

A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD

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Executive summary

New-generation CT scanners for coronary artery disease and congenital heart disease

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Executive summary

Background

Medical imaging, including computed tomography (CT), is important in diagnosing and managing many conditions. However, some potential disadvantages are associated with imaging [e.g. CT requires exposure to potentially harmful radiation, and invasive coronary angiography (ICA) is associated with increased risk of stroke, heart attack and death]. Imaging technologies have developed rapidly and new-generation computed tomography (NGCCT) scanners may offer advantages over CT and other imaging methods currently used (e.g. shorter imaging times, reduced radiation, increased accuracy). The development of NGCCT has focused on assessment of patients with coronary artery disease (CAD) and congenital heart disease. Current CT scanners can very accurately diagnose CAD requiring revascularisation in most patients. However, NGCCT may benefit patients who are difficult to image (e.g. obese patients, patients with high or irregular heart rates, and patients who have high levels of coronary calcium or a previous stent or bypass graft). Similarly, although patients with congenital heart disease can be diagnosed using existing technologies, NGCCT may provide additional information to help plan surgery in patients who have complex abnormalities.

Objectives

To assess the clinical effectiveness and cost-effectiveness of NGCCT, using Discovery CT750 HD (GE Healthcare), Brilliance iCT (Philips Healthcare), Somatom Definition Flash (Siemens Healthcare) or Aquilion ONE (Toshiba Medical Systems) for:

- diagnosis of clinically significant CAD in patients who are difficult to image using (64-slice) CT
- treatment planning in complex congenital heart disease.

Methods

A systematic review was conducted to assess the clinical effectiveness of NGCCT to diagnose clinically significant CAD in difficult-to-image patients [obese patients, patients with high heart rates (HHRs), arrhythmias, intolerance to beta-blockers, previous stent implantation(s) or bypass graft(s)], and for treatment planning in patients with complex congenital heart disease. Search strategies were based on target condition and intervention, as recommended in published guidance [Centre for Reviews and Dissemination (CRD). *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: University of York; 2009. URL: www.york.ac.uk/inst/crd/systematic_reviews_book.htm (accessed 12 January 2010); Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews*: Cochrane Collaboration, 2011. URL: <http://srdta.cochrane.org/handbook-dta-reviews> (accessed 12 January 2011); Whiting P, Westwood M, Beynon R, Burke M, Sterne JA, Glanville J. Inclusion of methodological filters in searches for diagnostic test accuracy studies misses relevant studies. *J Clin Epidemiol* 2011;**64**:602–7]. Eight bibliographic databases were searched (2000 to February/March 2011). Research registers and conference proceedings were also searched. Systematic review methods followed published guidance [Centre for Reviews and Dissemination (CRD). *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: University of York; 2009. URL: www.york.ac.uk/inst/crd/systematic_reviews_book.htm (accessed 12 January 2010); National Institute for Health and Clinical Excellence (NICE). *Diagnostics Assessment Programme: interim methods statement (version 2)*. London: NICE; 2010. URL: www.nice.org.uk/media/164/3C/DAPInterimMethodsStatementProgramme.pdf (accessed 12 January 2011)]. The risk of bias in included studies was assessed using the QUADAS-2. Results were summarised in tables and

text, stratified by patient group. Where four or more data sets were available, summary receiver operating characteristic (SROC) curves and summary estimates of sensitivity and specificity, with 95% confidence intervals (CIs) were calculated using a bivariate model (Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;**58**:982–90; Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. Unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2006;**1**:1–21). Where a bivariate model could not be fitted, pooled estimates of sensitivity and specificity, with 95% CIs, were estimated using a random-effects model. Between-study heterogeneity was assessed using the chi-squared test and inconsistency was quantified using the I^2 -statistic (Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58).

The health economic analysis assessed the cost-effectiveness of NGCCT in two populations (NGCCT vs ICA in difficult-to-image patients with CAD, and NGCCT vs 64-slice CT in patients with congenital heart disease).

For the CAD population, five models were combined:

1. decision tree modelling the diagnostic pathway [Walker S. Email regarding CE-MARC model (Walker S, University of York, March 2011, personal communication)]
2. alive–dead Markov model for ‘healthy’ patients without CAD [Office of Population Censuses and Surveys, Government Statistical Service, Office for National Statistics. *Mortality statistics (Cause). Review of the Registrar General on deaths by cause, sex, and age, in England and Wales. Series DH2.* London: HMSO; 2006]
3. stroke model estimating the impact of test- and treatment-related stroke
4. model for prognosis of patients with CAD [the EUROpean trial On reduction of cardiovascular events with Perindopril in stable coronary Artery disease (EUROPA) model] (Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M, *et al.* Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. *Heart* 2007;**93**:1081–6)
5. model assessing the impact of imaging radiation on cancer morbidity and mortality (McKenna C, Wade R, Faria R, Yang H, Stirk L, Gummerson N, *et al.* *EOS 2D/3D X-ray Imaging System: a Diagnostics Assessment Report.* York: Centre for Reviews and Dissemination/Centre for Health Economics, University of York; 2011. URL: <http://guidance.nice.org.uk/DT/1/AssessmentReport/pdf/English>).

Model 5, the York Radiation Model (YRM), was also used to assess the cost-effectiveness of using NGCCT to lower imaging-associated radiation in patients with congenital heart disease.

The difficult-to-image CAD population was divided into two subgroups (suspected and known CAD). NGCCT has different purposes in these two populations (to diagnose CAD and to determine if revascularisation is necessary).

Three imaging strategies were evaluated: ICA only, ICA following a positive NGCCT (NGCCT–ICA) and NGCCT only. ICA was assumed to have 100% sensitivity and specificity; however, ICA has a risk of serious complications, including stroke, non-fatal myocardial infarction (MI) and death.

The diagnostic decision tree identifies patients as true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN), depending on performance of the test or test strategy and prior likelihood of test outcome. Estimates of sensitivity and specificity of NGCCT varied between difficult-to-image patient groups, but were assumed to be equal for the suspected and known CAD populations within these groups.

Two versions of the diagnostic model were created because the known (treatment options coronary artery bypass graft and percutaneous coronary intervention) and suspected CAD (treatment options as for known

CAD or drug treatment) populations are treated differently after a positive test. Patients without the disease (TN and FP from the suspected CAD population) were modelled with a simple alive–dead Markov model based on UK life tables. The costs and health expectancy of patients who experienced a stroke due to initial ICA or revascularisation were modelled using a simple alive–dead stroke model. Life expectancy was based on updated UK life tables, combined with a multiplier for age-specific mortality among stroke patients. Patients with CAD, who have not experienced a stroke due to initial ICA or revascularisation, enter the EUROPA model. This model predicts the probability of cardiovascular events [cardiac arrest, (non-)fatal MI], mortality, decrease in quality of life, and costs associated with these events. The impact of radiation reduction on lifetime cancer risk and subsequent life expectancy, health-related quality of life (HRQoL) and costs was assessed using the YRM. Each CAD population, while going through the various models, accumulates costs and quality-adjusted life-years (QALYs). The impact of uncertainty about the various input parameters on the outcomes was explored through sensitivity analyses.

The YRM was used to compare the costs and QALYs of NGCCT and 64-slice CT in the congenital heart disease population. In this model, only the effect of reduced radiation was assessed; other potential benefits of NGCCT in costs or QALYs were not explored, owing to lack of data.

Results

Twenty-four studies, reporting data on the accuracy of NGCCT for the diagnosis of clinically significant CAD in difficult-to-image patients, were included in the systematic review. No study reported data on changes to patient management or outcomes, test-related adverse events or patient preferences. No clinical effectiveness studies of NGCCT in patients with congenital heart disease were identified.

Most included studies were judged at low risk of bias with respect to the reference standard domain of QUADAS-2; the inclusion criteria of the review specified a single reference standard (ICA). Risk of bias with respect to patient selection was frequently unclear because of uncertainty regarding the potential impact of inappropriate exclusions; difficult-to-image patient groups (e.g. obese patients) were often reported with prior exclusion of patients with one or more additional criteria which may contribute further to difficulty in imaging and the proportions of participants excluded in this way were frequently unclear. Inclusion of multiple measurements per patient (per-arterial segment, per-artery or per-stent data) was also common. Where studies excluded non-diagnostic arterial segments from analyses, the potential impact of this was frequently unclear because their distribution between patients was not reported.

Where per-patient estimates of test accuracy were possible, these were generally high. The pooled estimates of sensitivity were 97.7% (95% CI 88.1% to 99.9%), 97.7% (95% CI 93.2% to 99.3%) and 96.0% (95% CI 88.8% to 99.2%), for patients with arrhythmias, HHRs and previous stent implantation(s), respectively. The corresponding estimates of specificity were 81.7% (95% CI 71.6% to 89.4%), 86.3% (95% CI 80.2% to 90.7%) and 81.6% (95% CI 74.7% to 87.3%), respectively. The high per-patient estimates of sensitivity (> 95%) indicate that NGCCT could be used to reliably rule out significant stenosis, potentially avoiding some invasive investigations (ICA) in these patient groups. Although there were no data for beta-blocker-intolerant patients, it should be noted that no study reporting per-patient data for patients with HHRs used additional beta-blockers before scanning. It may therefore be inferred that NGCCT could be used to image patients who are intolerant to beta-blockers who could not otherwise be reliably imaged by 64-slice CT. With the exception of one small study, data on the accuracy of NGCCT in patients with high coronary calcium scores, previous bypass grafts, or obesity were limited to per-arterial segment or per-artery data. Sensitivity estimates remained high (> 90% in all but one study).

A further important consideration, when assessing the practical utility of a new diagnostic technology, is the proportion of patients in whom the results of testing are likely to be non-diagnostic. Few studies reported numbers of non-diagnostic images; where these data were reported, they were often for the

whole study population, rather than the difficult-to-image subgroup. Three studies did report subgroup-specific non-diagnostic image rates; these were 5% for patients with arrhythmias, 6.8% for patients with HHRs and 9% for patients with previous stent implantation. These results indicate that the proportions of otherwise difficult-to-image patients in whom imaging would remain non-diagnostic, even with NGCCT, are likely to be low; further studies are needed to confirm this.

The health economic analysis showed that the use of NGCCT in difficult-to-image CAD patients may be considered cost-effective. In patients with suspected CAD, the NGCCT-only strategy might be considered the most attractive; although NGCCT-ICA is slightly more effective, the additional costs are such that the resulting incremental cost-effectiveness ratio (ICER), £71,000, is so high that it is unlikely (given the conventional willingness-to-pay threshold range of £20,000–30,000) that commissioners of health care would consider this a cost-effective use of NHS resources. Likewise, ICA only is slightly more effective than NGCCT-ICA, but again the additional costs are high enough (ICER £83,000) that it is unlikely to be considered cost-effective. In patients with known CAD, the most attractive strategy would be NGCCT-ICA; this scenario yields the highest cost saving and dominates ICA only. The ICER of NGCCT only compared with NGCCT-ICA is so high (£726,230) that it is unlikely to be considered cost-effective. When taking uncertainty into account, these findings were confirmed. In the suspected population, in the range of thresholds of < £70,000, the NGCCT-only strategy has the highest probability of being cost-effective. For thresholds of > £70,000, the three different strategies are similar. For the known CAD patients, the NGCCT-ICA strategy has the highest probability of being cost-effective, over the whole range of thresholds, whereas the ICA-only strategy always has the smallest probability of being cost-effective.

The key drivers behind these results are percentage of patients misclassified (a function of both diagnostic accuracy and prior likelihood) and complication rates for ICA and revascularisation. Overall, in the population with suspected CAD, the NGCCT-only strategy has the lowest overall procedure-induced mortality rate, less than half that of ICA only. To some extent, the same results apply for the known CAD population; here the overall procedure-induced mortality and morbidity is lowest in the NGCCT-ICA strategy. ICA only has the highest overall procedure-induced mortality and morbidity rate. There is currently uncertainty about the estimate of cost for an NGCCT scan. Therefore, a scenario analysis was performed; increasing cost from £150 to £207 per scan did not alter our findings. Including the effects of reduced radiation had minimal impact on outcomes.

Analysis showed that, when only considering radiation exposure, the use of NGCCT instead of 64-slice CT is unlikely to be considered cost-effective in patients with congenital heart disease. The ICER ranged from £521,000 per QALY gained for the youngest patients to £90,000 per QALY gained for adults. The reduction in radiation by replacing a single 64-slice CT scan with NGCCT is small, and leads to only a minor decrease in radiation-related cancer incidence. Therefore, it cannot justify the additional costs of the NGCCT scan. Various scenarios were explored to assess the impact of the main assumptions. Only in the most unlikely scenario, i.e. an average radiation dose of 25 millisieverts for a 64-slice CT, do the ICERs decrease significantly.

Conclusions

The results of our systematic review suggest that NGCCT may be sufficiently accurate to diagnose anatomically significant CAD in some, or all, difficult-to-image patient groups. These technologies may be particularly useful in ruling out patients from further invasive investigations. However, data were sparse, particularly for obese patients, patients with high coronary calcium and those with previous bypass grafts.

The limited available data indicate that the proportions of difficult-to-image patients, in whom imaging would remain 'non-diagnostic', even using NGCCT, are likely to be low; further studies are needed to confirm this.

The results of the economic evaluation suggest that NGCCT is likely to be considered cost-effective for difficult-to-image patients with CAD, at current levels of willingness to pay in the NHS. Although ICA can diagnose these patients, this comes at the cost of procedure-induced mortality and morbidity. Overall, taking uncertainty into account, we may conclude that strategies including NGCCT are cost saving while yielding approximately the same amount of QALYs. For the population of patients with suspected CAD the scenario with only NGCCT would be most favourable, whereas for the known CAD patients the combination of NGCCT with ICA would be most favourable.

Suggested research priorities

Test accuracy cannot provide information on the contribution of NGCCT to therapeutic decision-making, or subsequent impact on patient outcomes. The ideal study to address these questions would be a large multicentre RCT. However, one possible alternative might be to establish a multicentre tracker study. Such a study should enable the collection of data comparing numbers of misdiagnoses, clinical outcomes, and HRQoL resulting from alternative imaging strategies.

High-quality test accuracy studies – particularly in obese patients, patients with high coronary calcium and those with previous bypass grafts – are needed to confirm the findings of our systematic review. Studies should include and fully report details of patients with more than one difficult-to-image criterion, so that the potential cumulative impact on accuracy of multiple criteria can be assessed. Studies should also report the numbers of patients in whom imaging is non-diagnostic.

If NGCCT is introduced on the basis of evidence in patients with CAD and is opportunistically used in patients with congenital heart disease, before-and-after population survey studies could be considered to investigate the impact of this change upon treatment decisions and/or outcomes. Such studies might also inform the cost-effectiveness of NGCCT in this population.

The data on which the estimated likelihood of CAD are currently based date from 1979, in a US population, and may not be applicable to contemporary UK populations. The establishment of a national registry of people undergoing initial assessment for stable angina, as recommended in the National Institute for Health and Clinical Excellence clinical guideline *Chest pain of recent onset* [National Institute for Health and Clinical Excellence. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Clinical Guidelines 95*. London: NICE, 2010 URL: <http://guidance.nice.org.uk/CG95> (accessed 20 April 2011)] could provide data to increase robustness of the health economic findings.

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