 1992 to June 1999 English language Bibliographies of retrieved articles	Inclusion criteria: prospective and retrospective; reference standard=PA; all pt(s) undergoing both PA and CTA; TP, TN, FP and FN data plus observed sensitivity and specificity; number of readers and consensus versus individual readings; helical CT or EBCT; and PA technique described. Exclusion criteria: case reports Process of selection of included articles not fully described Studies (n=9 for CT): Blum *et al.*, 1994 (n=10) Drucker *et al.*, 1998 (n=47) Garg *et al.*, 1998 (n=54) Goodman *et al.*, 1995 (n=20) Mayo *et al.*, 1997 (n=139) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) van Rossum *et al.*, 1996 (n=149) van Rossum *et al.*, 1996 (n=249) For EBCT: Teigen *et al.*, 1993 (n=86) Teigen *et al.*, 1995 (n=60) Arteries analyzed in the studies: central (6); all, to sub segmental level (2); central and sub segmental in separate analyses (3). Helical CT used in 9, EBCT in 2	Sensitivity of CTA in the Dx or exclusion of PE: in the central pulmonary arteries (to the level of the segmental pulmonary arteries) 0.74 to 0.81, on the basis of specificities of 0.89 to 0.91; in all pulmonary arteries (to the level of the subsegmental pulmonary arteries) 0.68, on the basis of a specificity of 0.91.	"On the basis of the studies in the current literature, most of which use 5mm collimation and single-detector CT, CTA may be less accurate in the Dx of PE than previously reported. With improvements in data acquisition, particularly the use of thinner section collimation and multi-detector CT, and in the increased use of workstations for data analysis, the accuracy and utility of CTA will require continued investigation." Limitations (as per authors): all studies differed in their methods of assessment. For example, in 6 out of 11 studies all pt(s) had CTA versus PA whereas in 5 out of 11 only a subset of pt(s) did. Intervals between CTA and PA varied, as did prevalence of PE; some study populations may have been biased (high PE prevalence).	3 2 Search strategy limited, inclusion and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Kelmenson *et al.*, 2003;[45] Institute for Clinical Systems Improvement (ICSI), Bloomington MN ICSI Technology Assessment Report, 2003 The technology assessment report Computed Tomography (CT) for the Diagnosis of Pulmonary Embolism (PE) was originally approved in 1997. Since that revision, helical CT has increasingly been used as the initial diagnostic procedure or as f/u to a non-diagnostic V/Q scan. Thus, an update is needed. Funder: ICSI is an independent not-for-profit organization funded by 6 Minnesota health plans.	Literature sources, dates and strategy not provided Evidence is graded according to a classification developed by ICSI (conclusions are graded as well)	Inclusion and exclusion criteria were NR Process for selection of literature was NR The 6 studies used in the 1997 edition of the report included: Goodman *et al.*, 1995 (n=20) Mayo *et al.*, 1997 (n=139) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) Sostman *et al.*, 1996 (n=53) van Rossum *et al.*, 1996 (n=249) Evidence for 1998 to 2003 was updated and included 4 additional studies: Blachere *et al.*, 2000 (n=216) Perrier *et al.*, 2001 (n=299) Ruiz *et al.*, 1996 (n=66) van Rossum *et al.*, 1998 (n=123) The more recent studies were discussed in the document (study design, methods and findings); and sensitivities and specificities displayed in a table (along with those from the 1997 report). Authors used an SR performed by Rathbun *et al.,* in 2000 which included 15 studies published from 1986 to 1999.	10 studies were presented: 6 in the 1997 report and 4 additional studies in the 2003 update. Studies in the 1997 report: sensitivities ranged from 77% to 100%; specificities ranged from 78% to 97%. Studies in the 2003 report: Sensitivities ranged from 70% to 94%; specificities ranged from 82% to 94%.	"Contrast-enhanced helical CT has good diagnostic accuracy and higher sensitivity and inter-observer agreement than VQ scintigraphy. Reported accuracies are highly dependent on proper technique and accurate assessment by experienced radiologists. Compared to PA and VQ scintigraphy, the reduced time required for and less invasive nature of contrast-enhanced helical CT would appear to be beneficial for the critically ill patient. For institutions with 24-hour expert interpretation of contrast-enhanced helical CT, full time access to helical CT may provide an advantage over other techniques." "CT may be of limited value in the diagnosis of subsegmental emboli. Information from CT led to alternative diagnoses in 51%-93% of cases."	1 2 Literature search and findings were not discussed, nor were inclusion criteria or the process of study selection

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Kruip MJHA *et al.*, 2003;[46] St. Elisabeth Hospital, Tilburg; Medisch Spectrum Twente, Enschede; University of Maastricht, Maastricht; and Academic Medical Centrre, Amsterdam; the Netherlands Annals of Internal Medicine, 2003. To evaluate various diagnostic strategies for excluding PE The number of studies related to CT was small (3 out of 25) as a number of diagnostic strategies were examined. Funder: NR, but response to "potential conflicts of interest" is "none disclosed"	MEDLINE Inception to Feb. 2003 EMBASE and DARE English language Included published abstracts that contained enough detail for analysis Contacted investigators Reference lists of original and review articles	Inclusion criteria: prospective study; involved consecutive pt(s); defined *a priori* the diagnostic strategy used to confirm or exclude the Dx of PE; withheld anticoagulant Rx when PE was excluded; a detailed description of f/u; ≥3 months f/u with <10% lost; and detailed descriptions of Dx management in pt(s) with recurrent Sx of venous thromboembolism. 77 studies identified; 25 met inclusion criteria (but only 3 examined CT) Studies examining CT for PE (n=3): Ferretti *et al.*, 1997 (helical CT) Anderson *et al.*, 2001 (spiral CT) Musset *et al.*, 2002 (spiral CT)	"Only 3 studies have evaluated the role of spiral CT in proper clinical outcome studies" Anderson *et al.,* found normal results on CT and one instance of normal results on compression ultrasound excluded PE in 287 consecutive pt(s). No complications were noted in f/u (failure rate 0%, upper CI limit 1.3%). Feretti *et al.,* examined pt(s) with low to moderate clinical probability after non-Dx lung scan and normal compression ultrasound and found normal CT results were associated with an unacceptable failure rate (5.5%, upper CI limit 11.6%). Musset *et al.,* excluded PE with normal results on CT and compression ultrasound in 507 pt(s) with low to moderate clinical probability. In f/u 9 pt(s) had a TE event (failure rate 1.8%, upper CI limit 3.3%); 5 died.	Overall report conclusions: "Many diagnostic strategies to exclude PE have been evaluated in consecutive patients. Interest is likely to increase in a simple, fast strategy, starting with a normal perfusion lung scan or a combination of normal d-dimer levels and low clinical probability. After the initial round of testing, a reliable diagnostic method, such as angiography or lung scintigraphy, is warranted." "Accumulating evidence shows that normal results on spiral CT may also safely exclude the disease." Limitations (as per authors): Test outcome interpretations of authors were accepted; the *a priori* likelihood of disease in pt(s) with suspected PE varies across hospitals, countries, etc.; studies examined did not directly compare different diagnostic strategies, but rather inferred relative safeties	3 2 CT was a small part of this already short report (9 pages): only 3 trials (of 25 included) examined CT. Inclusion and validity assessment process also unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Mullins MD *et al.*, 2000;[47] University of Virginia Health Sciences Center, Charlottesville VA Archives of Internal Medicine, 2000. To evaluate the evidence for the use of spiral volumetric CT (SVCT) in the Dx of acute PE Funder: NR	MEDLINE Inception to 1998 Current Contents Jan. to July 1998 English language Bibliographies of included articles	Inclusion criteria: evaluated the role of SVCT in the Dx of PE; used a reference standard: PA or high-probability V/Q scan combined with high clinical suspicion. 14 articles considered; 11 included Study summary: publication dates ranged from 1992 to 1998; studies were conducted in 6 different countries; and the number of reported exams varied from 10 to 185. 6 out of 11 studies provided data comparing SVCT with PA versus another reference standard Studies (n=11): Blum *et al.*, 1994 (n=10) Christiansen *et al.*, 1997 (n=70) Cross *et al.*, 1998 (n=59) Garg *et al.*, 1998 (n=54) Goodman *et al.*, 1995 (n=20) Mayo *et al.*, 1997 (n=139) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) Sostman *et al.*, 1996 (n=53) van Rossum *et al.*, 1996 (n=149) van Rossum *et al.*, 1996 (n=249)	With respect to quality assessment of the studies: only 5 fulfilled 5 or more of the 11 standards against which they were measured. Data from the 11 studies was presented but was not pooled due to variability in the studies. The authors also commented on the ability of SVCT examinations to detect other pulmonary abnormalities (e.g. pleural effusion, masses, enlarged mediastinal nodes), although only 4 of the included studies reported on this. In the 6 studies comparing SVCT with PA, some data were reported: sensitivities 64% to 93%; specificities 89% to 100%.	"SVCT may be relatively sensitive and specific for diagnosing central pulmonary artery PEs, but it is insensitive for diagnosing subsegmental clots. SVCT may have a role as a "rule-in" test for large central emboli, but additional research is required to establish its place in clinical practice." Limitations as per authors: it is premature to assign SVCT values of sensitivity and specificity for diagnosing PE as the research base for SVCT in the Dx of PE is small and still evolving. Pt(s) were highly selected and enrollment criteria were inconsistent, this caused variation in study results.	4 2 Inclusion process unclear, however, this report emphasizes the quality of the included trials more than most.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Rathbun SW *et al.*, 2000;[48] University of Oklahoma Health Sciences Center, Oklahoma City OK Annals of Internal Medicine, 2000. To determine the sensitivity and specificity of helical CT for the Dx of PE; and to determine the safety of withholding anticoagulant therapy in pt(s) who have clinically suspected PE and negative results on helical CT. Funder: College of Medicine Alumni Research Award	MEDLINE 1986 to Oct. 1999 Bibliographies of retrieved articles English language	Inclusion criterion: all prospective studies identified by the literature search (including abstracts). Exclusion criterion: retrospective studies, review articles and case reports. 26 documents identified (including 5 abstracts); 15 were retained and subjected to further appraisal. Appraisal criteria: consecutive series of pt(s); pt(s) had CT plus PA (or VQ scan); readers blind to other test results; breadth of pt types; generations of vessels imaged; size of PE on PA; and sensitivity and specificity of CT. Studies (n=15): Blum *et al.*, 1994 (n=10) Cross *et al.*, 1998 (n=59) Dresel *et al.*, 1995 (n=25) Drucker *et al.*, 1998 (n=47) Ferretti *et al.*, 1997 (n=164) Garg *et al.*, 1998 (n=54) Goodman *et al.*, 1995 (n=20) Kim *et al.*, 1999 (n=110) Mayo *et al.*, 1997 (n=139) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) Russi *et al.*, 1997 (n=20) Sostman *et al.*, 1996 (n=53) van Rossum *et al.*, 1996 (n=149) van Rossum *et al.*, 1996 (n=249)	No study met all predefined criteria for adequately evaluating sensitivity and specificity. Reported sensitivity 53% to 100%; and reported specificity 81% to 100%. Blinding of test readers: yes (8), no (3), NR (4). Most studies (10 out of 15) reported no f/u In no prospective study was anticoagulant therapy withheld without further testing for venous thromboembolism in consecutive patients with suspected PE. One prospective study reported the outcome of selected pt(s) with negative results on CT who did not receive anticoagulant therapy.	"Use of helical CT in the Dx of PE has not been adequately evaluated. The safety of withholding anticoagulant treatment in patients with negative results on helical CT is uncertain." "On the basis of the current best evidence, clinicians should not use negative results on helical CT as the diagnostic end point for excluding PE. The data show that helical CT may fail to detect PE that is shown on angiography to involve segmental or lobar vessels." "Definitive large, prospective studies should be done to evaluate the sensitivity, specificity, and safety of helical CT for diagnosis of suspected PE." Limitations (as per authors): most studies are missing relevant data; all studies include relatively few pt(s) who have undergone both CT and an appropriate reference test; studies varied widely with respect to pt selection, extent of PE, technology and testing methods, methods of interpretation, reader experience and inter-observer variability (e.g., a range of 62% to 92% among 5 readers in Sostman *et al.*)	3 2 Review is from February 2000 and technology has advanced significantly since. Search strategy limited.

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Safriel Y & Zinn H, 2002;[20] State University of NY at Brooklyn, Brooklyn NY Clinical Imaging, 2002. To determine the overall sensitivity and specificity for CTA in the diagnosis of PE using a meta-analysis of the published literature Funder: NR	MEDLINE Jan. 1990 to 2000 English language Recent results from prospective multi-centre trials presented at the Scientific Meeting of the Radiological Society of NA	Inclusion criteria: detection of acute and chronic PEs; comparison of CTA with PA or scintigraphy; and PE confirmed by PA or high probability VQ scan. Exclusion criteria: letters, review articles and case reports. Process of study selection NR Studies [n=12 studies, 1,250 pt(s)]: Bergin *et al.*, 1997 (n=47) Drucker *et al.*, 1998 (n=47) Garg *et al.*, 1998 (n=54) Goodman *et al.*, 1995 (n=20) Herold *et al.*, 1999 (n=391) Pruszczyk *et al.*, 1997 (n=49) Mayo *et al.*, 1997 (n=139) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) Sostman *et al.*, 1996 (n=53) van Rossum *et al.*, 1996 (n=149) van Strijen *et al.*, 1999 (n=238)	For the 12 included studies: sensitivity 57% to 100%; median 80.5%; and overall value, after correction for sample size 74.1%. Specificity 68% to 100%; median 89.5%; and overall value, after correction for sample size 89.5%. No trend was detected with respect to year of publication or sample size. Overall diagnostic accuracy of CTA for PE=94.5%, using an ROC curve.	"Results show that CTA can be a valuable diagnostic tool with overall high sensitivities and specificities. There is recent evidence to suggest that CTA may be more effective than VQ scintigraphy in the Dx and screening for PE. CT is more likely to yield an alternative Dx in the event of no PE being discovered. Furthermore, the use of CT reduces the likelihood of requiring further Dx tests compared to scintigraphy, where up to 75% of pt(s) require further testing to establish a final Dx." "CTA has acceptable sensitivity and specificity with a strong ROC curve making it a good first line investigation for PE." Limitations (as per authors): Inclusion criteria for studies varied widely from narrowly defined groups to inclusive; the included multi-centre trials have only been reported in abstract form; in the absence of an established method for pooling data from laboratory or imaging studies, a new system was created for this analysis.	2 2 Search strategy was limited; study selection was NR; the authors admit limitation to the English language excluded several useful non-English studies.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Segal JB *et al.*, 2003;[50] The Johns Hopkins University Evidence-based Practice Center, Baltimore MD Evidence Report / Technology Assessment, Number 68; US Agency for Healthcare Research & Quality (AHRQ), 2003. This report summarizes evidence on 9 research questions related to deep vein thrombosis, including PE. Only 1 is relevant to the current report: Question #7 – What are the test characteristics of helical CT, MRI and MRA, relative to PA or VQ scintigraphy, for diagnosis of PE? Funded by AHRQ (US government)	MEDLINE, MICROMEDEX, the Cochrane Controlled Trials Register and the Cochrane Database of SRs. Reference lists of articles identified through the electronic search Contact with technical experts Tables of Contents review of recent relevant journal issues English language	Inclusion criteria: addressed the key question; included original human data; and used a systematic approach to searching and synthesizing the literature. Exclusion criteria: case reports; and for MRI and MRA, studies that did not use PA or VQ scintigraphy as the reference test. It was found that the relevant literature had been synthesized on use of CT, therefore these reviews were used, as were some of the primary trials. Only primary research was found related to MRI and MRA Included articles were assessed as to quality, with specific scales used for reviews versus primary trials. The strength of evidence was graded (strong, moderate, weak or insufficient), using a grading scheme derived from previous projects. Studies included: for CT and PE 6 SRs, published 2000 to 2002 and 8 original studies, published 1994 to 2001; for MRI and MRA 7 original studies, published 1993 to 2001.	CT Sensitivity 45% to 100%; calculated from primary studies: 86% (95% CI: 80%; 90%). Specificity 78% to 100%; calculated 92% (95% CI: 88%; 95%) MRA MRA was sensitive and specific in detecting acute PE of the lobar and segmental branches of pulmonary arteries in pt(s) presenting with clinical suspicion for PE, although the studies were small. Accuracy of detecting smaller emboli was reduced substantially for emboli distal to the lobar segment of the arteries.	"Helical CT was fairly sensitive and had high specificity for detecting PE. MRA was accurate in detecting PE of the lobar and segmental branches of pulmonary arteries…moderate evidence exists to support a role…for helical CT or MRA for diagnosis of PE." Limitations (as per authors): "Interpretation of these estimates [for CT] should be done with caution due to potential selection bias and heterogeneity in the reviewed studies. Variation in reported CT sensitivity of…CT cannot be entirely explained by variation in study design or by the level of pulmonary arteries (segmental or sub-segmental) included in CT interpretation." "…the use of helical CT would benefit from more high quality prospective studies in which helical CT is compared to PA for detecting PE. Future studies of MRI/MRA need to be standardized in terms of speed, image acquisition, number of breath holds, presence or absence of cardiac gating, and dose of contrast to yield precise estimates of test characteristics. The feasibility of MRI/MRA in patients with symptomatic PE (with tachypnea and tachycardia) needs to be studied."	5 2 The section on Dx of PE was a part of a much larger report

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Stein PD *et al.*, 2003;[51] St. Joseph Mercy Oakland Hospital, Pontiac, MI; Washington University, St. Louis, MO; University of Calgary, Calgary; Oakland University, Rochester, MI: George Washington University, Washington DC. Chest, 2003. To review the published experience with gadolinium-enhanced MRA for the detection of acute PE, to test the hypothesis that gadolinium-enhanced MRA may be potentially sensitive and specific enough to include it among diagnostic alternatives in the evaluation of patients with suspected PE. Funder: NR	MEDLINE 1987 to 2002 Reference lists of all original and review articles	Inclusion criteria: prospective study; pt(s) were enrolled consecutively; PE was suspected in all pt(s); pt(s) with and without PE were included; Dx of PE was made on the basis of objective tests; all MRA images used gadolinium as a contrast agent; MRA Dx of PE was visualization of an intra-luminal filling defect for a cutoff vessel; data acquisition was 3D; gadolinium-enhanced and Dx tests for PE were interpreted independently; decision to perform the reference test was made independently of the MRA result; MRA methods were described well enough to allow replication; and sensitivity and specificity were presented or derivable. 28 studies reported on MRA for PE; 3 met inclusion criteria All 3 included studies were case series which used PA as the reference standard Studies (n=3): Gupta *et al.*, 1999 (n=36) Meaney *et al.*, 1997 (n=30) Oudkerk *et al.*, 2002 (n=141)	Reported results from the 3 included trials: sensitivity 85%, 100% and 77%; specificity 96%, 95% and 98%.	"Gad-enhanced MRA may be a useful diagnostic alternative in some patients with suspected acute PE, particularly if they have an elevated creatinine level, have an allergy to radiographic contrast material, or should, if possible, avoid exposure to ionizing radiation." Limitations: (as per authors): data are sparse, limiting interpretation, particularly of sensitivity; among the 3 studies, pt demographics may have differed (NR) and there were differences in MRA technique; in the study reporting 100% sensitivity, the average sensitivity of the 3 blinded readers before the consensus reading was 87% (closer to the values in the other 2 studies). The authors comment that the use of MRA of the pulmonary vasculature has been hampered by artifacts due to respiratory and cardiac motion, poor signal-to-noise ratio, long image acquisition times and limited spatial resolution – drawbacks that have been overcome by improvements in hardware and software and by the use of MRI contrast agents. New intravascular contrast agents are being developed.	3 2 The literature search was limited and only 3 studies were included with a total n=207

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van Beek EJ *et al.*, 2001;[68] Royal Hallamshire Hospital, Sheffield, UK; Academic Hospital Rotterdam, Rottterdam, the Netherlands; West China University of Medical Sciences, Chengdu, People's Republic of China; and State University Hospital, Groningen, the Netherlands. Clinical and Applied Thrombosis/Hemostasis, 2001. To assess, for lung scintigraphy and helical CT, in pt(s) with suspected PE: the diagnostic value of the technologies, inter-observer variability and evidence of clinical utility in clinical practice (as demonstrated by management studies) Only information relevant to CT is reported here. Funder: NR	MEDLINE and Current Contents Final inclusion date June 1, 1999 English language	Inclusion criteria: studies of diagnostic accuracy as well as management; prospective; consecutive enrollment of pt(s); adequate description of pt(s); reference standard PA; sensitivity and specificity reported (as compared with PA); blinded comparisons; for management studies, adequate description of f/u; f/u ≥3 months; description of Dx in pt(s) with recurrent Sx; original (non-duplicated) studies. Exclusion criteria: abstracts. Process for selecting included studies was NR Included studies (n=12): • Blum *et al.*, 1994 (n=10) • Dresel *et al.*, 1995 (n=25) • Drucker *et al.*, 1998 (n=40) • Garg *et al.*, 1998 (n=54) • Goodman *et al.*, 1995 (n=20) • Kim *et al.*, 1999 (n=110) • Mayo *et al.*, 1997 (n=139) • Pruszczyk *et al.*, 1997 (n=49) • Remy-Jardin *et al.*, 1996 (n=75) • Steiner *et al.*, 1994 (n=38) • van Rossum *et al.*, 1996 (n=149) • van Rossum *et al.*, 1996 (n=249)	Articles assessed for methodology strength, based on 9 *a priori* criteria. CT studies were compared with PA and lung scintigraphy in 1,171 patients with a 39% prevalence of PE CT sensitivity 88%; (95% CI: 83%; 91%); 283 out of 320 pt(s); specificity 92%; (95% CI: 89%; 94%); 374 out of 408 pt(s) Only one prospective management study using CT was found. In patients in whom anticoagulants were withheld (normal CT), recurrent TE events occurred in 6 out of 109 pt(s) 5.5%; (95% CI: 2%; 12%, with one fatality 1%; (95% CI: 0.02%; 4.3%). Inter-observer agreement was high in all studies Sensitivity in the subgroup with previous nonDx studies and smaller PEs dropped to 67%; important as 30% of pt(s) with suspected PE have emboli limited to the subsegmental arteries.	"Helical CT has similar PPV to a high-probability lung scan (~50%). However, the exact role of CT in the management of patients with suspected PE needs to be determined in prospective studies." "…at present, it should be regarded unsafe to withhold anticoagulant therapy in pt(s) with normal CT findings." "…it is expected helical CT will play a significant role in the future in the management of pt(s) with suspected PE…not only because of its diagnostic accuracy, but also because of its non-invasive nature and wide availability." Limitations (as per authors): some studies may have been focussed more on central PE, thus influencing overall figures; between 3% and 6% of CT exams were technically inadequate	2 2 Process for selecting included studies was NR. Search strategy was limited.

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Villaneuva E *et al.*, 1999;[14] Centre for Clinical Effectiveness, Monash Medical Centre, Clayton Australia Evidence Centre Report, Centre for Clinical Effectiveness, Southern Healthcare Network / Monash Institute of Public Health & Health Services Research, 1999. To determine whether CT has better diagnostic properties in diagnosing PE compared with PA in hospitalized pt(s). Funder: Australian Southern Healthcare Network / Monash Institute of Public Health & Health Services Research.	MEDLINE, the Cochrane Library, Best Evidence CD-ROM, National Library of Medicine, Agency for Health Care Policy and Research, NHS Centre for Reviews and Dissemination, Aggressive Research Intelligence Facility and Turning Research into Practice (TRIP) Search spanning 10 years, ending August 31, 1999.	Inclusion criterion: primary studies comparing spiral CT with PA in the diagnosis of PE in hospitalized adults. Exclusion criteria: study examined <5pt(s); language other than English; and duplication of data. 72 studies; 6 met inclusion criteria. Studies (n=6): Blum *et al.*, 1994 (n=10) Garg *et al.*, 1998 (n=54) Remy-Jardin *et al.*, 1992 (n=42) Remy-Jardin *et al.*, 1996 (n=75) van Rossum *et al.*, 1996 (n=149) van Rossum *et al.*, 1996 (n=249)	Spiral CT versus PA: sensitivity 67% to 100%; specificity 67% to 100%; and PPV 83% to 100%	Generally favourable diagnostic characteristics were attributed to the use of spiral CT in the Dx of PE. Compared with PA, its sensitivity ranged from 67% to 100%. Specificity was equally variable; the ability of the CT to classify as negative those without PE varied between 67% and 100%. PPV ranged from 83% in pt(s) with a clinical suspicion of PE based on Hx, physical examination or laboratory findings, chest x-ray or ECG changes to 100% in a population with suspected massive PE, indeterminate VQ scans, or clinical suspicion of PE by VQ scan. Limitations (as per authors): "There were distinct problems with the methodology of the retrieved studies that included: inadequate description of patient setting, spectrum, characteristics and entry criteria; wide variations in the prevalence of PE; and dependence of results on sample size."	3 2 Perspective restricted to hospitalized pt(s). Inclusion and validity assessment unclear. Primarily a summary of published material.

CI=95% confidence interval; CTA=CT angiography; Dx=diagnosis; EBCT=electron beam; CT: ER=emergency room; FN=false-negative; FP=false-positive; F/T=Fryback & Thornbury (quality score); f/u=follow up; HTA=health technology assessment; Hx=history; MA=meta-analysis; O/G=Oxman & Guyatt (quality score); PA=pulmonary angiography; PE=pulmonary embolism; pt(s)=patient(s); PPV=positive predictive value; R&D=research and development; Rx=treatment; SR=systematic review; SVCT=spiral volumetric CT; Sx=symptoms; TE=thromboembolic; TN=true negative; TP=true positive; VP or V/Q scan=ventilation/perfusion.

Table 6: Carotid artery disease – CTA and MRA

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Berry E *et al.*, 2002;[19] University of Leeds, Leeds General Infirmary; and St. James's Hospital, Leeds; University of Manchester; University of York; UK HTA, NHS R&D HTA Programme, 2002. (Also published as Westwood *et al.*) For carotid artery disease, to identify literature on MRA for pre-surgical assessment; and to synthesize evidence about the diagnostic performance of MRA compared with DSA, at surgical decision thresholds (report is also about PVD). Funder: The UK NHS R&D HTA Programme.	MEDLINE, EMBASE, Health STAR, Science Citation Index, Index to Scientific/Technical Proceedings, the Cochrane Library, Inside (British Library), Online Computer Library Centre, EconoLIT, HTA databases, HEED and NHS EED 1990 to March 2000 Internet (limited) Hand search of 10 key journals and Department of Health databases. Reference lists No language restrictions	Inclusion criteria: MRA versus DSA or cut-film angiography; sufficient data for a 2x2 table; stenosis: 50% to 99%, 70% to 99%, or 100%; not a duplicate study (if a duplicate, the study with largest "n" was used); all pt(s) had DSA or cut-film angiography; described method used to determine stenosis; no asymptomatic pt(s) included; and tests within 1 month of each other. 10 included studies (9 were described): Chiesa *et al.*, 1993 Dadachanji MC *et al.*, 1995 Huston J *et al.*, 1993 Laster REJ *et al.*, 1993 Link J *et al.*, 1996 Magarelli N *et al.*, 1998 Scarabino T *et al.*, 1998 Scarabino T *et al.*, 1999 Uehara T *et al.*, 1995 White *et al.*, 1994	"There were too few articles on the latest contrast-enhanced techniques for quantitative synthesis, but the results appear better than those for 2D and 3D TOF methods. The TOF methods are highly accurate for detecting occlusion and 70-99% stenoses, but are less accurate for 50-99% stenoses."	"In carotid artery disease, 2D & 3D TOF MRA techniques are accurate for identifying both occlusions and 70-99% stenosis as defined by conventional angiography. The evidence does not support their use for identifying 50-99% stenosis." Limitations discussed in Westwood *et al.*	7 2 Overlaps with Westwood *et al.* and could be assumed to be the same study, although 2 additional studies were added to the 8 of Westwood; this large HTA document is primarily to determine cost-effectiveness, with clinical as a prelude.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Hollingworth W *et al.*, 2003;[52] University of Washington, Seattle WA European Journal of Radiology, 2003. To determine the accuracy of CTA for atherosclerotic, penetrating and blunt lesions in the carotid and vertebral arteries. Funder: NR	MEDLINE and EMBASE 1992 to Aug. 1, 2002 Updated to Dec. 31, 2002 Hand searching included articles, biographies. No language limitations	Inclusion criteria: >10 pt(s); evaluated the Dx accuracy of CTA; imaged carotid or vertebral arteries; and used DSA or surgical findings as a reference standard. Exclusion criteria: non-traumatic aneurysms or tumours; multiple publications with same data; and insufficient data. Articles were assessed for quality using a 14-point checklist; possible score 0 to 1. Articles scoring ≥0.5 were included in the atherosclerosis analysis, but all articles were included for traumatic injury. 940 studies: 112 requested in full text (105 obtained); 43 included. Summary of studies (43 total): • Publication year 1992 to 2002 • Focus: atherosclerosis (30); blunt trauma (2); penetrating (2); other (9) • Mean pt age: atherosclerosis 55 to 75, trauma 27 to 38 • Median sample size <30 (10 to 216) • Median delay between tests, 3 days • 41 out of 43 studies used single slice CT.	Pooled data from the 15 higher quality studies concerned with carotid atherosclerosis. Severe >70%; stenosis; sensitivity 95%; specificity 98%; moderate plus >30% stenosis; sensitivity 95%; specificity 98%. Blunt trauma Both studies raised concerns about CTA sensitivity. Study 1: (carotid/vertebral) sensitivity 47% and 53%; specificity 99% and 99%. Study 2: sensitivity 68%; specificity 67%. Penetrating trauma Study 1: sensitivity 90%; specificity 100%. Study 2: sensitivity 80%; specificity 100%.	"CTA is both a sensitive and specific imaging technique for identifying severe atherosclerotic stenosis and occlusion of the carotid arteries. However there is currently not enough high quality evidence to accurately estimate the sensitivity and specificity of CTA in the setting of blunt or penetrating trauma." "The pooled sensitivity and specificity of CTA for severe atherosclerosis was 95% and 98% respectively, indicating CTA is accurate enough to play an important role in imaging prior to endarterectomy. The high specificity implies that CTA does not systematically overestimate the degree of stenosis."	6 2 Grey literature not included; CT technology has advanced significantly

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Long A *et al.*, 2002;[53] Hôpital Européen Georges Pompidou, Paris; ANAES, Paris; and Hôpital d'Adultes Timone, Marseilles France European Journal of Vascular & Endovascular Surgery, 2002. To assess the performance of non- or minimally-invasive methods (DUS, CTA and MRA) in measuring stenosis of the proximal internal carotid artery before endarterectomy, without the performance of pre-operative DSA. Funder NR; possibly ANAES (the government-funded French health technology assessment agency).	MEDLINE, EMBASE, HealthSTAR, PASCAL and the Cochrane Library 1990 to Feb. 2001 English & French languages Tables of Contents of specialty journals published Jan. 2000 to Mar. 2001 Reference list of retrieved papers	Inclusion criteria: prospective studies, aside from 1 retrospective providing long-term f/u For reproducibility for CTA and MRA: stenosis expressed as a function of diameter as per NASCET or ECST For reproducibility for DUS: discussed variability among centres; evaluated inter-equipment variability; evaluated inter- and intra-observer reproducibility. For Dx efficacy of DUS, CAT and MRA: DSA was the control procedure; stenosis expressed as per the NASCET or ECST; method of evaluating degree of stenosis specified; sensitivity and specificity provided or could be calculated. For MRA reproducibility, sensitivity and specificity in particular: relating to 3D gadolinium MRA only. Approximately 70 articles were included and were grouped to assess reproducibility DUS (11), CTA and MRA (2); sensitivity and specificity, DUS (22); CTA (19); MRA (11). Articles were also located which reported on endarterectomy without pre-operative DSA assessment (n=6).	Sensitivity ≥80%; for ≥70% stenosis: CTA 8 out of 9 studies MRA 6 out of 6 studies For occlusion: CTA 8 out of 9 studies MRA 4 out of 4 studies Specificity ≥90%; for ≥70% stenosis: CTA 9 out of 9 studies MRA 5 out of 6 studies For occlusion: CTA 9 out of 9 studies MRA 4 out of 4 studies	"Sensitivity exceeded 80% and specificity 90% in over 2/3 of methodologically sound studies, regardless of technique, although direct comparisons between results had to be avoided since the findings originated from different populations." "Only a few studies have addressed the reproducibility of CTA and MRA." "When non- or minimally-invasive techniques are combined, the additional investigation more frequently used after DUS seems to be MRA. When the results of DUS and MRA agree, the combination… provides a better Dx than either technique taken alone." "All 3 techniques (DUS, CTA, MRA) appear suitable for measuring stenosis of the proximal internal carotid when compared to DSA."	4 2 Selection process and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Meenan RT *et al.*, 2002;[54] Kaiser Permanente Northwest and Oregon Health & Science University Evidence-based Practice Centre, Portland OR US Agency for Health Care Research & Quality (AHRQ), 2002. To discuss the effectiveness and cost-effectiveness of various imaging strategies for evaluating and managing new stroke patients: transthoracic echocardiography, trans-esophageal echocardiography, carotid ultrasound, MRA and cerebral angiography. Fifteen "key questions" were posed in the report, one related to the subject of interest: "What are the operating characteristics of available tests for measuring carotid artery stenosis?" Funder: AHRQ	MEDLINE, HealthSTAR, the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness (DARE) and HTA databases 1966 or inception but end date NR Limited to English language	This extensive report (320 pages) reviewed a number of topics beyond use of MRA for carotid artery imaging. Inclusion criteria are therefore not included here. Included studies of MRA accuracy=6. Also located was a systematic review (deemed by the authors to be of good quality) of studies assessing the accuracy of non-invasive measurement of carotid artery stenosis: Blakeley DD *et al.* Noninvasive carotid artery testing. A meta-analytic review. Ann Intern Med 1995; 122(5):360-7.	Pooled accuracy of MRA was calculated versus degree of stenosis: Stenosis ≥50% Sensitivity 86.3% (95% CI: 53.9%; 99.7%); specificity 75.7% (95% CI: 40.5% to 97.3%). Stenosis ≥50% excluding studies using only 2D TOF imaging) Sensitivity 89.6% (95% CI: 81.6; 95.5%); specificity 94.8% (95% CI: 88.4%; 98.7%). Stenosis ≥70% Sensitivity 94.2% (95% CI: 84.2%; 99.3%); specificity 79.3% (95% CI: 52.0%; 96.5%). Stenosis ≥70% excluding studies using only 2D TOF imaging): sensitivity: 91.8% (95% CI: 72.2%; 99.8%); specificity: 86.9% (95% CI: 71.7%; 98.7%).	"Despite numerous studies of the accuracy of noninvasive carotid imaging, relatively few have been conducted in which all patients undergoing noninvasive tests also undergo diagnostic confirmation with DSA. The lack of diagnostic verification in these studies creates biased estimates of sensitivity and specificity." "Whether the accuracy of MRA varies by center is not clear. There have not been multicenter studies of MRA. Published data, excluding studies with obvious or likely verification bias, suggest a sensitivity and specificity of 92% and 97% for detecting severe stenosis. However, studies of MRA were generally of fair to poor quality…it is possible that centers publishing their accuracy data are not representative of all users of MRA. Until there are more high-quality data on the accuracy of MRA, current estimates of MRA accuracy in measuring carotid stenosis must be interpreted cautiously."	6 2 Report published July 2002 but unclear when literature search ended; formatting problems with electronic version of report made it hard to use (e.g. references referred to numerically in text but not listed numerically so couldn't be identified).

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Nederkoorn PJ *et al.*, 2003;[55] University Medical Centre Utrecht, Utrecht; and Erasmus Medical Centre, Rotterdam, the Netherlands; and Harvard School of Public Health, Boston MA Stroke, 2003. To review and compare published data on the diagnostic value of DUS, MRA and DSA, for the Dx of carotid artery stenosis Funder: Grant from the Dutch Ministry of Health, Welfare and Sports; and by a program grant from the Netherlands Organization for Scientific Research	PubMed Jan. 1994 to Dec. 2001 English language only Reference lists of original and review articles Contact with authors of included studies to obtain additional data	Inclusion criteria: published 1994 to 2001; MRA or CE-MRA and/or DUS performed to estimate the severity of carotid artery stenosis; DSA used as a reference standard; and absolute numbers of TP, FP, TN and FN available or derivable for at least 1 cut-off criterion for the degree of stenosis based on DSA. Exclusion criteria: studies with occlusion as the main outcome, if authors did not provide additional data on nonocclusion group; <15 pt(s). For publications with overlapping data, the article included was the one from which data could be best extracted. Categories of carotid stenosis for data collection: 0% to 29%; 30% to 49%; 50% to 69%, 70% to 99% and 100%. Analyses were presented only for 70% to 99% (severe stenosis) versus <70% and 100% (occlusion) versus <100%. 900 references: 151 full text; 62 met inclusion criteria [85 separate study populations: MRA (21); DUS (64)].	For the Dx of stenosis of 70% to 99% versus <70%: pooled sensitivity MRA 95% (95% CI: 92%; 97%); DUS 86% (CI: 84 to 89). Pooled specificity MRA 90% (95% CI: 86%; 93%); DUS 87% (95% CI: 84%; 90%). For recognizing occlusion: Pooled sensitivity: MRA 98% (95% CI: 94; 100); DUS 96% (95% CI: 94; 98). Pooled specificity MRA 100% (95% CI: 99; 100); DUS 100% (95% CI: 99; 100). Type of MRI scanner predicted the performance of MRA	"MRA has a better discriminatory power compared with DUS in diagnosing 70% to 99% occlusion and is a sensitive and specific test compared with DSA in the evaluation of carotid artery stenosis. For detecting occlusion, both DUS and MRA are very accurate." "To determine whether non-invasive tests can replace DSA in clinical practice, however, not only the test results, but also the associated costs and effectiveness should be taken into account." Limitations (as per authors): only studies with complete data could be used (29 out of the 42 study authors contacted did not respond to requests for data); DSA was the reference standard and limits projections used, thus it limits information on stenosis. An accompanying editorial by M. Forsting & I Wanke (University of Essen, Germany) concludes: "We do not need DSA in pt(s) with carotid artery stenosis. DUS is already excellent; MRA is better."	3 2 Selection process and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Westwood ME *et al.*, 2002;[56] University of Leeds & Leeds Teaching Hospitals NHS Trust, Leeds; and Centre for Health Economics, University of York, York; UK BMJ, 2002. To determine if sufficient information exists to support the use of MRA as a means of selecting pt(s) with recently symptomatic high-grade carotid stenosis, for surgery. Funder: Financial support from the secretary of state for health under the NHS Technology Assessment Programme. Conflict-of-interest statements include prior reimbursement of several authors by Schering UK and Philips Medical Systems	MEDLINE, EMBASE, Health STAR, Science Citation Index, Index to Scientific & Technical Proceedings, the Cochrane Library, Inside (British Library) and Online Computer Library Centre Jan. 1990 to Dec. 1999 Hand search of 10 key journals in imaging and vascular disease Reference lists of all retrieved articles	Inclusion criteria: MRA versus DSA or cut-film angiography sufficient data for a 2x2 table; stenosis: 50% to 99%, 70% to 99% or 100%; not a duplicate study (if a duplicate, the study with largest "n" was used); pt(s) had DSA or cut-film angiography; described method used to determine stenosis; no asympto-matic pt(s) included; and tests within 1 month of each other. Exclusion criteria: review, editorial, letter, case report or conference abstract; technical evaluation; and pediatric participants ≤10 participants. 16,185 references: 206 remain after application of exclusion criteria; 26 included in MA; 8 remain after application of all inclusion criteria. 8 included studies (n=NR): Dadachanji MC *et al.*, 1995 Huston J *et al.*, 1993 Laster REJ *et al.*, 1993 Link J *et al.*, 1996 Magarelli N *et al.*, 1998 Scarabino T *et al.*, 1998 Scarabino T *et al.*, 1999 Uehara T *et al.*, 1995 Study summary: n=11 to 101 (mean=40) Most pt(s) were men (mean 69%) Age range of study pt(s) 18 to 87	A meta-analysis showed maximal joint sensitivities and specificities: for 70% to 99% stenosis 99% (95% CI: 98%; 100%); for 50% to 99% stenosis 90% (95% CI: 81%; 99%).	"Results indicate MRA is very effective for detecting 70% to 99% stenosis as defined by conventional angiography… there is a promising trend towards better performance from contrast-enhanced methods [but] further research is essential as only 4 articles were included." "Our review does not support the use of MRA to select surgical candidates with 50-99% stenosis… users of MRA [should] ensure rigorous training and audit are in place, including feedback from surgeons and continuing quality control comparisons with US." Limitations (as per authors): Potential bias in studies arises from pre-screening MRA pt(s) using US, proceeding only if US shows significant stenosis; unsure which studies to determine surgical candidates, should distinguish >50% stenosis from <50% and 100%, studies often did not do this; for impact, should study MRA versus DSA re decision making and outcomes.	4 2 Details of included studies NR; final "n" of included pt(s) NR; studies used for analysis old (1993 to 1999) considering advancing technology and methods (e.g., use of contrast)

AHRQ=US Agency for Health Care Research & Quality; CA(s)=cerebral aneurysm(s); CE-MRA=contrast-enhanced MRA; CI=95% confidence interval; CTA=CT angiography; DSA=digital subtraction angiography; DUS=duplex ultrasound; Dx=diagnosis; ECST=European Carotid Surgery Trialists' Collaboration; FN=false negative; FP=false-positive; F/T=Fryback & Thornbury (quality score); f/u=follow-up; HTA=health technology assessment; MRA=MR angiography; NASCET=North American Symptomatic Carotid Endarterectomy Trial; NPV=negative predictive value; NR=not reported; pt(s)=patient(s); O/G=Oxman & Guyatt (quality score); PVD=peripheral vascular disease; Rx Rx=treatment; SAH=subarachnoid hemorrhage; Sx=symptoms; TOF=time of flight; TN=true negative; TP=true positive; US=transcranial Doppler ultrasound.

Table 7: Cerebral aneurysms – CTA and MRA

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Chappell ET *et al.*, 2003;[57] University of California, Irvine, Orange CA; University of California, San Francisco-East Bay, Oakland CA; University of California, Berkeley, Berkeley CA Neurosurgery, 2003. To compare a novel diagnostic radiological technique, CTA, with the standard method, DSA, in the Dx of CAs, based on strict clinical indications Funder: NR	MEDLINE (keywords searched in title of articles only) Search years NR Bibliographies of articles Non-English articles were included and translated (unless the necessary data were in the abstract)	Inclusion criteria: pt(s) presented with SAH or Sx suggestive of a CA; pt(s) underwent angiography on the basis of accepted criteria; CTA was prospectively (or blindly) compared with DSA in an effort to exclude the possibility of a CA; and CTA was performed and interpreted before DSA or by an examiner blinded to the results of the DSA and skilled in the interpretation of images of the cerebral vasculature. 78 articles identified; 21 selected Summary of studies: publication year 1995 to 2002; sample size 16 to 117; total n=1,251 in 21 studies; a test for homogeneity showed a meta-analysis was possible; and sensitivity and specificity of CTA versus DSA were calculated for each study and then pooled.	Weighted calculations (adjusted for study sample sizes): sensitivity 92.7%; specificity 77.2%. Advantages and disadvantages of CTA were identified Advantages of CTA versus DSA: data obtained quickly and easily at the time of the initial CT; provides more complete anatomic information; can be used for rapid and definitive Rx planning, including clip ligation and coil embolization; and virtually no risk and little discomfort. Disadvantages of CTA versus DSA: less sensitive and specific for CAs; unavailable at most institutions; requires capital outlay, personnel training and initiative; and may provide less information about blood flow patterns in the circle of Willis.	"DSA remains the standard method. However, many who use CTA have reported it to be as good or better than DSA in the Dx and Rx of CAs, as well as less risk & discomfort for their pt(s) and easier and less expensive." "…DSA can also be used [after CTA] until confidence and experience are gained." Limitations (as per the authors): "an inherent and unavoidable bias is present …there were relatively few cases without disease (true negative cases), casting doubt on any effort to assess the specificity and negative predictive value of CTA."	2 2 Literature search was limited and did not seek grey literature. Selection process and validity assessment unclear. Heterogeneity issues.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
van Gelder JM, 2003;[49] Department of Neurosurgery, Southwestern Sydney Health Service, University of New South Wales, Sydney, Australia Neurosurgery, 2003. To examine the efficacy of CTA for the detection of ruptured and unruptured CAs, after adjustment for their size distributions, under various conditions of CA prevalence. Funder: No grants or other funding received.	A review done by White *et al.* in 2000 was updated in Sept. 2002. No other detail was supplied in this article. White *et al.* searched MEDLINE and EMBASE from 1988 through 1998, checked reference lists of included articles and review articles, hand searched journals not indexed with the electronic databases and publications subsequent to relevant meeting abstracts (unpublished abstracts were not included). A separate literature search was conducted to find articles reporting on ruptured and unruptured CAs and their sizes	Inclusion criteria for main search: sensitivity and specificity of CTA reported for detection of CAs; DSA or surgical findings used as the gold standard; interpreting radiologists blinded to the results of the gold standard; >20 cases described; and sensitivity described with stratification according to aneurysm size. Study selection process: NR Included studies: 9 provided enough data to derive the sensitivity of CTA stratified according to CA size; median year of study period ranged from 1993 to 1998; total n=619; and average number of CAs per pt=0.4 to 1.1. Studies: Alberico *et al.*, 1994 (n=68) Hope *et al.*, 1993 (n=80) Ogawa *et al.*, 1996 (n=65) Anderson *et al.*, 1996 (n=40) Rohnert *et al.*, 1996 (n=106) Korogi *et al.*, 1999 (n=49) Villablanca *et al.*, 1998 (n=39) Seruga *et al.*, 2001 (n=30) White *et al.*, 2000 (n=142) For the second search, it appears 12 studies were located and 6 used in the analysis (unclear)	Efficacy of CTA: sensitivity of CTAs=66% to 98%; regression model predicted for CAs >7.7 mm, false negative results are not possible; sensitivities by CA size: 53% for 2 mm CAs to 95% for 7 mm CAs (displayed as a continuous curve in a graph); specificity CTA 77% to 100%; overall estimated specificity 99%; publication bias was not found. Likelihood ratios were calculated	"Small aneurysms detected on CTA should be investigated further, unless there is a high pretest probability of a ruptured aneurysm. During screening for unruptured CAs, a negative CTA results in a very low probability of a clinically important aneurysm." A commentary by BL Hoh from Boston follows the article, contributing a "simplification": With no SAH, a CTA finding of a CA >6 mm can be trusted; specificity decreased for CAs <2 mm. With a SAH, CTA findings can be trusted for large and small CAs. With SAH and no CA on CTA, DSA is warranted. He also states his group had previously treated 74% of CA pt(s) (177 out of 238) with surgery or endovascularly on the basis of CTA alone.	3 2 As studies range from 1993 to 1998, data is older; it is unclear how the various study objectives and separate literature searches relate to each other or are reported. Adequacy of search, inclusion criteria and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
White PM *et al.*, 2000;[58] Departments of Neurosurgery, Neuroradiology, Clinical Neurosciences; and Medical Statistics, Glasgow and Edinburgh, Scotland. Radiology, 2000. To determine the accuracy of CTA, MRA and transcranial Doppler ultrasound (US) in depicting CAs as compared with DSA Funder: British Brain & Spine Foundation from the Davie Cooper Scottish Aneurysm Study grant, administered by the University of Glasgow; and the UK Medical Research Council	MEDLINE and EMBASE 1988 through 1998 No language restrictions Reference lists of included articles and review articles Hand searching of journals not indexed with the electronic databases in which relevant articles had been located Publications arising from relevant meeting abstracts (unpublished abstracts were not included) Validation was performed by hand searching the RSNA Index to Imaging Literature Hand searching Neurosurgery, Stroke and the Journal of Neurosurgery	Inclusion criteria: Dx accuracy of a non-invasive imaging exam compared with DSA; <10 subjects underwent both the non-invasive imaging exam and DSA in the same time period; and CAs of any size. Exclusion criteria: studies pre-1988 and pediatric studies. Included studies were quality assessed using a weighted checklist of 26 to 27 items relevant to diagnostic performance, with items divided into 3 categories: study design and methodology; image review process; and presentation of data. Studies received a quality score of 0 to 10; those with scores >5 were retained for the meta-analysis. 1,473 articles identified: 103 met initial inclusion criteria; 38 included after quality assessment. Summary of 38 included articles: English (32), German (3), Italian (1); n=1,765 pt(s) Median prevalence of CAs: CTA 80%, MRA 76%, US 90% Technology articles: CTA versus DSA (14); MRA versus DSA (18); CTA and MRA versus DSA (2); US versus DSA (4).	Use of a quality assessment scoring system reduced the included articles from 103 to 38 (those scoring 5 out of 10 or better). CTA and MRA had accuracies per aneurysm of 89% (95% CI: 87%; 91%) and 90% (95% CI: 87%; 92%). Sensitivity was significantly greater for the detection of aneurysms >3 mm versus those <3 mm: CTA 96% versus 61%; MRA 94% versus 38%; and Dx accuracy was similar for anterior and posterior circulation CAs.	"CTA and MRA detected CAs with an accuracy of about 90%. Most studies were performed in populations with high aneurysm prevalence, which may have introduced bias toward non-invasive examinations." "For US, data were scanty and accuracy lower." "NPVs were significantly lower than the other analysis parameters, both with CTA and MRA – 67% and 77% respectively." "Sensitivity was significantly poorer for the detection of aneurysms smaller than 3mm." "The current data are too limited to determine confidently the accuracy of non-invasive methods when they are used for screening."	5 2 As studies range from 1993 to 1998, data may be old; detail about individual included studies was unavailable; and as stated by the authors, use of high-prevalence populations may make extrapolation of findings limited.

CA(s)=cerebral aneurysm(s); CI=confidence interval; CTA=CT angiography; DSA=digital subtraction angiography; Dx=diagnosis; F/T=Fryback & Thornbury (quality score); MRA=MR angiography; NPV=negative predictive value; NR=not reported; O/G=Oxman & Guyatt (quality score); pt(s)=patient(s); Rx=treatment; SAH=subarachnoid hemorrhage; Sx=symptoms; US=transcranial Doppler ultrasound.

Table 8: Headaches – CT and MRI

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Lewis DW *et al.*, 2002;[59] Quality Standards Subcommittee, American Academy of Neurology & Practice Committee of the Child Neurology Society American Academy of Neurology, 2002. To review available evidence on the evaluation of children with recurrent headaches and make patient management recommendations Funder: NR	MEDLINE and Current Contents No language restrictions 1980 to 2000 5 articles pre-1980 containing epidemiological information Relevant position papers from professional organizations Bibliographies of included articles	Inclusion criteria: investigation of headache looking for a possible etiology; children aged 3 to 18; study sample size >25 pt(s); and information about pt(s) neurological examinations. Included studies=6* Maytal J *et al.*, 1995 (n=133) Medina LS *et al.*, 1997 (n=315) Dooley JM *et al.*, 1990 (n=157) Wober-Bingol C *et al.*, 1996 (n=429) Chu ML & Shinnar S, 1992 (n=104) Lewis DW & Dorbad D, 2000 (n=137)	• Imaging abnormalities were found in 97 of 605 children (16%) • In 79 of 97 (82%), the abnormalities were considered to be incidental, nonsurgical or not requiring medical management • 18 of 605 (3%) had a condition which required treatment with surgery (n=14) or medicine (n=4) • Of the 14 with surgical lesions, 10 had tumours, 3 had AVMs and 1 had an arachnoid cyst • In all 14, findings on physical exam had been discovered, (e.g., papilledema, nystagmus) • No pt with a normal physical exam had a lesion requiring surgical Rx	Obtaining a CT or MRI on a routine basis is not indicated in children with recurrent headaches and a normal neurological exam. It should be considered with an abnormal neurological exam. Neuroimaging should be considered in children with a recent onset of severe headaches, changes in types of headaches or associated features suggesting neurological dysfunction.	3 2 Analysis was limited to children; and the document focussed on other aspects besides neuroimaging. Inclusion criteria, process and validity assessment unclear.

*Headache types were: migraine (62%), tension (22%), other (16%). Of the total n=1,275 in the 6 studies, only 605 had neuroimaging: CT (n=116); MRI (n=483); both (n=75)
AVM=arteriovenous malformations; F/T=Fryback & Thornbury (quality score); NR=not reported; O/G=Oxman & Guyatt (quality score); Rx=treatment.

Table 9: Head injury – CT and MRI

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
af Geijerstam JL & Britton M, 2003;[60] Swedish Council on HTA in Health Care & Unit of Clinical Epidemiology, Karolinska Hospital, Stockholm, Sweden Acta Neurochir, 2003. For patients with mild head injury, to estimate the mortality, complication rates and frequency of pathological findings on CT as accurately as possible. Funder: NR. Probably the Swedish Council on HTA in Health Care (SBU), a government-funded research organization.	MEDLINE Inception to May 2001, then updated to Oct. 2002 The Cochrane Library Reference lists of key studies and review articles No language restrictions	CT findings were tracked but were a secondary consideration in the study Inclusion criteria: pt series with CT performed in >90%; mild head injury defined as short-term LOC and amnesia due to skull trauma; in the ER pt(s) must have normal LOC and normal neuro findings; and for MA, pt(s) must have GCS>15. Exclusion criteria: letters, comments, guidelines, recommendations and case histories A grading checklist was developed to assess all studies, based on: use of inclusion criteria; use of GCS; ordinary case mix of pt(s); adequacy of follow-up; and study size. 1,143 abstracts; 410 full text; 88 assessed for quality; 48 retained as medium or high quality; and 24 in final set 24 studies used in the MA were assessed as high (10) or medium (14) quality; n=53,855 pt(s) (24,249 with GCS >15 used in MA); published from 1986 to 2001; source: US (21), Italy (2) and Canada (1).	Overall findings: mortality rate 0.1%; complications 0.9%. Interventions: neurosurgical operations 75%; transfer to ICU 23%; IC pressure monitoring 2%. Use of CT (reported in 15 of 24 studies, n=13,311 pt(s)). Pathological findings 7.8%: skull fracture 3.2%; IC hemorrhage or contusion 2.8%; subdural hemorrhage 1.3%; epidural hemorrhage 1%; and subarachnoid hemorrhage 1%.	Of 1,000 pt(s) arriving at hospital with a mild head injury, 1 will die, 9 will require surgery or another intervention, 80 will show pathological findings on CT and 80 will require inpatient care. The reported rate of abnormalities on CT varied significantly from 3.3% to 34%. The authors state that the routine use of skull x-ray to triage pt(s) with mild head injury is of less diagnostic value, but equal cost to CT, meaning the optimal use of CT requires definition. Limitations as per the authors: the included studies showed substantial variation – case mix of pt(s), differences in definitions, differences in practice.	3 2 CT was only considered secondarily and no assessment of the value of CT was carried out. Validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Eng J & Chanmugam A, 2003;[61] Johns' Hopkins University School of Medicine, Baltimore MD Neuroimaging Clinics of North America, 2003. To determine the incidence of injury-related abnormalities on CT in pt(s) with minor head injuries. Funder: NR	MEDLINE Inception to April 2002 Limited to English articles Reference lists of retrieved articles	8 inclusion criteria: prospective design; population primarily adults; article included original data or results; pt(s) presented for acute care after non-penetrating minor head trauma; pt(s) had a GCS of 13, 14, or 15; probability sampling method used; pt(s) had clinical evaluation and head CT or clinical follow-up; and positive and negative CT results reported. Exclusion criteria: letters and editorials; case reports; studies of pediatric populations; studies of severe head injuries; and studies of pt(s) with major neuro deficits; and studies of pt(s) sustaining general head trauma of unselected severity. Main outcomes recorded: incidence of positive CT; Dx performance of any clinical prediction rule Included studies (10); n=9,362: Haydel *et al.*, 2000 (n=1,429) Holmes *et al.*, 1997 (n=264) Jeret *et al.*, 1993 (n=712) Livingston *et al.*, 1991 (n=111) Livingston *et al.*, 2000 (n=2,005) Miller *et al.*, 1996 (n=1,382) Miller *et al.*, 1997 (n=2,143) Nagy *et al.*, 1999 (n=1,170) Uchino *et al.*, 2001 (n=88) Vilke *et al.*, 2000 (n=58) All but 1 were conducted in the US and all but 1 were conducted at a single centre.	• Quality assessment of the studies in 4 dimensions was carried out using a 17-item adapted tool, plus an overall score was calculated (median study score=64% (range 42% to 78%) • The overall incidence of a positive CT ranged from 3% to 14% (weighted mean 7.5% or 703 of 8,659) • For pt(s) with a GCS of 15, the overall incidence of a positive CT ranged from 3% to 10% (weighted mean 6.2%) • Incidence of injuries requiring neurosurgery 0.3% • Clinical factors associated with a positive CT: nausea; vomiting; physical signs of head trauma; GCS <15 • Clinical prediction rules were examined by 4 of the studies, with the CT result serving as the basis for calculation of sensitivity and specificity of the rule: sensitivity 33% to 100%; specificity 25% to 69%; trade-offs were evidence for each sensitivity or specificity pair.	"In patients sustaining minor head injuries with a history of LOC or amnesia, the proportion who subsequently have a positive CT is not negligible" (7.5% for pt(s) with GCS of 13, 14, or 15; 6.2% for pt(s) with GCS of 15). "Published clinical prediction rules for selecting pt(s) for subsequent CT examination are associated with a trade-off between sensitivity and specificity." Limitations (as per the authors): the studies were heterogeneous; only prospective studies were included, thus narrowing study numbers; only 1 database was searched and only English language articles were included, due to limited resources.	3 2 Search strategy limited and selection process unclear. Heterogeneous population.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Homer CJ and Kleinman L, 1999;[62] Department of Medicine, Children's Hospital, Harvard Medical School, Boston MA PEDIATRICS [American Academy of Pediatrics (AAP) Technical Report], 1999. To evaluate the literature on minor head trauma in children, to enable development of a CPG for the AAP Funder: NR. Possibly the US Agency for Healthcare Research & Quality	MEDLINE and Health databases 1966 to 1993 Additional citations identified by bibliographic review and expert suggestions Unpublished data identified through contact with authors, when study questions could not be addressed through published literature. Process repeated in 1998, seeking articles published between 1993 and 1997.	Inclusion criteria: publication in a peer-reviewed journal; data exclusively for children; assurance that cases in the article were comparable to cases in the CPG; prevalence of IC injury; sensitivity and specificity of imaging modalities including skull x-ray, CT and MRI; utility of early Dx of IC injury; effectiveness of alternative management strategies; and impact of minor head injury on subsequent child health. Exclusion criteria: review articles and expert opinion 1,033 abstracts; 108 articles included. Articles were divided to provide information in 5 areas: risk of IC injury; imaging modalities; utility of early Dx; effectiveness of alternative management strategies; and outcome of mild head trauma. For imaging modalities, 5 studies were included comparing skull x-rays and CT: Rosenthal & Bergman, 1989 (n=358) Royal College of Radiologists (UK), 1983 (n=1,907) Zimmerman, 1978 (n=144) Chan *et al.*, 1990 (n=418) Hahn & McLone, 1993 (n=791)	Prevalence of IC injury in children with mild head injury and GCS of 15, 0% to 7%: without LOC, amnesia, headache or vomiting, risk <1%; with LOC, amnesia, vomiting or seizures, risk 1% to 5%; and 20% to 80% of children with abnormal CTs underwent a neurosurgical procedure, a proportion being IC pressure monitoring only. Specific results related to imaging: 5 studies examined skull x-rays for IC injury, using CT as the gold standard: sensitivity 50% to 100%; specificity 53% to 97%; and 7 studies examined the use of MRI in head trauma (not limited to children); although subtle forms of neural injury can be better detected, in acute settings with children. "MRI offers no advantage in detecting lesions of clinical concern."	"The literature on mild head trauma does not provide a sufficient scientific basis for evidence-based recommendations about most of key issues in clinical management." "Published data indicate: a small proportion of children with mild head injury will have significant IC injury; the presence of LOC or amnesia increases the probability that an injury is present in many, but not all studies; CT is the most sensitive, specific, and clinically safe mode of identifying such injury, versus plain radiographs; extremely rarely children with normal exams and CTs will experience delayed bleeding or edema; and long-term outcomes for children with minimal or mild head injury, in the absence of significant IC hemorrhage are generally very good, with a small increase in risk for subtle specific deficits in particular cognitive skills."	3 2 Review limited to pediatric population; literature sources may be outdated (≤1997). Search strategy and inclusion criteria unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Teasdale G. (chair of Guidelines Development Group composed of 19 members) *et al.*, 2000;[23] Scottish Intercollegiate Guidelines Network (SIGN), 2000. To make recommendations which will inform the initial management of head injuries, focusing on topics of importance to the management of pt(s) through the NHS in Scotland. Funder: NHS Scotland	MEDLINE, EMBASE, Healthstar and the Cochrane Library 1985 to Sept. 1997 Materials supplied by members of the development group. Evidence base updated during the course of guideline development (no details provided) This search was for the entire guidelines project	Inclusion criteria: management, diagnosis and treatment of injuries of the head and neck, from accident through to discharge or transfer from the ER; meta-analyses, systematic reviews, RCTs; and observational studies in areas where more rigorous studies were weak of non-existent. Exclusion criteria: head injured pt(s) requiring intensive care; and maxillofacial injuries. Included studies: NR	• Early imaging reduces delay in assessment and Rx of head injuries and results in better outcomes • A progressive shift from skull x-rays to CT to provide a definitive Dx • Criteria for use of CT in less severe head injuries was the most controversial part of the guidelines development process • Risk factors for a surgically significant IC lesion: the most firmly established are LOC and skull fracture; others are >60 years, MVA or assault; headache and vomiting; focal neuro signs, Hx of alcohol use or use of anticoagulants • CT scanning is appropriate, either as a primary investigation or after skull x-ray, if the likelihood of abnormality is ≥10% (extrapolates to a likelihood of surgery of ≥1% to 2%). This occurs if the pt has a skull fracture or a GCS ≤14. • For pt(s) with GCS 15 out of 15, the risk of IC hemorrhage is <1%; CT scanning is only appropriate if risk is high as indicated by the presence of other features.	Guideline recommendations*: B=Selection of imaging should be based on known risk factors for the presence of a skull fracture or IC lesion. C=CT scanning should be readily available on a 24-hour basis to ERs responsible for assessing head-injured pt(s). B=MDs who interpret and make clinical decisions based on skull films or CT scans should be trained to do so. All imaging should be reviewed by a expert radiologists ASAP. B=Transport or transmission of images should be used to communicate about pt(s) where appropriate management is unclear. Guideline key: A=Requires at least 1 RCT as part of a body of literature of overall good quality and consistency B=Requires the availability of well conducted clinical studies, but no RCTs on the topic C=Requires evidence obtained from expert committee reports or opinions; or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.	1 N/A The brain imaging section of this report was short and details about study selection and interpretation were not included. Search strategy, selection criteria and validity assessment unclear.

AAP=American Academy of Pediatrics; ASAP=as soon as possible; CPG=clinical practice guideline; ER=emergency room; F/T=Fryback & Thornbury (quality score); GCS=Glasgow comma scale; HTA=health technology assessment; Hx=history; IC=intracranial; LOC=level of consciousness; MA=meta-analysis; MVA=motor vehicle accident; NR=not reported; O/G=Oxman & Guyatt (quality score); RCT=randomized controlled trial; Rx=treatment.

Table 10: Seizures and epilepsy – CT and MRI

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Roberts R. (chair of Guidelines Development Group composed of 25 members) *et al.*, 2003;[63] Scottish Intercollegiate Guidelines Network (SIGN), 2003. To provide evidence-based recommendations on the diagnosis and treatment of epilepsy. Funder: NHS Scotland	MEDLINE, EMBASE, Healthstar, Cinahl, PschINFO and the Cochrane Library 1996 to 2001 Internet searches of various web sites Information identified by members of the guidelines group This search was for the entire guidelines project	NR NR	See Conclusions	"MRI is the current standard of reference in the investigation of pt(s) with epilepsy. Routine MRI using simple standard sequences will detect lesions (e.g., small tumours…) that are not detected by CT scanning. MRI carried out for the assessment of drug-resistant epilepsy requires specialized protocols and expertise." "CT scanning has a role in the urgent assessment of seizures, or when MRI is contraindicated. A non-contrast CT will fail to identify some vascular lesions and tumours. CT has only a limited role in the assessment of intractable epilepsy." Recommendation levels*: C=MRI for pt(s) with epilepsy; D=CT for urgent assessment or if MRI is contraindicated.	3 N/A The brain imaging section of this report was short and details about study selection and interpretation were not included.

F/T=Fryback & Thornbury (quality score); O/G=Oxman & Guyatt (quality score).
*Possible range is from A (most rigorous) to D (least rigorous): C=evidence from well-conducted case control or cohort studies with a low risk of confounding or bias, directly applicable to the target population and demonstrating overall consistency of results; and D=evidence from non-analytic studies (e.g., case reports and case series) or expert opinion, or extrapolated from case control or cohort studies.

Table 11: Stroke – CT and MRI

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Keir SL & Wardlaw JM, 2000;[64] Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK Stroke, 2000. Determination of the efficacy, feasibility and reliability of information on MRI diffusion-weighted imaging (DWI) and perfusion imaging (PI) or combinations of the two in pt(s) with stroke. Funder: The UK National Coordinating Centre for HTA, a branch of the NHS R&D development body.	MEDLINE and EMBASE Inception to Oct. 1999 No language restrictions Hand-searching of 6 relevant journals (Stroke, Radiology, American Journal of Neuroradiology, American Journal of Roentgenology, Magnetic Resonance in Medicine and Journal of Magnetic Resonance Imaging): from Nov. 1999 to Jan. 2000. Reference lists of identified articles	Inclusion criterion: published studies in which DWI, PI or both in combination, had been conducted in humans with stroke. Exclusion criteria: case reports and abstracts. Included studies=84: DWI alone (47); DWI and PI (19); PI alone (14); and PI and other modality [e.g., SPECT (4)]. Summary of study details: sample sizes 3 to 224; total n=3,235 Many studies were prospective; studies provided good technical detail; general methodological details of study reports were limited (e.g., about pt selection, radiologist blinding, exclusions and pt tolerability considerations).	DWI alone: 47 studies had 10 purposes. Some findings: more lesions were found with DWI than with conventional MRI or CT; DWI could distinguish new lesions from old; DWI identified appropriate subcortical areas of ischemia; DWI could not distinguish between TIA and stroke Sx. DWI and PI: The DWI and PI combination may not provide additional information versus previously available imaging. PI alone: 13 out of 14 studies concentrated on technical aspects. PI and other modality: of the 4 studies, 3 combined PI with SPECT and 1 with xenon CT; all found PI correlated with perfusion deficits found with the other modalities.	There is insufficient information available to enable firm conclusions about the sensitivity and specificity of these techniques for the identification of either ischemic lesions invisible by other means or salvageable tissue. Limitations (as per the authors): studies were often small; some pt(s) were included in >1 study; should use a comparator technology (e.g., CT); future studies must be larger; carefully select pt(s), assess DWI over and above other imaging modalities; and obtain proper f/u; investigators should be encouraged to combine data in meta-analyses to allow robust assessments; and DWI and PI should be assessed in randomized trials.	4 N/A No listing or details about included studies; no grey literature sought; selection process and validity assessment unclear.

Authors and Affiliation Publication and Date Purpose of Review Research Funders	Literature Sources and Dates	Inclusion and Exclusion Criteria Included Studies	Results	Conclusions Limitations as per SR Authors	Quality Score Efficacy Grade Comments
Wardlaw JM *et al.*, 2004;[21] UK Health Economics Research Unit (Aberdeen) HTA Report 8(1): NHS R&D HTA Programme, 2004 (Chapter 3). For intracerebral stroke, to determine the sensitivity and specificity of CT and MRI in the distinction of infarct from hemorrhage, in the positive Dx of infarct and in the identification of the major factors that may affect the accuracy of the Dx. Funder: Chief Scientist Office of the Scottish Executive Department of Health. Detailed conflict-of-interest declarations contained in Appendix 11 (page 180)	MEDLINE and EMBASE Inception to Dec. 2000 Conference abstracts Reference lists of included studies	Inclusion criteria: reports on the accuracy of CT and/or MRI in the Dx of PICH or cerebral infarction (the WHO definition of stroke was used); prospective and retrospective; and examination of pt(s) by a stroke medical doctor or neurologist (to ensure clear definition of the included population). Exclusion criteria: case reports; descriptive studies concerned with only one specific sign of ischemia; and studies not primarily of stroke pt(s). 1,047 CT studies located; MRI and/or CT 2,098 studies located. The number of studies included: CT and hemorrhage (59), all pre-1998; CT and infarct (31); MRI and hemorrhage (22); and MRI and infarct (18). Details: included studies=130; publication year 1976 to 2000; study "n" range 5 to 1,191; and detail of studies described in text and table in report.	Results were reported for imaging for hemorrhage (10 categories) and infarction (4 categories). It became clear to the authors there was little published information comparing CT with MRI for the Dx of infarct of hemorrhage. They therefore conducted 2 prospective observational studies: a late hemorrhage study to examine MRI following PICH; and (2) CT versus MRI study to investigate the sensitivity of CT and MRI for hemorrhage in pt(s) with mild stroke.	• Rapid access to CT (<8 days) should be considered for pt(s) suspected of having suffered a stroke • In pt(s) with mild stroke, CT and MRI positively identify a similar proportion of recent infarcts	4 2 Reporting this extensive HTA document in an evidence table is very limiting. For more detail on the studies, the original document should be consulted. Heavy cost-effectiveness orientation. Validity assessment unclear.

DWI=diffusion-weighted imaging (MRI); Dx=diagnosis; F/T=Fryback & Thornbury (quality score); GRE=gradient echo MRI; O/G=Oxman & Guyatt (quality score); PI=perfusion imaging (MRI); pt(s)=patient(s); Rx=treatment; SPECT=Single Photon Emission Computed Tomography; Sx=symptoms; TIA=transient ischemic attack.