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Evidence review

CT perfusion imaging in the management of stroke and transient ischaemic attack

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Informing procurement - Encouraging innovation

Contents

Summary

The product

CT perfusion imaging (CTP) of the brain is a diagnostic imaging investigation for assessing cerebral vascularisation. CT perfusion studies can be performed on any modern CT scanner with CT brain perfusion software and a power injector for iodinated contrast administration. A sequence of images is acquired at a selected region of the brain over a period of about 45 seconds following the contrast injection. Colour-coded maps created from the image data highlight areas of impaired blood flow.

Field of use

Although CT perfusion imaging can be performed on any organ, it is currently used mainly for brain perfusion studies, particularly in the assessment of patients with acute ischaemic stroke, but also for the assessment of brain tumour vascularisation.

National guidance

The Darzi report, ‘High quality care for all’ [1], recommends development of specialised stroke centres with access to 24/7 brain imaging and thrombolysis. The Department of Health National Stroke Strategy imaging guide [2] and the NICE Stroke guideline [3] recommend non-enhanced CT (NECT) for suspected stroke and MR imaging for patients suspected of having had a transient ischaemic attack (TIA). The use of CT perfusion imaging in acute stroke is currently deemed to be a local decision.

Evidence reviewed

We reviewed clinical and economic evidence on the use of CT perfusion imaging in the detection of acute stroke and transient ischaemic attack (TIA), published in peer-reviewed journals, concentrating on original studies on human subjects, published in English between 2000 and 2008. Studies were examined on the basis of clinical outcome.

CEP’s verdict – Significant potential

CT perfusion imaging shows significant potential in the assessment of patients with symptoms of acute ischaemic stroke. The scan can be performed immediately following a non-enhanced CT (NECT) scan, thereby minimising delay in treatment. Studies indicate a higher sensitivity than NECT for detection of ischaemia, particularly in the first few hours from onset of symptoms, thereby reducing the need for subsequent referrals to MRI. There is also evidence that CT perfusion imaging can distinguish salvageable brain tissue from infarct and could therefore help in triaging patients for intravenous thrombolytic treatment particularly outside the

recommended time window, or when the time of onset of symptoms is unknown. Contraindications to CT are significantly fewer than those to MR, the main competing technology in this field. CT is also more readily available. Recent developments in CT scanners, enabling perfusion imaging of the entire brain, should increase the potential of this technique.

Evidence is currently lacking on the efficacy of CT perfusion imaging in making treatment decisions related to thrombolytic therapy, so studies are needed to demonstrate that its use improves patient outcomes.

There was a lack of published evidence on the cost-effectiveness of CT perfusion imaging. The economic analysis section of this review presents an economic model which illustrates the potential cost-effectiveness of the technique using quality-adjusted life years (QALYs). An interactive version is available on the CEP web site, allowing users to model outcomes based on their own data.

Stroke is the third most common cause of death, and the greatest single cause of adult disability in England. Every year, approximately 110,000 people in England have a stroke. A further 150,000 suffer suspected TIA or minor stroke, following which there is a 20% risk of a full stroke occurring within four weeks [4].

Stroke can be defined as an acute neurological event which results in a reduction of blood supply, and therefore oxygen, to part of the brain. Neurons in the affected area are killed rapidly, therefore an urgent response to stroke is needed to save lives and reduce long term disability

Broadly speaking, there are two main categories of intracerebral stroke [4]:

- haemorrhagic (or primary intracerebral haemorrhage, PICH), caused by bursting of blood vessels producing bleeding in the brain (~15% of strokes)
- ischaemic, caused by occlusion or stenosis of arteries supplying oxygen to the brain (~85% of strokes).

A TIA is a minor stroke in which symptoms resolve spontaneously within 24 hours. When patients present with acute, mild neurological deficit it is not possible to predict which patients will become TIA cases. This diagnosis can only be made once symptoms have resolved. Patients suspected of having had a TIA also require urgent management in order to prevent a subsequent stroke.

Imaging in acute stroke

Clinical examination is the first line approach in suspected stroke cases, but although it can diagnose stroke with a high degree of sensitivity, it cannot differentiate between haemorrhage and ischaemia. Non-enhanced CT (NECT) is currently the recommended first line diagnostic imaging investigation [4]. It has a high sensitivity for detecting intracranial haemorrhage within 8 days of onset of symptoms [5], and is generally more readily available than magnetic resonance imaging (MRI), particularly in emergency situations [6]. Around 30% of acute stroke patients are unable to tolerate MRI [7], compared with less than 10% of patients in the case of CT [8]. Current evidence indicates that the most effective, and least costly, imaging strategy in suspected acute stroke is immediate NECT of all patients [9].

If ischaemic stroke is diagnosed, a thrombolytic drug, recombinant tissue plasminogen activator (rtPA), may be used. The rtPA drug alteplase, is currently the only approved thrombolytic therapy for acute ischaemic stroke. It has been shown to be effective in suitable patients if administered intravenously within 3 hours of onset of symptoms [10]. Most recently published evidence shows improved clinical outcomes in acute ischaemic stroke patients at up to 4.5 hours [11]. The short time window is one of the reasons why the Department of Health (DH) Stroke Strategy, 2007 [4] highlights rapid access to imaging as a key element in the provision of a gold standard stroke service. DH has also published an associated imaging guide [2] to assist local decision making in this area.

Selection of patients for thrombolytic therapy

The aim of thrombolytic therapy with rtPA is to re-perfuse the affected part of the brain by dispersing the thrombus, the source of occlusion. It is however associated with an increased risk of secondary intracerebral haemorrhage. Some patients are more susceptible to this, and there is also evidence of reduced benefit, and increased morbidity and mortality with delayed administration of rtPA. Apart from exceeding the recommended time window, exclusion criteria for intravenous (IV) rtPA therapy include a tendency to haemorrhage, and middle cerebral artery (MCA) ischaemia extending over more than one third of the MCA territory [12].

Currently less than 1% of acute ischaemic stroke patients receive IV rtPA. The aim is to increase this to at least 4% and a realistic maximum of 10% [4]. The low administration rate is largely because most patients are not diagnosed within the appropriate time interval, due to late arrival in hospital and/or delays in clinical assessment and imaging. This problem has been addressed by the recommendations of the DH Stroke Strategy [4]. Some suitable candidates for thrombolytic therapy may be excluded from treatment because the time of onset of symptoms was not known.

The NICE stroke guideline provides recommendations on the administration of alteplase in the acute stroke setting [3]. As there is increasing evidence that favourable outcomes in acute ischaemic stroke patients can be achieved with rtPA beyond the 3 hour time window [11, 12], there is potential for this therapy to be offered to a greater number of patients. An ideal imaging investigation for the screening process would therefore provide:

- exclusion of primary intracerebral haemorrhage (and stroke mimics) and evidence of ischaemic change
- an accurate measure of the ischaemic area
- an indication of the prognosis (the probability of ischaemia worsening or improving)
- an assessment of major vessel occlusion and the quality of collateral circulation
- evidence of tissue viability (penumbra) in the ischaemic region
- an assessment of risk of haemorrhage following thrombolysis.

Such an investigation might enable improved selection of suitable candidates for thrombolytic therapy.

Product description

Field of use

Although CT perfusion imaging can be performed on any organ, it is currently used mainly for brain perfusion studies, particularly in the assessment of patients with acute ischaemic stroke, but also in the assessment of brain tumour vascularisation. The CT perfusion scan is usually performed following non-enhanced CT (NECT), the recommended first line imaging investigation for stroke. CT angiography (CTA) may be performed in the same session to assess arterial patency.

Dynamic CT perfusion scanning

Dynamic CT perfusion studies of the brain can be performed on any modern CT scanner with a CT brain perfusion software package and a power injector. Currently the software is not included in the national framework agreement for CT scanners available through the NHS Supply Chain [13] and must be purchased as an additional cost item.

To perform a dynamic CT perfusion scan, the patient is injected with an intravenous bolus of iodinated contrast, typically 50 ml (300 mg of iodine per ml) at a rate of 4-5 ml per sec. After a delay of about 5 seconds, a volume of brain is continually monitored in ‘cine mode’ over the first pass of the bolus through the cerebral circulation, a time period of approximately 40 seconds. The scanning is generally performed at a tube kilovoltage of 80 kV, as this provides a higher contrast to noise ratio than at 120 kV, and can result in lower radiation doses [14]. The tube current (mA) used varies, as it depends on scanner model and local preferences.

The extent of tissue monitored in CT perfusion imaging also depends on the CT scanner model. Whilst the coverage offered by 4- and 16-slice scanners is around 20 mm of tissue, current 64-slice systems are capable of up to 40 mm coverage. Some can also employ ‘jog’ techniques, thereby doubling the coverage to 80 mm [15]. Others use a ‘dynamic spiral’ to cover the whole brain with repeated spiral scans in alternating directions [15]. Two recently developed scanners employ even longer detector arrays with 80 mm and 160 mm coverage [15]. Reconstructed slice width is also variable. For example, for a 20 mm coverage, some users choose to reconstruct 4 x 5 mm slices, whereas others select 2 x 10 mm to produce lower noise images.

The images obtained from the ‘cine mode’ acquisition are used to generate time attenuation curves for an arterial region of interest (ROI), a venous ROI, and for the whole image on a pixel by pixel basis. Employing mathematical techniques, a number of perfusion parameters can be obtained from the resulting data [16]. These are:

- CBV - cerebral blood volume (ml/100g): volume of blood per unit volume of tissue (normal range, 4-5 ml/100g)
- CBF - cerebral blood flow (ml/100g/min): volume of blood flow per unit volume of tissue per minute (normal range in grey matter, 50-60 ml/100g/min)
- MTT - mean transit time (sec): the time difference between the arterial inflow and the venous outflow. If deconvolution analysis has been used, this parameter is derived from the central volume principle: MTT = CBV/CBF
- TTP - time to peak (sec): the time from the beginning of the contrast material injection to the maximum concentration of contrast material within a region of interest.

The software produces colour-coded maps of all the perfusion parameters available. The packages from the various CT manufacturers use different mathematical approaches to obtain them. Those using deconvolution methods are able to provide MTT maps. The others provide CBV, CBF and TTP maps.

The assessment of different manufacturers' software, and the variability it might introduce in the CT perfusion parameters obtained on different systems, is outside the scope of this review.

The severity of ischaemia is reflected in the values of the perfusion parameters. Ischaemic tissue suffering from the most severe hypoperfusion rapidly progresses to irreversible damage. This region is represented by the 'ischaemic core' or infarct. The surrounding hypoperfused tissue is termed the 'penumbra'. Tissue within the penumbra is functionally impaired and contributes to clinical deficit, but is still viable and potentially salvageable if reperfused. It is sometimes referred to as 'tissue at risk'. With time, the penumbra decreases as it converts to ischaemic core, hence the need for rapid intervention [17]. The following observations have been made in relation to changes in the perfusion parameters in the core and penumbra [16]:

- Core: severely decreased CBF (< 30% normal) and CBV (< 40% normal) with increased MTT
- Penumbra:
  - either increased MTT with moderately decreased CBF (> 60% normal) and normal or increased CBV (80 -100% normal or higher)
  - or increased MTT with markedly decreased CBF (> 30% normal) and moderately reduced CBV (> 60% normal).

The areas of abnormality on the MTT map therefore reflect the core and penumbra, whereas on the CBV maps only the core is significantly abnormal. It could therefore be possible to use the 'mismatch' between the MTT lesion and the CBV lesion, in a similar way to that obtained from comparison of MR- perfusion weighted imaging (PWI) and diffusion weighted imaging DWI, to identify salvageable tissue [18].

Whole brain CT perfusion imaging

On most CT scanners currently in clinical use, it is not possible to obtain dynamic CT perfusion maps of the whole brain. As a result, some ischaemic volumes may be underestimated, and others missed completely. Other methods sometimes used allow perfused blood volume mapping of the whole brain even on current scanners. They include using CT angiography source images (CTA-SI) [19] or multiphasic CT perfusion imaging[20].

CTA source images are normally used to create 3-D reconstructions of the brain vasculature. CTA can be performed immediately following the NECT scan, to determine the site and extent of any vessel stenosis or occlusion. The images are acquired with a helical scan following administration of an iodinated contrast agent. Quantitative CBV values are obtained by subtracting the non-enhanced CT data from the CTA data. Although this technique has the advantage of imaging the whole brain it cannot be used to evaluate CBF, MTT or TTP, so its potential to distinguish between the core and penumbra is limited.

Multiphasic CT perfusion imaging uses data obtained from a pre-contrast helical scan and four more scans at different times following contrast administration. Two types of perfusion maps can be obtained from these data - a peak perfusion map (PPM), and a total perfusion map (TPM) which might be used to differentiate between core and penumbra.

Hazards of CT perfusion imaging of the brain

Ionising radiation

Any technique using ionising radiation will have a small associated risk of radiation-induced biological effects, and so doses should be kept as low as reasonably practicable (ALARP). The examination must also be justified, *ie* the benefit to the patient must outweigh the risk of the radiation delivered [21]. Effective doses from head scans are generally lower than those from body scans because the head contains fewer radio-sensitive organs. The 2003 UK survey of doses from computed tomography estimated the typical effective doses from NECT head scans for acute stroke were around 1.5 mSv [22]. Effective doses from body scans were generally in the range of 5 to10 mSv. Published effective doses measured in an Alderson-Rando anthropomorphic phantom, with lithium fluoride (LiF) thermoluminescent dosimeter (TLD) chips, for three different protocols for CT perfusion imaging of the head, were 1.2, 1.1 (for protocols using 80 kV) and 5 mSv (for a protocol using 120 kV) [23]. Using the same scan protocols, we obtained effective doses using the *ImPACT CT Patient Dosimetry Calculator* [24], which reports doses to a mathematical anthropomorphic phantom using Monte Carlo simulations. The resulting doses from this method were 3.3, 2.5 (for 80 kV) and 7.9 mSv (for 120 kV); *ie* significantly higher than the published data. Protocols quoted in the literature for CT perfusion imaging of the head generally employ 80 kV, so based on the ImPACT calculator, the effective dose will be approximately 2 to 3 mSv. Bearing in mind the age of the population concerned, and the seriousness of their condition, these doses are unlikely to present any significant risk.

Iodinated contrast agents
Iodinated contrast media are usually safe if administered within recommended levels and if particular 'at risk' groups are excluded [25].The main contraindications are renal disease, diabetes and heart disease. Infants and the elderly are also more at risk, as are people on certain medications. Non ionic media are generally preferred, but the patient's risk must be assessed prior to administration.

National guidance

National guidelines pertaining to brain imaging in acute stroke management make no definitive recommendations for the use of CT perfusion imaging, leaving the decision to local clinical judgement. The guidelines are:

- Department of Health, National Stroke Strategy, 2007 [4]
- Department of Health, Implementing the National Stroke Strategy – an imaging guide, 2008 [2]
- NICE guideline, Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA), July 2008 [3]
- Department of Health. High quality care for all, NHS Next Stage Review [1].

The National Stroke Strategy states that 'High-quality imaging of the brain and blood vessels is a key part of a successful stroke service', and identifies 'timely imaging' available over a 24-hour period as a marker of a quality service [4].

More explicit recommendations on the imaging pathways for acute stroke and TIA are provided in the associated imaging guide [2]. They can be summarised as follows.

- For suspected stroke:
    - non-enhanced CT (NECT) urgently, or within 24 hours, depending on clinically determined symptoms
    - additionally, CT angiography (CTA) with or without CT perfusion imaging should be considered according to local imaging protocol, or MRI used instead if available
    - MRI should be used in cases of atypical or delayed presentation (> 7 days), or continued diagnostic uncertainty after CT.
- For suspected TIA:
    - depending on whether patient has high or lower risk of subsequent stroke, imaging within 24 hours or 7 days

- MRI (including DWI) if there is uncertainty in diagnosis or vascular territory involved
- if MRI contraindicated, CT should be used
- carotid imaging, if TIA is confirmed and patient is fit for carotid intervention.

The recommendations provided in the NICE guideline are in line with those presented in the National Stroke Strategy publications. Additionally, NICE have published two flow charts showing recommended imaging pathways, one for TIA and the other for stroke patients [26,27]. These pathways are also in line with those in the National Stroke Strategy imaging guide.

Another guideline published by the Royal College of Physicians was prepared by the National Collaborating Centre for Chronic Conditions (NCC-CC) on behalf of NICE and is essentially the same document as the NICE publication. [28].

CEP has recently published an evidence review on diffusion-weighted magnetic resonance imaging for the diagnosis of stroke and TIA [29].

Clinical effectiveness

Sources

A literature search was undertaken to identify published articles on the clinical effectiveness of CT perfusion imaging (CTP) and other diagnostic imaging technologies for the detection of stroke or transient ischaemic attack. The following databases were searched for articles covering the time period 2000 – 2008:

- Medline (via PubMed www.pubmed.gov)
- The Cochrane Library (www.cochrane.org)
- The TRIP database (www.tripdatabase.com)
- Centre for Reviews and Dissemination database http://www.york.ac.uk/inst/crd/

Search terms

S1: exp BRAIN ISCHEMIA/ OR exp ISCHEMIC ATTACK, TRANSIENT/ OR exp STROKE/
S2: stroke.ti,ab
S3: TIA OR Transient isch?emi*.ti,ab
S4: brain OR cerebral.ti,ab
S5: isch?emi* OR infarct*.ti,ab
S6: S4 AND S5
S7: 1 OR 2 OR 3 OR 6
S8: (CT OR computed AND tomograph*).ti,ab
S9: perfus*.ti,ab
S10: 8 AND 9
S11: (MR* OR magnetic AND resonance).ti,ab
S12: (DWI OR PWI OR diffusion OR perfusion).ti,ab
S13: 11 AND 12
S14: (Positron AND emission AND tomography OR PET OR PET-CT OR Single AND photon AND emission AND tomography OR SPECT).ti,ab
S15: 10 OR 13 OR 14
S16: 7 AND 15
S17: 16 [Limit to: Publication Year 2000-2008 and Humans and English Language]

Inclusion and exclusion criteria

Only studies on human subjects published in English between 2000 and 2008 were included in this evidence review. Papers on SPECT and PET were subsequently excluded. The papers describing clinical studies were selected according to their relevance to the questions below.

- Can CTP improve diagnosis in ischaemic stoke in comparison with NECT in terms of accuracy as well as extent of lesion?
- Can CTP predict patient outcome?

- Can CTP be used to differentiate between penumbra and infarct in ischaemic lesions?
- Can CTP be used to assess risk of haemorrhage following rtPA therapy?
- Can CTP be used in the management of TIA?

Many of the studies identified involved low patient numbers and variable methodologies. However, they were all included in the review to see if general trends could be identified.

Cost effectiveness

Sources

A literature search was undertaken to identify published articles which either reviewed or described studies relating to the economic impact of using CT perfusion imaging for the detection of stroke or transient ischaemic attack. The following databases were searched for articles covering the time period 1999 – 2008:

- Medline (via PubMed www.pubmed.gov and Web of Knowledge www.isiknowledge.com).
- The Cochrane Library (www.cochrane.org), which includes:
    - The Health Technology Assessment database (HTA)
    - The NHS Economic Evaluation Database (NHSEED)
- The TRIP database (www.tripdatabase.com)
- The Health Economic Evaluation Database (HEED www.heed.wiley.com)
- The Science Citation Index Expanded (via Web of Knowledge)

Search terms

Each of the databases was queried with the following search strings, which were matched against articles titles, abstracts and keywords (where appropriate):

S1: (CT OR “computed tomography”) AND perfusion
S2: ischaemia OR ischemia OR ischaemic OR ischemic OR stroke OR “transient ischaemic” OR “transient ischemic” OR TIA
S3: economic OR economics OR cost OR costs OR “cost-benefit” OR “cost-effectiveness”

Inclusion and exclusion criteria

Articles were included for review only if they matched *all* of the search terms (S1 AND S2 AND S3). Articles not written in English were excluded. The titles and abstracts of all articles matching these criteria were reviewed manually and articles were retained only if they provided either evidence or analysis on the cost-effectiveness or economic outcomes associated with perfusion CT utilised in a stroke or TIA context. So, for example, an article discussing CT perfusion imaging for stroke which simply mentioned the lower cost of CT relative to MRI was not considered sufficient grounds for inclusion.

Clinical effectiveness

Literature search results

A total of 1426 papers were identified from the Medline search. The titles of these were screened for relevance and 394 selected for further appraisal. A second screening was performed on the basis of abstracts, and a third on the basis of the full text. Finally, 31 papers were selected to form the core of this evidence review.

Further papers including subject reviews, guidelines and case reports were referenced for background information.

The search of the Cochrane database identified one relevant publication, which did not provide any findings that could add value to this evidence review.

The search of the Centre for Reviews and Dissemination database identified two relevant publications, one of which provided useful findings [30].

The search of the TRIP database revealed one relevant guideline [31].

Best practice guidelines

The recommendations of UK national guidelines are presented in the *Introduction*. Five further sets of recommendations from national and international panels and professional bodies were identified. The Canadian best practice recommendations for stroke care 2006 [31]. and the European guideline on management of ischaemic stroke and transient ischaemic attack 2008 [32], both state that the first line imaging strategy in stroke should be immediate NECT. The European guidelines also state that although CT perfusion imaging, or MRI and angiography, may be used on selected patients with ischaemic stroke to aid decisions on thrombolytic therapy, there is no clear evidence to recommend routinely making treatment decisions on this basis.

The European Federation of Neurological Societies (EFNS) guideline on neuroimaging in acute stroke recommends that CT perfusion imaging is helpful when MRI is not available or contraindicated, although this is a low level recommendation (class IV, level GCPP) [33].

The American Heart Association guidelines and recommendations for perfusion imaging in cerebral ischaemia published in 2003 make a grade C recommendation that quantitative CT perfusion imaging may be useful in differentiating between core and penumbra, but that appropriate extra studies are required to determine the value of the technique [34]. They also state that there are no data available that show if the potential for haemorrhage can be predicted from this investigation. With regard to qualitative whole brain perfusion information from CTA-based studies, they make a grade C recommendation that it may be of value to determine emergent forms of therapy for acute stroke patients.

Joint guidelines from the American Heart and Stroke Associations 2007, on the early management of adults with ischaemic stroke make a class I recommendation for the use of multimodal CT (NECT, CTP & CTA) and MRI in diagnosis of ischaemic stroke [35].

A report prepared in 2005 for the Agency for Healthcare Research and Quality in Canada [30], considered the evidence for effectiveness of a number of interventions on the evaluation and treatment of acute stroke. Addressing the question '*Do CT perfusion / angiography affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke?*', it was concluded from two rigorously selected studies that, although no evidence was found to support selection of patients for thrombolysis on the basis of CT perfusion imaging / CT angiography, these techniques showed promise and warranted further research.

Limitations of clinical studies

The majority of evidence available was from non-randomised case series studies and must therefore be treated with caution.

Significant variations in approach were apparent between the clinical studies identified, as outlined below.

- Time interval from onset of symptoms to scan varied greatly, from up to 48 hours [36] to within 3 hours [37].
- The severity and type (brain territory involved) of ischaemic stroke was variable and not always reported. Not all studies reported the NIHSS[1] score on admission or vascular territory affected.
- Variation in tissue coverage on CT perfusion scans. Generally coverage was 20 mm, but some studies employed a coverage of up to 48 mm [38].
- Different CT perfusion analysis software was used, including the maximal slope model [39,40], the central volume principle [38,41,42] and the box modulation transfer method [36].
- Different scoring systems were used to assess presence and extent of ischaemia. Some studies used structured methods for scoring, such as ASPECTS[2]; others used more qualitative methods.

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[1] NIHSS= National Institute of Health Stroke Scale (USA)
[2] ASPECTS = Alberta Stroke Program Early CT Score (Canada)

- Follow-up modality, or ‘gold-standard’, against which the accuracy was scored, varied. In general a combination of NECT and MRI was used. The type of MRI sequence used was not always reported.
- The time interval between initial scan and follow-up was variable but, if reported, was generally around 2 to 5 days.
- Tissue type (white or grey matter, or both) varied when defining ischaemic thresholds.
- Expertise of scorers / observers was variable.

The papers identified were divided into the following six categories:

- diagnostic accuracy of CTP relative to NECT
- diagnostic accuracy of whole brain CTP
- CTP threshold values for ischaemia, core and penumbra
- CTP parameters for assessing extent of ischaemia and prognosis
- CTP versus MR-DWI and PWI
- CTP and diagnosis of TIA.

No papers were identified that provided specific evidence for the role of CT perfusion imaging in guiding clinical decision making. A recently published systematic review of perfusion imaging for acute cerebrovascular disease also failed to identify any such evidence [43].

Diagnostic accuracy of dynamic CT perfusion imaging relative to NECT

We identified seven papers comparing the diagnostic accuracy of dynamic CT perfusion imaging with NECT; findings are summarised in table 1. NECT generally has a high specificity for ischaemic stroke, but sensitivity is lower, particularly for mild stroke [40] and when scanning at an early stage after onset of symptoms [37,41].

In comparison with NECT, the specificity of dynamic CT perfusion imaging is equally high, if not higher, and sensitivity appears increased. The range of sensitivity in the studies examined here was found to be 77.6% to 100% if studies with non-territorial infarcts [36] and mild strokes [40] are excluded. The low sensitivity in the case of non-territorial infarcts is likely to be due to the fact that with the scanners used in the studies, complete coverage of the brain could not be achieved for dynamic CT perfusion scans.

Table 1: Detection accuracy for ischaemic stroke with NECT & dynamic CT perfusion imaging (d-CTP)

Study	Sub-group	No. in study	Sensitivity (%)		p-value	Specificity (%)		p-value
			NECT	d-CTP		NECT	d-CTP	
Lin et al, 2008 [37]		28	44	91	<0.0001	100	100	-
Langer et al, 2007 [38]		50	58.3	84.2	0.027	85.7	91.6	NS[1]
Scharf et al, 2006 [39]		67	52	84.5	<0.005	87	78.5	NS[1]
Pepper et al, 2006[2] [41]	Expert raters	15	48	95	<0.001[3]	100	100	<0.001[3]
	All raters		43	94	<0.001[3]	73	100	<0.001[3]
Wintermark et al, 2005 [42]	Observers	46	69.2	77.6[4]	<0.01	65	92.7[4]	<0.01
	Computerised		-	68.2	-	-	92.3	-
Maruya et al, 2005 [36]	Overall	29	-	65.5	-	-	93.3	-
	Large territory	8	-	100[5]	-	-	100	-
	Non-territorial	21	-	47.4[5]	-	-	91.3	-
Kloska et al, 2004 [40]	Overall	41	55.3	76.3 (78.9[6])	-	-	-	-
	Mild stroke	14	18.2	- (77.1[6])	-	-	-	-

Notes: [1] NS = Not significant; [2] CTP source images (CTP-SI) used; [3] Significance between proportion of correct decisions for NECT & CTP-SI; [4] Maximum value from all PCT maps; [5] Statistically significant findings between large territory & non-territorial ischaemia; [6] CTP + CTA

Diagnostic accuracy of whole brain CT perfusion imaging

We identified six papers that considered whole brain perfusion techniques. Three of these used CT angiography source images (CTA-SI) [37,44,45], and another three, whole brain contrast-enhanced multiphase scans [46,47,20].

Sensitivities for detection of ischaemia ranged from 57 - 100% for CTA-SI, compared with 44 – 66.6% for NECT. The 57% value for CTA-SI [37] involved patients scanned within three hours of onset of symptoms. Specificity was 100% for NECT in all three studies. CTA-SI had a specificity of 100% in two studies, and 99.4% in the third.

The whole brain perfusion multiphase studies dealt with cases of severe stroke and looked at the accuracy of assessing extent of ischaemia to predict outcome. In one study, total perfusion maps (TPMs) from multiphase contrast studies where found to be more sensitive than NECT images in predicting large ischaemic lesions (involving more than two-thirds of a hemisphere), 91% versus 73% ($p=0.05$). Overall accuracy for the two techniques was not significantly different [46]. A second study suggested that multiphase CT images were more accurate than NECT in predicting development of severe brain oedema [47]. A third study using multiphase CT perfusion imaging found that peak perfusion maps (PPMs) indicated total ischaemic tissue at risk, whereas TPMs reflected severely hypoperfused tissue that was likely to result in infarct [20]. They could therefore be used in a similar way to MR-PWI and MR-DWI for distinguishing between infarct core and penumbra.

CTP threshold values for ischaemia, core and penumbra

Thrombolytic therapy can only improve outcome if salvageable tissue (penumbra) exists around the infarct core. This section looks at the evidence for using CT perfusion imaging to identify ischaemia and differentiate between infarct core and penumbra.

A recent systematic review analysed results from seven studies using MR-PWI and MR-DWI, or positron emission tomography (PET) to identify the cerebral blood flow (CBF) threshold of ischaemic penumbra and infarct core, but concluded there was currently insufficient evidence for use of these thresholds [48].

We identified six papers, summarised in table 2. There was variability in the parameter identified as being the best identifier of ischaemia and the best discriminator between core and penumbra on CTP maps but accuracy, where reported, was in general, relatively high. Two studies [49,50], both by Murphy et al, found the product of cerebral blood volume (CBV) and CBF to be the best discriminator between penumbra and core. These two studies were in fact on the same cohort, but one set the threshold for ischaemic white matter, whilst the other was for grey.

A large multicentre trial of 130 patients [51] found that the most accurate identifier of ischaemia was a relative MTT > 145%. Within this region, tissue with a CBV < 2 ml/100g, defined the infarct core. The accuracy of these discriminators was 96.2% and 92.7% respectively.

Another study on 42 patients found that relative threshold values, rCBF) or rCBV, could be used to differentiate between core and penumbra. They set the cut off between the two to be an rCBF of 48% and an rCBV of 60% of normal [52]. These findings differed from a very small study which set thresholds for the core to be MTT > 220% and rCBF < 63% [53].

Another large study of 118 patients identified the thresholds for ischaemia in the acute stage to be an rCBF of < 50% and an rCBV < 90% [54].

Evidence review

Table 2: Studies to determine parameters defining ischaemic lesion and/or infarct core and penumbra in ischaemic stroke

Study	No. in study	Aim of descriminator	Threshold values determined	Sensitivity (%)	Specificity (%)	Accuracy (%)
Murphy et al, 2008 [49]	25	To determine best discriminator between core & penumbra in white matter	Best discriminator: CBF. CBV = 8.14	95	94	
Hagiwara et al, 2008 [53]	13	To predict tissue destined to infarct with no treatment	rCBF < 63% normal rMTT > 220% normal	91 88	71 89	
Wintermark et al, 2006 [51]	130	To determine thresholds for core and penumbra	Penumbra: rMTT > 145% Core: CBV < 2ml/100g			96.2 92.7
Murphy et al, 2006 [50]	25	To determine best discriminator between core & penumbra in grey matter	Best discriminator: CBF. CBV = 31.3	97.0	97.2	97.1
Suzuki et al, 2005 [54]	118	To determine the threshold for ischaemia in hyperacute stage	rCBF < 0.5 rCBV < 0.9 MTT most sensitive for detecting ischaemia			
Koenig et al, 2001 [52]	42	To determine thresholds for core and penumbra	rCBF = 0.48 rCBV = 0.6 rTTP not discriminator	76.1 80.4	73.0 86.5	

CT perfusion parameters for assessing extent of ischaemia and prognosis

It has been suggested that one of the contraindications to thrombolytic therapy is ischaemia extending over more than one third of the MCA territory [12]. This section considers the evidence available on the use of CT perfusion imaging in assessing the extent of ischaemia in acute ischaemic stroke, particularly when compared with NECT.

We identified 9 papers in this category [55,56,42,57,58,59,60,61,62].

Three studies scored CT perfusion maps using the ASPECTS scoring system to assess ischaemic extent. A study on patients treated with IV rtPA within 3 hours of onset of symptoms found that an ASPECTS score of greater than 6 on admission CBV maps predicted favourable patient outcome, but did not predict recanalisation [55]. A second study, where only some patients received IV rtPA [56], also found that CBV and CT perfusion source image (CTP-SI) maps scored with ASPECTS were the most reliable predictor of good patient outcome in cases where major reperfusion occurred. In patients with no reperfusion, good outcome was best correlated with CBF and MTT map scores. The third study [42] looked at the accuracy of ASPECTS for assessing ischaemia involving less than 1/3 of the MCA territory, and found that relative CBV maps were most accurate at 87.9%. This compared with an accuracy of 62.8% for NECT images also scored with ASPECTS.

One study [57] was concerned with finding the best CT perfusion parameter for predicting malignant brain infarction (MBI). 10% of MCA patients suffer MBI, and mortality in these patients is 80% unless treated. CBV maps with an area of ischaemic tissue > 27.9% were found to be best predictors of MBI with a positive predictive value (PPV) and negative predictive value (NPV) of 51.8% and 94.7% respectively. This compared with 82% PPV and 92% NPV for MRI.

Four studies considered the type of ischaemic tissue represented by various CT perfusion parameters, i.e. which of them represented infarct core, and which represented salvageable penumbra. Two of the studies [58,59] found that the core was representative of the lesion as seen on CBV maps, whereas the lesion on MTT (or TTP) maps represented the total ischaemic volume. This supported the hypothesis that the difference between the MTT lesion and CBV lesion volumes represents the salvageable penumbra volume. However, another study where scanning was performed on patients within 3 hours of onset of symptoms, found that at this early stage, the CBV lesion does not necessarily represent non-viable tissue and should be considered as potentially salvageable [60]. The authors hypothesised that potentially salvageable tissue can be assessed by CBF or MTT maps alone. The fourth study in this group [61] assessed the ischaemic area by using a 'window narrowing' approach. The window width was adjusted until the normal hemisphere became homogeneous, and the area still visible in the affected hemisphere was defined as 'tissue at maximum risk' (TARM). It is proposed that this represents already infarcted tissue. They found that the TARM correlated slightly better than entire ischaemic area with the final infarct size, and was best assessed by CBF TARM maps.

The final study in this group [62] used a multi-modality approach, MOSAIC[1], by combining the results of NECT, CTA and CTP studies. Although CT perfusion imaging was the best single study in terms of correlation with initial clinical score (NIHSS), as well as infarct size and clinical outcome at 3 months (modified Rankin score), the MOSAIC approach improved on this.

CT perfusion imaging versus MR-DWI and PWI

Four studies (table 3) were considered in this category, aiming to assess how infarct core and penumbra defined on CT perfusion (CTP) maps compared with MRI findings.

The first study [63] suggested that lesions defined on CTP maps could be used to triage patients for rtPA treatment in the same way as in MRI-DWI & PWI. The efficacy of this triaging on patient outcome has not, however, been assessed.

The authors of the second study [8] also concluded that CT perfusion imaging could be used for triaging patients for rtPA therapy. However, how they reach these conclusions is not clear, as lesion volumes on CTP-CBF maps correlated with both PWI and DWI volumes, and these MRI parameters are assumed to define total ischaemic volume and infarct core respectively.

The last two studies concerned patients scanned in the very early stages of stroke (less than 3 hours from onset of symptoms). They considered how MRI lesions on DWI and PWI correlated with infarct core and penumbra as defined on CTP maps. Both studies used predetermined (but different) thresholds to outline total lesion volume and core volume on the CTP maps. In one study [64], the CTP core size correlated best with the DWI abnormality, and the total ischaemic lesion with the PWI-MTT abnormality. In the other study [65] MR-PWI was not employed, but the CTP-CBF lesion was found to have the highest correlation with the MR-DWI lesion. However, the CTP-CBF core lesion correlated more strongly with final infarct volume than DWI lesion in this group of patients, who were not treated with rtPA.

CT perfusion imaging and management of TIA

Patients with acute neurological deficit, whose symptoms spontaneously resolve, need to be investigated for the possibility of having had a TIA. We identified only one

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[1] MOSAIC = Multimodal Stroke Assessment Using Computed Tomography

paper on the use of CT perfusion imaging in the diagnosis of TIA [66]. The small study used CTP to identify the haemodynamic status of 20 patients presenting with TIA symptoms. A prolonged TTP was found in the affected hemisphere compared with the normal side in 13 out of the 20 patients. No significant difference was found in CBF values. 19 out of the 20 patients were found to have arterial occlusions or stenosis on transcranial ultrasound. Therefore in this small study the sensitivity of CT perfusion imaging in detecting TIA could be assumed to be 68.4%

Time taken to perform CT perfusion scans

Thrombolytic drugs, where they are appropriate, must be administered as soon as possible after the onset of ischaemia. It is therefore crucial that the diagnostic regime employed is rapid.

CT perfusion scans can be performed immediately following the NECT scan, and so time is saved in patient transfer and positioning. Times reported in the literature for positioning and scanning the patient in a combined CT protocol of NECT, CTP and CTA are generally 10 minutes or less [39,40,53,63]. Time for data analysis is also generally reported as 10 minutes or less [39,40,53]. One author quotes the total scan and analysis time as less than 15 minutes [8].

For an MRI stroke protocol, scan times of around 25 minutes have been reported [8,63].

Table 3: Comparison of CT perfusion imaging (CTP) with MRI-DWI and PWI

Study	No. in study	Time from onset	Aim	Findings
Wintermark et al, 2007 [63]	42	3 – 9 hrs	To determine if decision to treat would have differed on CTP relative to MR findings. Treatment decision based on: core > 1/3 MCA and penumbra > core by > 20%.	Same decision to treat with rtPA would have been made based on CTP as on MRI (DWI & PWI) in 13 out of 14 patients
Schramm et al, 2004 [8]	22	<6 hrs	To determine diagnostic value of CTP and CTA-SI compared with MRI.	TTP and CBV lesions on CTP were correlated with those on PWI. Lesions on CTA-SI and CTP-CBV were correlated to DWI. CTP-CBV lesion correlated with follow-up CT lesions. Conclusions of this study not clear.
Bisdas et al, 2004 [65]	20	≤3 hrs	To compare CTP and DWI for assessing ischaemia in hyperacute (< 3 hrs from onset) stroke. CTP-CBF thresholds used to delineate total lesion, penumbra and core.	Total ischaemic lesion on CTP-CBF correlated with admission DWI lesion. CTP-CBF core lesion correlated more strongly than DWI lesion with final infarct volume in patients not treated with rtPA.
Wintermark et al, 2002 [64]	13	≤3 hrs	To compare size of ischaemic penumbra and infarct core defined on CTP, with lesion sizes on MR PWI and DWI in hyperacute (< 3 hrs from onset) stroke. CTP-CBF & CBV thresholds used to delineate penumbra and core.	Highest correlation found between CTP core size and DWI abnormality. Highest correlation was found between total ischaemic lesion on CTP and PWI-MTT lesion.

Cost-effectiveness

Literature search results

The initial search yielded 107 abstracts, of which 44 were contained in Medline. Searching the Cochrane Library resulted in 5 clinical trials, no health technology assessments and no results from NHSEED. No results were found within the Health Economic Evaluation Database, and only 4 results were found in the TRIP database. Overall the available published evidence on the economic consequences of CT perfusion imaging of the brain in stroke diagnosis is extremely limited, with only one paper published in 2001 by Gleason *et al* [67] meeting the inclusion criteria.

The study by Gleason *et al* focused on the potential impact on inpatient costs of implementing a combined non-enhanced CT (NECT), CT angiography (CTA) –CTP (whole brain) protocol immediately on arrival at hospital for all patients presenting with ischaemic stroke symptoms. Their work was based on an analysis of the outcomes of different stroke types amongst 189 patients presenting with stroke symptoms at a hospital in the USA. The estimated cost savings were in the region of $1.2 billion assuming that lacunar (most benign) strokes were treated in a non-acute setting, and based on a total annual occurrence of 700,000 strokes in the USA. (This figure would equate to a saving of ~£100 million p.a. based on the incidence of stroke in England.) If all stroke type were assumed to be treated in an acute setting, then the estimated savings rise to $1.8 billion.

The main cost benefit in the Gleason analysis is based on a reduced hospital stay through the earlier diagnosis of patients with more minor stroke by early application of combined NECT, CTA – CTP brain imaging. This benefit is partially offset through the potential costs of complications arising through misdiagnosis, and is thus sensitive to the diagnostic accuracy achieved. The study did not deal with the relative cost benefits of CTA – CTP compared with alternative early imaging strategies using MRI. Nor did the scope of the analysis include the role and cost-effectiveness of using CT perfusion imaging in guiding thrombolytic therapy.

In this section, we present an economic model which calculates the total imaging and thrombolytic therapy costs for four different scenarios of stroke and TIA management, and compares these costs with the gain in quality adjusted life years (QALYs) for patients retaining independence rather than suffering disability or death after a stroke. An interactive version of the model may be downloaded from the CEP web site: http://www.pasa.nhs.uk/PASAWeb/NHSprocurement/CEP/outputs/Imaging.htm.

An economic model for CT perfusion imaging

Although the National Stroke Strategy [4], and also the National Service Framework for older people, recommend that patients who have had a stroke are admitted to a specialist stroke unit, the National Sentinel stroke audit in 2007 [68] reported that only about 10% who have had a stroke are currently admitted directly to an acute stroke unit and only 42% with acute stroke had brain imaging to confirm their diagnosis within 24 hours of the onset of their symptoms. Of the patients who received brain imaging and for whom the time of the scan was reported, only 9% received a scan within 3 hours of stroke onset. This suggests that there is a long way to go to achieve rapid imaging of all stroke and TIA patients. However, in developing the economic model presented here, we have assumed a future scenario in which rapid imaging is available for all patients. Users should note that results might be misleading where this assumption does not hold true.

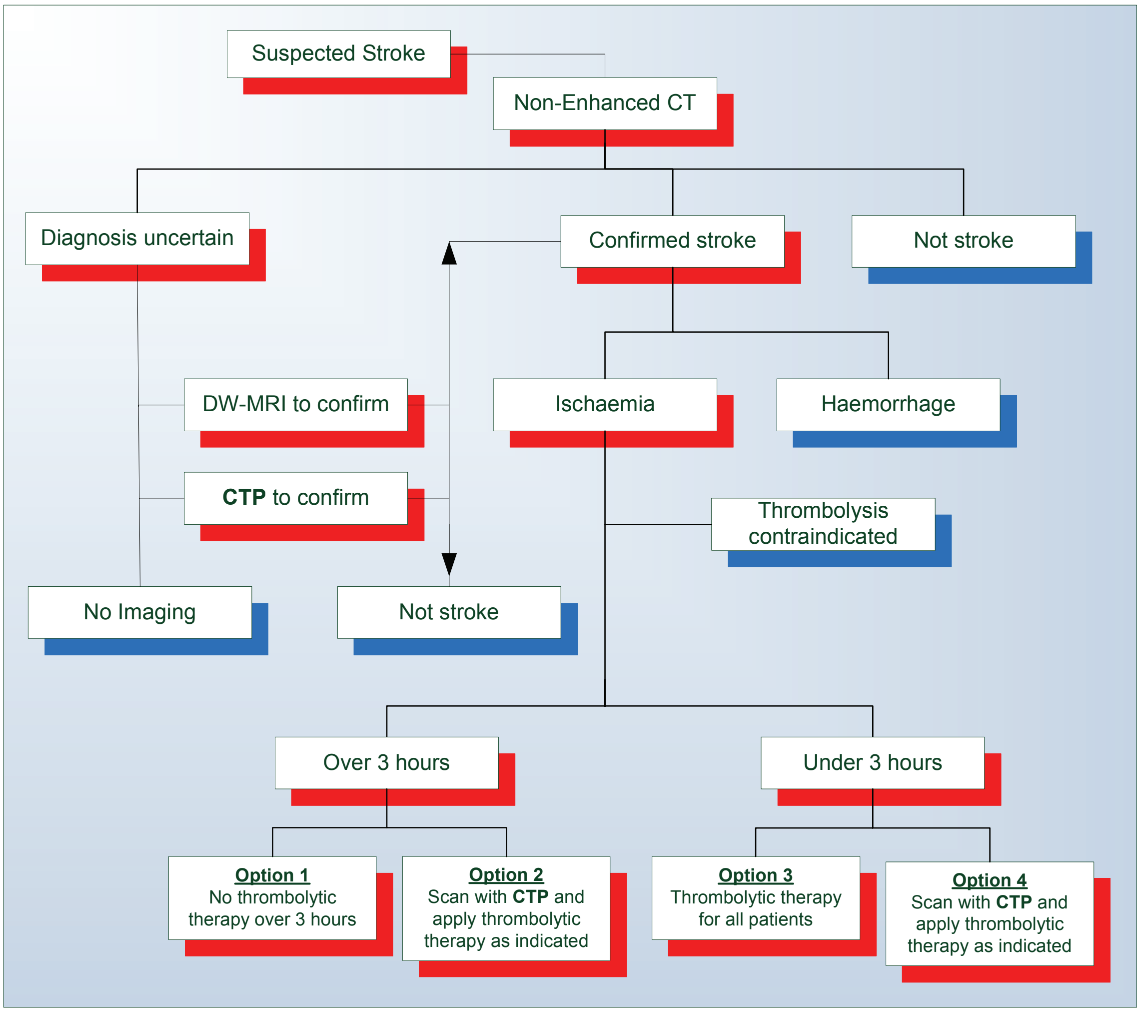
The economic analysis specifically focuses on two issues, and the options presented by each:

- the value of CT perfusion imaging, as compared to MR imaging with diffusion weighted imaging (DWI), following non-enhanced CT (NECT) in cases where diagnosis is not confirmed by NECT
- the value of CT perfusion imaging following NECT in assessing the appropriateness of thrombolytic therapy in cases where ischaemic stroke has been confirmed.

Appendix 1 summarises user-definable inputs to the model, which is based on the pathway illustrated in figure 1 for patients presenting at hospital with a suspected stroke. It is assumed that all patients will undergo initial brain imaging with non-enhanced CT at the earliest opportunity; cases that are diagnosed as non-stroke at this stage are not considered within the analysis. The remaining patients are divided into two branches – those where stroke has been confirmed, and an estimated 20% [69] where the diagnosis is uncertain. The cost of the NECT scan is not included since it is applied in all cases.

For patients with an uncertain diagnosis, three subsequent options are considered. Follow-up diagnostic imaging can be conducted using either CT perfusion imaging or diffusion weighted MRI, or alternatively no further action may be taken. CT perfusion imaging is presumed to occur in the same scanning slot as the initial NECT. Where follow-up imaging results in additional strokes being diagnosed, these cases are then added to the 'confirmed stroke' pathway within the model. Cases where the diagnosis remains uncertain are not considered further as the outcomes will be unknown.

Figure 1: The pathway for stroke management upon which the economic model is based



Of the confirmed stroke cases, approximately 85% will be the result of occlusion or stenosis (ischaemia) [70], while the other 15% will result from haemorrhage, and are therefore not candidates for thrombolytic treatment. Amongst those ischaemic strokes where thrombolysis is not contra-indicated, the pathway includes separate treatment strategies for patients where the time elapsed since onset of stroke symptoms is either less or greater than 3 hours. The different treatment options are summarised at the bottom of figure 1. For patients with time from onset of symptoms of under 3 hours, the case where all patients are given thrombolytic therapy (option

3) is compared with using CT perfusion imaging to direct treatment as necessary (option 4). Similarly, in cases over 3 hours the option of using CT perfusion imaging to direct treatment as necessary (option 2) is compared with the alternative of not using thrombolysis at all (option 1). It should be noted that current NICE guidelines do not recommend the use of thrombolytic therapy beyond the 3 hour window [71].

Discussion and limitations

The total cost of stroke to the United Kingdom economy is estimated at £7 billion per annum [72], with direct costs to the NHS accounting for £2.8 billion and some £4.2 billion arising from the cost of disability and lost productivity in the wider economy.

The model examines the costs of using different stroke CT perfusion imaging strategies in guiding treatment by thrombolytic therapy compared with a hypothetical base case of using no thrombolytic therapy. The main output of the model compares these costs with the overall gain in quality adjusted life years (QALYs) from the use of such strategies. QALY gains are calculated based on three stroke outcomes: Patients returning to independent lives, patients surviving with a disability and patients who die. Minimum QALY gain estimates have been derived from the DH Impact Assessment of the National Stroke Strategy [73].

Economic gains might arise through better outcomes by targeting thrombolytic therapy at those patients most likely to benefit from treatment, and the resulting increase in the numbers of patients who regain independence. Cost savings could be made by a reduction of poor outcomes in cases where inappropriate thrombolytic therapy might otherwise have been applied. In addition it might be possible to achieve further economic benefits by increasing the number of candidates for thrombolytic therapy by using imaging to extend the current 3 hour time window during which therapy can be successfully applied.

As with any model, the outputs are determined by the quality of the inputs and the available evidence to accurately ascertain them. Furthermore, the current model is focused mainly on a specific set of scenarios regarding the provision, or otherwise, of thrombolytic therapy. No account has been made of any associated changes in care costs (i.e. those other than the direct cost of imaging or thrombolysis) accompanying the different treatment scenarios. However, if available, such costs could be incorporated into the model via the imaging and therapy cost inputs.

There are additional potential cost benefits associated with the adoption of rapid CT perfusion imaging that have not been considered here, for example a reduction in the average duration of hospital stay as proposed by Gleason [67]. Such cost benefits might, however, not be associated specifically with the adoption of a CTP-based strategy. Finally a refinement of the model could be achieved through consideration of the details associated with the various stroke sub-types, but such an approach would lead to a significant increase in complexity and is beyond the scope of this document.

Overall the outputs of the current model are sensitive to the clinical outcomes associated with particular treatment and imaging strategies for stroke. Quantitative evidence for many of these parameters is currently unavailable and it is therefore not possible to draw detailed conclusions on the value of CT perfusion imaging in guiding thrombolytic therapy. Conclusions arising from the future use of the model will be driven by the improved availability of these parameters through future clinical studies.

Conclusions

The main findings of this evidence review are summarised below.

- A CT perfusion scan can be performed immediately following NECT, thereby minimising any delays in administration of thrombolytic drugs.

- In comparison with NECT for detecting ischaemic stroke, CT perfusion imaging appears to have an increased sensitivity and a comparable, if not slightly higher, specificity. Its increased sensitivity is particularly apparent in mild strokes and in cases examined within 3 hours of onset of symptoms. Sensitivity of CT perfusion imaging is however poor for non-territorial infarcts, due to its current restricted coverage. Developments in CT technology in terms of increased coverage should overcome this problem.

- There is evidence to show that CT perfusion parameters can be used to differentiate between ischaemic core and penumbra. This gives potential for CT perfusion imaging to be used in selecting candidates who are likely to benefit from thrombolytic therapy. This is particularly the case for patients beyond the recommended time window, or if time of onset of symptoms is unknown, where currently NICE do not recommend IV rtPA.

- CT perfusion maps appear to be more accurate than NECT at assessing the extent of ischaemia on the admission scan and predicting patient outcome. This again can help in selecting patients for thrombolysis.

- A multimodal CT approach using NECT, CTP and CTA might provide greatest prognostic accuracy.

- Source images obtained from CT angiography scans (CTA-SI) appear to have improved sensitivity for detection of ischaemia compared with NECT. They have the advantage of imaging the whole brain and are automatically available if a CTA scan has been performed. They cannot however differentiate between the core and penumbra in ischaemic regions.

- Whole brain perfusion using multiphasic CT appears to show slightly improved sensitivity over NECT for assessing large ischaemic lesions. An approach differentiating between core and penumbra has also been explored with this method. However, with the increased availability of scanners with a greater coverage, this approach does not appear to have future potential.

- Decisions to treat with thrombolytic therapy on the basis of CT perfusion findings agree with those made with MRI. Moreover, CT has major practical advantages in that it is more readily available and fewer patients have contraindications to it. It is quicker to perform, particularly if the patient has already had an NECT scan. However, most scanners do not currently cover the entire brain for dynamic CT perfusion scans, and the hazards of ionising radiation and iodinated contrast media must also be considered.

- Evidence is currently lacking on the efficacy of CT perfusion imaging in making treatment decisions related to thrombolytic therapy. Studies are needed to demonstrate that the use of CT perfusion imaging improves patient outcomes.

- Insufficient evidence was identified to assess the use of CT perfusion imaging in patients who are suspected of having had a TIA.

- The availability of published economic evidence in this area is extremely limited and only one paper of direct significance was found.

- The economic model is available to download from the CEP website. The model considers the costs, based on user supplied inputs, of using different imaging strategies to confirm the diagnosis of stroke and to guide thrombolytic treatment. Outputs are presented in terms of the imaging and treatment costs and in the gain in quality adjusted life years for different scenarios once the appropriate variables have been entered. Users should note that the model assumes that rapid access to brain imaging is available for all patients.

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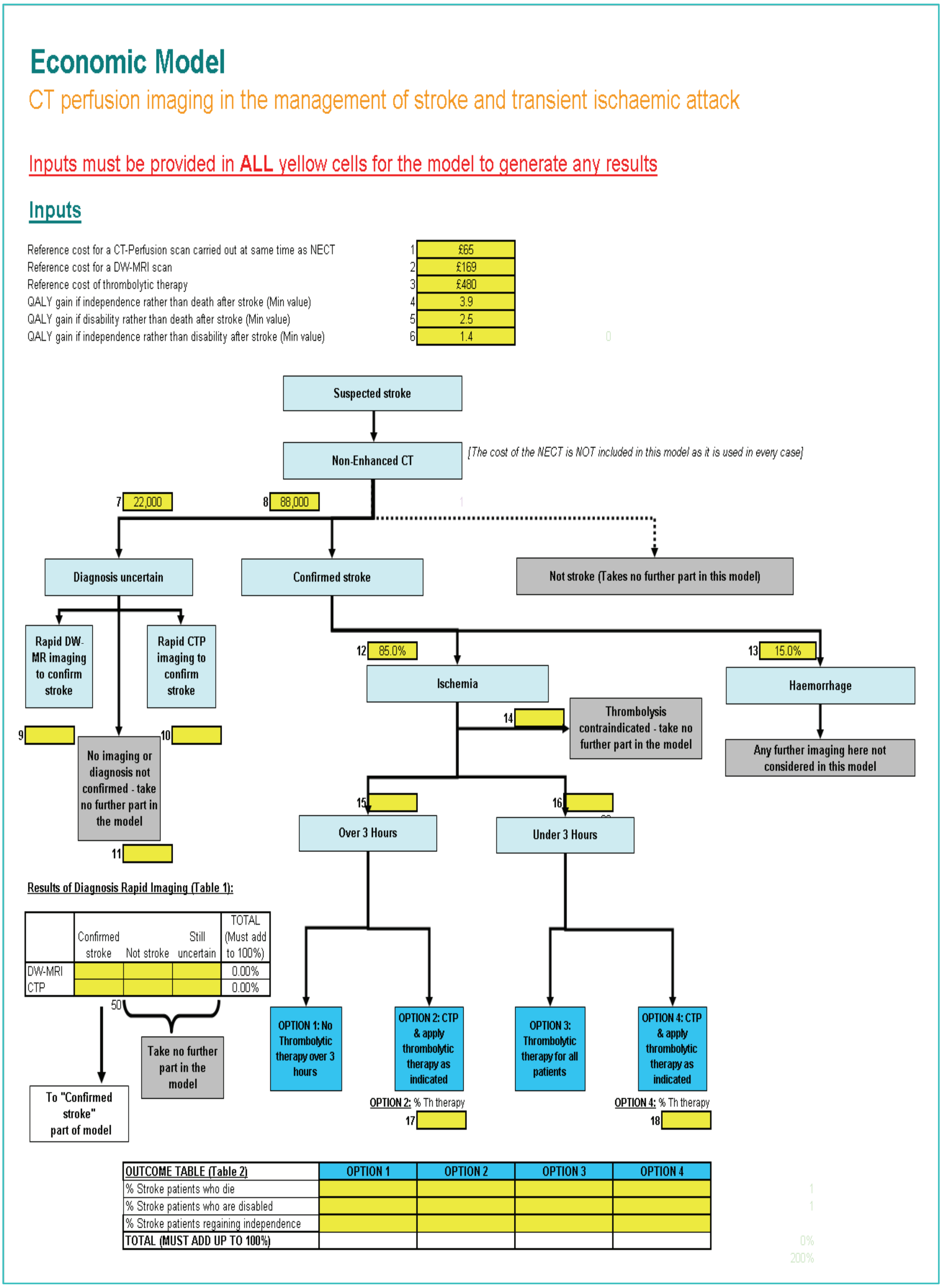
CTP economic model interface



Economic Model

CT perfusion imaging in the management of stroke and transient ischaemic attack

Inputs must be provided in **ALL** yellow cells for the model to generate any results

Inputs

Reference cost for a CT-Perfusion scan carried out at same time as NECT	1	£65
Reference cost for a DW-MRI scan	2	£169
Reference cost of thrombolytic therapy	3	£480
QALY gain if independence rather than death after stroke (Min value)	4	3.9
QALY gain if disability rather than death after stroke (Min value)	5	2.5
QALY gain if independence rather than disability after stroke (Min value)	6	1.4

Results of Diagnosis Rapid Imaging (Table 1):

	Confirmed stroke	Not stroke	Still uncertain	TOTAL (Must add to 100%)
DW-MRI				0.00%
CTP				0.00%

OUTCOME TABLE (Table 2)	OPTION 1	OPTION 2	OPTION 3	OPTION 4
% Stroke patients who die				
% Stroke patients who are disabled				
% Stroke patients regaining independence				
TOTAL (MUST ADD UP TO 100%)				

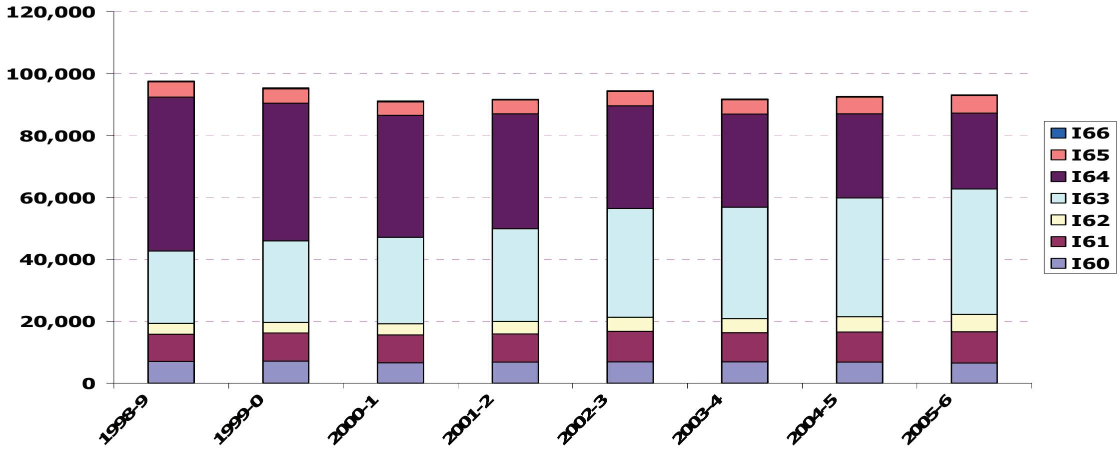
CTP economic model inputs

- **Box 1** – Reference cost for a CTP scan carried out at the same time as NECT. The default value for this is £65, which is 50% of the DH Radiology Indicative tariff for a CT scan [74]. This is a sensible value because where the CTP scan is carried out directly after the NECT scan, the overall cost of the scan to the provider will be less as there will be no cost for time to bring the patient in and out of the scanner room.
- **Box 2** – Reference cost for a DW-MRI scan. The default value for this is £169, which is equivalent to the DH radiology indicative tariff for an MRI scan [74].
- **Box 3** – Reference cost for thrombolytic therapy. The default value for this is £480, which is taken from the NICE - Alteplase costing template [71].
- **Boxes 4 to 6** – Quality Adjusted Life Year (QALY) gains for outcomes other than death for stroke patients. The default values for boxes 4 to 6 are 3.9, 2.5 and 1.4 respectively which are the minimum values taken or inferred from the DH Impact Assessment of the National Stroke Strategy [73]
- **Boxes 7 and 8** – Input populations for suspected stroke patients after an initial NECT scan who have either an uncertain diagnosis or a confirmed stroke respectively. The NICE stroke guidelines costing report [70] quotes national audit office figures that there are a total of 110,000 strokes each year in England of which it is estimated that 20% do not have confirmed diagnosis after an initial NECT scan. Alternative (but similar) figures can be obtained by analysis of the Hospital Episode Statistics (HES) primary diagnosis figures – the results of such an analysis can be found in Appendix 2. *Input populations must be provided before the model will generate any results.*
- **Boxes 9 to 11 and Table 1** – Proportion of stroke patients with uncertain diagnosis that under go either rapid DW-MRI or CTP imaging or the outcomes of this rapid imaging in terms of diagnosis of stroke. *Default values are not provided for these inputs, and must be entered before the model will generate any results. Boxes 9 to 11 must add up to 100%*
- **Boxes 12 and 13** – Proportion of confirmed strokes that are ischaemic or haemorrhagic). Default values are 85% and 15% respectively as confirmed in the NICE stroke guidelines costing report [70]. *Boxes 12 and 13 must add up to 100%*
- **Boxes 14 to 16** – Proportion of ischaemic strokes following different imaging and treatment strategies. *Boxes 14 to 16 must add up to 100%*
- **Boxes 17 and 18** – The proportion of patients who receive thrombolytic therapy after CTP imaging. *Default values are not provided for these inputs, but should be in the range of 0 to 100%. If values are not entered, the model will assume no patients receive thrombolytic therapy.*
- **Outcome Table (Table 2)** – The proportion of stroke patients who take this pathway who die, are disabled or regain independence. *Default values are not provided for these inputs, but each column of the table must add up to 100% before the model will generate any results*.

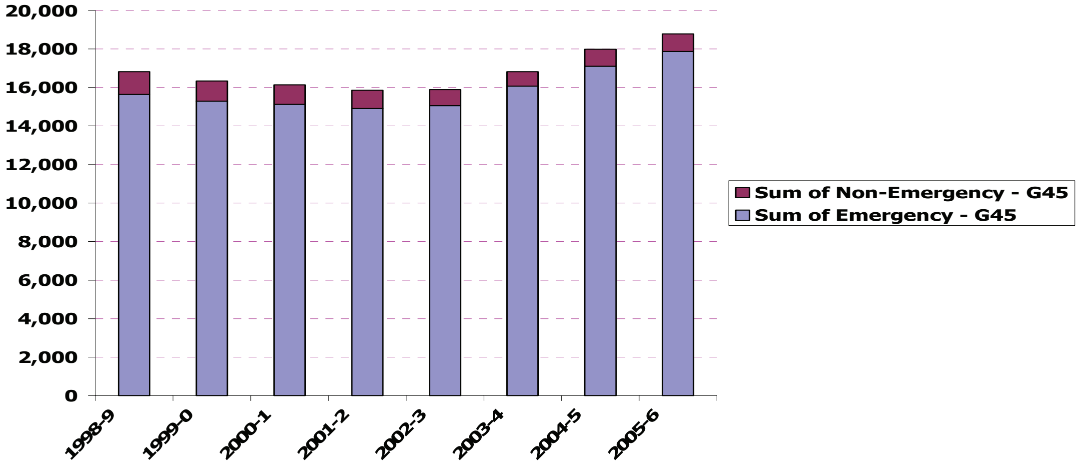
English hospital episode statistics for stroke and TIA

I60-I66 Stroke trend of admissions over last 8 years

I60 Subarachnoid haemorrhage
I61 Intracerebral haemorrhage
I62 Other nontraumatic intracranial haemorrhage
I63 Cerebral infarction
I64 Stroke not specified as haemorrhage or infarction
I65 Occlusion and stenosis precerebral arteries, not resulting in cerebral infarction
I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction



G45 Transient cerebral ischaemic attacks and related syndromes Trend of admissions over last 8 years – emergency / non-emergency split



Evidence review: CT perfusion imaging in the management of stroke and transient ischaemic attack

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We are here to help you make informed purchasing decisions by gathering evidence globally to support the use of innovative technologies, assess value and cost effectiveness of products, and develop nationally agreed protocols.

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