**INTRODUCTION**

In recent years imaging technologies have been developed rapidly leading to the introduction of new generation coronary computed tomography (NGCCT) scanners. The latest generation of dual-source instruments may have a significant benefit over the current technologies, especially for difficult-to-image patients through improvements in image quality, and reductions in the scan duration and radiation exposure.

Currently, for patients suspected of coronary artery disease (CAD) the diagnosis is usually based on tests such as an invasive coronary angiography (ICA), functional imaging, computed tomography (CT) coronary angiography (CTCA), or a computed tomography calcium scoring. The appropriate diagnostic test depends on the likelihood of having CAD as described in the NICE clinical guideline [1]. If the likelihood of CAD is between 10-90% then a patient will undergo further examination, i.e. 64-slice CT for the patients with a likelihood between 10-29%. In addition, these diagnostic tests can also be used to decide if a revascularization is necessary. The performance of 64-slice CT for diagnosing CAD has been well established. Recent systematic reviews have estimated that 64-slice CT, for the detection of ≥50% coronary artery stenosis, is very accurate [2-4]. However, 64-slice CT cannot be (routinely) used for specific groups of patients who are difficult to image due to decreased image quality [5]. These include patients with: i) arrhythmias, ii) heart rate >65 beats per minute, iii) obesity, iv) coronary calcium level >400, v) a previous coronary revascularisation with a stent, vi) β-blocker intolerance or vii) a previous coronary artery bypass graft (CABG). In these difficult-to-image patients, ICA a more invasive diagnostic procedure may therefore be indicated. Newer generation CT instruments may provide an alternative to an ICA for these patients, which has a lower procedure-related mortality and morbidity. One potential disadvantage may be a slightly lower sensitivity and specificity compared to ICA, which means a greater frequency of false positive (FP) and false negative (FN) results that may lead to incorrect treatment decisions, health loss and increased costs. We performed a cost-effectiveness study of the NGCCT compared with ICA for difficult-to-image patients for England and Wales.

**METHODS**

The lifetime cost-effectiveness of NGCCT for difficult-to-image patient groups was estimated for two separate populations: patients with suspected CAD and patients with known CAD. The suspected CAD population includes patients with chest pain or other symptoms suggestive of CAD. Patients with known CAD were defined as patients with a diagnosis of CAD whose symptoms are no longer controlled with drug treatment and/or are being considered for revascularization. The characteristics (e.g. age, systolic blood pressure) of the difficult-to-image subgroups are based on the studies that are included in a systematic review [6]. The NGCCT has a different purpose in each population. For the suspected population the purpose of NGCCT is to diagnose CAD and if so a patient is treated with a revascularization or medication. For the known population the purpose of NGCCT is to decide if a revascularization is necessary.

**Strategies**

Three strategies were examined: i) a strategy where patients only undergo an ICA (ICA–only strategy), ii) a strategy where patients only undergo the NGCCT (NGCCT–only strategy), and iii) a strategy where patients are first assessed with NGCCT and undergo an ICA if the NGCCT is positive (NGCCT–ICA strategy). NGCCTs are defined as dual-source cardiac CT scanners with >64 slices (Brilliance iCT (Phillips Healthcare), Somatom Definition Flash (Siemens Healthcare), Aquilion ONE (Toshiba Medical Systems), and Discovery CT750 HD (GE Healthcare)).

**Models**The cost-effectiveness analyses were conducted by combining five models which were adjusted for this specific decision problem: i) a decision model of the diagnostic pathway (diagnostic model)[7], ii) a Markov model reflecting the prognosis of CAD patients (disease progression model (DPM)[8]), iii) a Markov model to estimate the impact of radiation on cancer mortality and morbidity (York Radiation Model (YRM)[6][9]), iv) a Markov model to account for mortality amongst persons without CAD (general population model (GPM)[7]), and v) a Markov model was created by the authors to estimate the impact of stroke due to the initial test and treatment (stroke model). The diagnostic model (Figure 1 and Figure 2), where the entire cohort of patients starts, splits the cohort into separate subcohorts of patients based on the prior likelihood and treatment dependent diagnostic performance and complication rates. It determines if the long term costs and effects are modelled through the DPM (Figure 3), GPM (Figure 4) or the stroke model (Figure 4). For example, the prognosis of patients with a true positive (TP) test and no stroke was modelled with the DPM while the prognosis of stroke patients was modelled using the stroke model. The YRM (Figure 5) provided disutilities and costs due to radiation induced cancer based on the radiation dose of the diagnostic tests and treatments; this model was applied to all patients undergoing the respective test or treatment. We then combined the results for all of the different models (i.e. diagnostic, GPM, stroke, YRM and DPM) to derive a complete cost-effectiveness estimate for each specific difficult-to-image subgroup. In conclusion, the diagnostic model and the YRM was used for the entire cohort and the DPM, stroke and GPM were used depending on the test result and complications (Table 28 [6]). The aim of the study was to compare the overall cost-effectiveness of the three strategies in each of the two populations (suspected and known CAD). Expert opinion (N=4) from radiologists and cardiologists was used to gather information on the relative frequencies of patients (Tables 2 and 3) in the difficult-to-image subgroups in the known or suspected CAD population (appendix 7 [6]). Multiplication of the relative proportions with the subgroup-specific costs and effects produced an overall ICER for both populations.

The analyses were based on cohort simulations. Costs and effects were discounted at 3.5%, and the study was performed from a National Health Service perspective.

**Model variables**

Input parameters, based on published literature and expert opinion, are provided as supplementary data in Table S1 and in the full report [6].

*Transition probabilities*

Prior likelihood, accuracy estimates of the tests and complication rates of the procedures are important parameters in the diagnostic model. The prior likelihood (20%) of having CAD in patients with suspected CAD was based on the clinical guideline “Chest pain of recent onset”[1]. Patients with a prior likelihood of 20% are normally diagnosed with a 64-slice CT, the technology that the NGCCT will replace for patients who are difficult to image. The prior likelihood of performing a revascularisation in patients with known CAD was based on the CE-MARC study [7] (Table S1). We used this estimate due to lack of data despite the possibility that the CE-MARC population may not perfectly match our population. The sensitivity and specificity of ICA were assumed to be 100%, as in Mowatt *et al*. [2]. The estimates of the sensitivity and specificity for the NGCCT were based on a systematic review which aimed to identify accuracy estimates for all type of scanners [10]. This review found 21 studies evaluating the Somatom definition (flash), one study evaluating the Aquilion ONE and one study evaluating the Discovery CT750 HD. In the remainder of the paper we will assume that these accuracy estimates are generalizable to other NGCCTs. Complication rates of ICA and the procedures were based on West *et al.*[11], Tarakji *et al.*[12], Serruys *et al.*[13], Rajani *et al.*[14], and Bridgewater *et al.*[15].

The risks of cardiovascular events for patients with CAD in the DPM were based on the results of the EUROPA trial.[8] We used four equations to calculate: i) the probability of any event that will occur in one cycle of three months; ii) the probability that the event is fatal; iii) the probability of a subsequent event in the first year after a first non-fatal event; and iv) the probability of a subsequent event after one year. Tables 21-26,44 and 45 from Westwood et al. [6] present the input parameters and risk equations that were used in the DPM.

Life expectancy for patients without CAD was based on UK life tables[16]; the life expectancy for stroke patients was derived by adjusting the UK life tables for excess mortality risk based on an observational study of stroke patients[17] (Table 33 [6]).

The adjusted version of the YRM models the harmful consequences of radiation exposure. Based on age at exposure, gender, and radiation dose (mSv) we have estimated the probability of developing cancer. For patients developing radiation-induced cancer, the remaining quality-adjusted life-years (QALYs) given the average age of cancer incidence and the average treatment cost for cancer are calculated [9] (Tables 47 and 52 [6]).

*Costs*  
The costs of the three strategies included the cost of the diagnostic tests, non-fatal events (myocardial infarction (MI) and cardiac arrest), procedures (e.g., revascularisation), CAD management costs (e.g. medication), stroke-related costs and costs due to radiation-induced cancer (Table S1). Original cost prices were inflated to reflect costs for 2010 using PSSRU Health Unit costs of Health and Social Care 2010 [18]

The price of the NGCCT procedure was calculated using a bottom-up costing since only data for CT in general (i.e. not specifically for CTCA) was available (Table 30 [6]). The costs occurring in the first year after a non-fatal cardiovascular event, a fatal cardiovascular event, and a non-cardiovascular fatal event were based on the EUROPA trial [19]. For subsequent years after the non-fatal event, the additional cost was estimated at £986 [8]. CAD management costs for each difficult-to-image patient group were calculated using a previously published regression model, which estimates costs using patient characteristics such as age, diabetes mellitus, medication usage, and symptomatic disease.[8] Tables 35-38 from Westwood et al. [6] present the input parameters and risk equations that were used in the DPM. Costs due to radiation-induced cancer are based on a number of previous comprehensive assessments of the economic burden of treating several different types of cancer [9] (Table 46 [6]).

*Health related quality of life*

The overall effectiveness of the three strategies was expressed in QALYs. QALYs represent a combination of life expectancy and health-related quality of life (HRQoL). The HRQoL estimates of CAD patients were based on three sources: UK population norms for the EQ5D [20] (Table 34 [6]), EQ5D scores per Canadian Cardiovascular Society class of angina pectoris [21] and treatment effect on HRQoL based on the RITA2 trial [22] (Tables 39-42 [6]). These sources were used to calculate HRQoL for each difficult-to-image group [7]. It was assumed that a non-fatal event was associated with a disutility of 0.0102 for the subsequent three months [23]. Loss in QALYs due to radiation induced cancer were based on the UK population [9] (Tables 49 and 50 [6]). HRQoL of patients with stroke were estimated to be 0.37 using the results of the study of Sandercock et al.[17].

**Assumptions**

A number of assumptions were made in this study. First, the ICA (“gold standard”) was assumed to have a sensitivity and specificity of 100%. Second, we assumed that all diagnostic tests are performed immediately after each other without any relevant time delay. Third, we also assumed that the sensitivity and specificity of the tests for each difficult-to-image subgroup are the same for the both population. Lastly, the complication rates of revascularization and ICA were assumed to be the same in all subgroups. The full set of assumptions is provided in Westwood et al.[6]

**Analyses**

Base-case scenarios were based on a probabilistic sensitivity analysis (PSA) due to the non-linearity of the model. The PSA was performed by running a Monte Carlo simulation of 5000 simulations of the model. In the PSA, parameters were varied simultaneously using a priori defined distributions. Gamma distributions were used for costs, log-normal distributions for relative risks, and beta distributions were used for utility values and probabilities. In addition, a cost effectiveness acceptability curve (CEAC) was created to present the probability of the diagnostic tests being cost-effective at varying willingness-to-pay thresholds. Scenario analyses were performed to determine the impact of different values for the input parameters on the ICERs. The cost price of the NGCCT, the prior likelihood of CAD in the suspected population, and the complication rates were varied. The cost price of NGCCT was fixed at £150 for the lower limit and at £207 for the upper limit; this range was based on the bottom-up costing method where we have varied the number of procedures performed per year. The prior likelihood of the suspected population was increased to 0.3, which was the upper limit of the range when a 64-slice CT should be performed to diagnose patients suspected of CAD [1]. Worst-case and best-case scenarios for the NGCCT strategies were performed by varying the complication rates (lower and upper limits of 95% confidence interval) of a revascularization and of the test. Moreover, cost-effectiveness acceptability curves are created to present the probability of a strategy being cost-effective given the willingness-to-pay threshold. Currently, NICE applies a threshold of £20000 to £30000 per QALY gained [24]. More information concerning the modelling methods and input parameters can be found in Westwood et al.[6] All analyses were performed using Microsoft Excel 2010.

**RESULTS**

The base-case results, reflecting a frequency-weighted average of the results of the different subgroups, revealed that NGCCT was initially less expensive than ICA, but that the lower sensitivity and specificity of NGCCT leads to more incorrect diagnostic classifications (Table 1). Furthermore, the NGCCT reduces radiation induced cancer, complications (stroke & MI) and mortality due to the diagnostic procedure compared with ICA. An overall QALY estimate and a separate QALY estimate per model for every strategy, subgroup and population in Tables 57 and 58 in Westwood et al. [6].

**Suspected CAD population**

Table 2 presents the overall costs and effects for the suspected CAD population and the cost and effects per difficult-to-image subgroup. The strategies are arranged according to increasing effectiveness and ICERs are estimated for the two most effective strategies by comparing the strategies with the strategy that is ranked lower in effectiveness.

The three strategies differed very little in their effectiveness; the ICA-only strategy was only slightly more effective than the other strategies (i.e., 10.597 QALYs vs. 10.590 QALYs for NGCCT-ICA and 10.588 for NGCCT-only). However, the ICA-only strategy was also the most expensive strategy (£6534), followed by NGCCT-ICA (£5950) and the NGCCT-only strategy (£5808). The NGCCT-only strategy might be considered as a cost-effective strategy, since its effectiveness is very similar to that of the ICA-only strategy and its overall costs are lower than that of the other strategies. The ICER of NGCCT-ICA versus NGCCT-only is considerably higher (£71,000) than the currently used threshold of £20,000 to £30,000 per additional QALY. The ICA-only strategy generated the most effects but was also the most expensive strategy leading to an ICER that would exceed the threshold (£83,429). The subgroups analyses correspond with the overall results; however ICA-only is the most cost-effective strategy for patients with arrhythmias (ICER: £24,645) if a threshold of £30,000 per additional QALY is used. Figure 6 shows a cost-effectiveness acceptability curve; the NGCCT-only strategy has the highest probability of being cost-effective if the cost-effectiveness threshold is less than £70,000. For thresholds above £70,000, the three different strategies are more or less equivalent. However, the probability of NGCCT-only being the cost-effective strategy is still less than 50% compared with the other strategies since the strategies have very similar total costs and effects.

**Known CAD population**

Table 3 shows the cost-effectiveness results for the known CAD population. The NGCCT strategies were more effective than ICA-only in all subgroups. Overall NGCCT-only was the most effective strategy (9.538 QALYs) compared to NGCCT-ICA (9.537 QALYs) and ICA-only (9.516 QALYs). However, NGCCT-only was also more expensive (£28,228) compared with NGCCT-ICA (£27,785) leading to an ICER of £726,230 per QALY gained. Consequently, NGCCT-ICA seems to be cost-effective for the known CAD population since the ICER of NGGCT-only (£726,230) is considerably higher than the threshold of £30,000 per QALY gained. When uncertainty is taken into account, the above results still hold. The acceptability curve graph (Figure 6) shows that the NGCCT-ICA strategy has the highest probability of being cost-effective independent of the willingness to pay thresholds, while the ICA-only strategy has the smallest probability of being cost-effective.

**Scenario analyses**

The scenario analysis with a cost price of £150 for the NGCCT did not affect the overall results; the NGCCT-ICA strategy was still the most favourable strategy. However, when the price of the NGCCT was increased to £207, the ICA-only strategy became less expensive than the NGCCT-only strategy for the known CAD population. Varying the complication rates and the prior likelihood of having CAD for the suspected population did not change the overall results.

**DISCUSSION**

64-slice CT has proven accuracy for the diagnosis of CAD in most patients [2-4]. However, these scanners are less useful for difficult-to-image patient groups, e.g. those with irregular or fast heartbeats, those who are obese, or in whom artefacts produced by high levels of coronary calcium or existing stents might reduce image quality. Newer generation CT scanners have the advantage of being capable of producing diagnostic quality images in these patient groups. This study has estimated the cost-effectiveness of new generation CT scanners in these difficult-to-image patients.

For patients with suspected CAD, the NGCCT-only strategy might be considered as cost-effective, since its effectiveness is very similar to that of the most effective strategy (difference: -0.009 QALYs) and since its overall costs are much lower than those of the other strategies. For patients with known CAD, a cost-effective strategy is probably NGCCT followed by ICA if the NGCCT is positive (NGCCT-ICA), since it yields the highest cost-saving, and dominates the ICA-only strategy.

Several other studies have also concluded that little differences in health outcomes across diagnostic strategies exists [25-27]. Furthermore, it was concluded that coronary CT angiography can be a cost-saving technique [26-28] that can help to avoid unnecessary invasive angiograms [27]. Although these results were found in studies evaluating the cost-effectiveness of 64-slice CT which has lower accuracy estimates than NGCCT.

**Strengths and limitations**

The strength of this cost-effectiveness analysis is that we were able to capture as well as possible the whole range of patient experience from diagnostics to clinical pathway to complications and radiation by combining economic model components. Of course, combining evidence with the use of economic models could be viewed as a limitation because it introduces uncertainty and it was necessary to make several assumptions. However, assumptions and evidence sources have been explicitly reported and uncertainty accounted for by probabilistic and scenario analyses.

The estimated accuracy of the NGCCT is based on the accuracy of ICA, which was assumed to be 100%. However, the use of ICA as the gold standard is very common in this field [2] but this may have influenced our results since the estimated accuracy of the NGCCT is also based on the accuracy of the ICA. In addition, ICA in combination with fractional flow reserve is currently a frequently used procedure and can be considered as a better alternative than ICA-only [29]. Moreover, accuracy estimates for NGCCT were only based on studies evaluating Somatom definition Flash, Discovery CT750 HD and Aquilion ONE since none of the studies evaluating the Brilliance iCT were eligible for inclusion. Extrapolation of the cost-effectiveness results to the other NGCCTs is therefore debatable Furthermore, the accuracy estimates of the NGCCT are assumed to be the same for the known and suspected population and do not differ between the different types of NGCCT scanners. It is uncertain whether these assumptions may have led to an overestimate or an underestimate of the cost-effectiveness of NGCCT-only and NGCCT-ICA strategies.

The procedure costs of the NGCCT are estimated using a micro-costing approach. Unfortunately, no data were available on the consumables which are used during the procedure. However, the extra cost per person to make the NGCCT-only strategy not cost effective vs. the NGCCT-ICA strategy in the suspected CAD population would have to be about £80 given a willingness-to-pay threshold of £30,000/QALY. In the known CAD population, the extra cost would have to be over £1,100 to make the NGCCT-ICA strategy not cost-effective vs. the ICA-only strategy when a willingness-to-pay threshold of £30,000/QALY is used.

The prior likelihood of CAD in the suspected CAD population was based on the clinical guideline for chest pain of recent onset [1] and for the known population it was based on the prior likelihood estimated by the CE-MARC study [7]. For the suspected CAD group, we had to rely on the recommendations of the clinical guideline “Chest pain of recent onset”[1] to quantify the prior likelihood. According to the clinical guideline, CT scans are recommended for use in the diagnostic path of patients with a prior likelihood of CAD of 10-29% and a non-zero calcium score [1]. This likelihood is based on presence of certain clinical symptoms (suggestive of angina), age, gender, diabetes, smoking and hyperlipidaemia. However, scenario analyses showed that the overall results did not change when the prior probability of patients suspected of CAD increased. For the prior likelihood estimate in the known CAD population, it is not entirely certain that the CE-MARC study [7] and our study consider exactly the same patient population. It is therefore possible that the actual prior likelihood in our populations differs from that currently assumed in our model.

Complication rates for the initial procedures are a compilation of various sources and are assumed to be the same for all subgroups. This assumption may have led to an inaccurate estimation of the MI and stroke rates for CABG, PCI and ICA. Potential differences in any of these factors could lead to different conclusions for the various NGCCTs. However we have performed scenario analyses changing the parameters, which did not alter our conclusions.

**Implications**

The NICE recommendations about the use of these scanners in the UK were based in part on the results of this study. They recommended the use of new generation cardiac CT scanners as an option for first line imaging of the coronary arteries in patients with suspected CAD and for first-line evaluation of disease progression to establish the need for revascularization in patients with known CAD in whom imaging with earlier generation CT scanners is difficult [30]. However, the use of the less cost-effective diagnostic strategy ICA shall remain a clinical option despite its less favourable cost-effectiveness ratio [31]. According to this guideline it was estimated that the number of people in England in whom imaging with earlier generation CT scanners is difficult can range from 10 million to 18 million [30].

The results of this analysis may differ by setting due to differences in methodological, healthcare system or population characteristics [32]. Methodological characteristics including the perspective may not lead to a substantially different ICER since the mean age of the patients in most subgroups is above 60 and thus difference in productivity costs between strategies can be considered small. Most differences in costs and effects are incurred immediate and thus varying discount rates may not have a substantial impact. The intervention costs, prior likelihood, severity of the CAD, the availability of health care resources and clinical practice patterns are important aspects that need to be considered when the transferability of the results is assessed. However, the modelling methods and input parameters are presented in a transparent and reproducible way and therefore the developed model can be adapted to other jurisdictions.

**Conclusions**

The use of NGCCT in difficult-to-image CAD patients might be considered cost-effective based on the cost-effectiveness thresholds used in England and Wales. NGCCT is equal in effectiveness to ICA but is cost-saving in both the suspected CAD and the known CAD populations. NGCCT is therefore recommended in the assessment of patients who are difficult to image with earlier CT scanners.

**Supplementary Data**

Table S1 presents the input parameters that were used for the economic evaluation

**Funding**

This report was funded by the NIHR Health Technology Assessment Programme (project number 10/107/01) and commissioned on behalf of NICE. It will be published in full in Health Technology Assessment, Vol. 17, No. 9. See the HTA Programme website ([www.hta.ac.uk](http://www.hta.ac.uk) ) for further project information. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

**References**

1. 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. http://guidance.nice.org.uk/CG95

2. Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, Hillis GS, Fraser C: Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. Health Technol Assess 2008, 12(17):iii-iv, ix-143.

3. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M: Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. Ann Intern Med 2010, 152(3):167-177.

4. Khan R, Rawal S, Eisenberg MJ: Transitioning from 16-slice to 64-slice multidetector computed tomography for the assessment of coronary artery disease: are we really making progress? Can J Cardiol 2009, 25(9):533-542.

5. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA: Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 2005, 46(3):552-557.

6. Westwood M, Al M, Burgers L, Redekop K, Lhachimi S, Armstrong N: 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. Health Technol Assess. 2013;17(9):1-243

7. Walker S, Girardin F, McKenna C, Ball SG, Nixon J, Plein S, Greenwood JP, Sculpher M: Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. Heart 2013, 99(12):873-881.

8. Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M, Deckers J, Ferrari R, Remme WJ, Bertrand M, Fox K, EUROPA Trial Investigators: Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart 2007, 93(9):1081-1086.

9. McKenna C, Wade R, Faria R, Yang H, Stirk L, Gummerson N, Sculpher M, Woolacott N: EOS 2D/3D X-ray imaging system: a systematic review and economic evaluation. Health Technol Assess 2012, 16(14):1-188.

10. Westwood ME, Raatz HD, Misso K, Burgers L, Redekop K, Lhachimi SK, Armstrong N, Kleijnen J: Systematic review of the accuracy of dual-source cardiac CT for detection of arterial stenosis in difficult to image patient groups. Radiology 2013, 267(2):387-395.

11. West R, Ellis G, Brooks N, Joint Audit Comm British Cardiac S: Complications of diagnostic cardiac catheterisation: results from a confidential inquiry into cardiac catheter complications. Heart 2006, 92(6):810-814.

12. Tarakji KG, Sabik JF,3rd, Bhudia SK, Batizy LH, Blackstone EH: Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. JAMA 2011, 305(4):381-390.

13. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA, Arterial Revascularization Therapies Study Group: Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001, 344(15):1117-1124.

14. Rajani R, Lindblom M, Dixon G, Khawaja M, Hildick-Smith D, Holmberg S: Evolving trends in percutaneous coronary intervention. 2011, 18:73-76.

15. Bridgewater B, Grayson AD, Brooks N, Grotte G, Fabri BM, Au J, Hooper T, Jones M, Keogh B, North West Quality Improvement Programme in Cardiac Interventions: Has the publication of cardiac surgery outcome data been associated with changes in practice in northwest England: an analysis of 25,730 patients undergoing CABG surgery under 30 surgeons over eight years. Heart 2007, 93(6):744-748.

16. 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 2006, DH2:.

17. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, Lewis S, Lindley R, Neilson A, Wardlaw J: Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. Stroke 2004, 35(6):1490-1497.

18. Personal Social Services Research Unit. Unit Costs of Health and Social Care. Canterbury: University of Kent; 2010. [<http://www.pssru.ac.uk/pdf/uc/uc2010/uc2010.pdf>]

19. Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators: Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003, 362(9386):782-788.

20. Kind P, Hardman G, Macran S: UK population norms for EQ-5D. 1999, Discussion paper 172. http://www.york.ac.uk/che/pdf/DP172.pdf

21. Longworth L, Buxton MJ, Sculpher M, Smith DH: Estimating utility data from clinical indicators for patients with stable angina. Eur J Health Econ 2005, 6(4):347-353.

22. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA, Second Randomized Intervention Treatment of Angina (RITA-2) Trial Participants: Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. J Am Coll Cardiol 2003, 42(7):1161-1170.

23. Sullivan PW, Ghushchyan V: Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making 2006, 26(4):410-420.

24. National Institute for Health and Clinical Excellence: Guide to the methods of technology appraisal (N1618). 2008, http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf:.

25. Ladapo JA, Jaffer FA, Hoffmann U, Thomson CC, Bamberg F, Dec W, Cutler DM, Weinstein MC, Gazelle GS: Clinical outcomes and cost-effectiveness of coronary computed tomography angiography in the evaluation of patients with chest pain. J Am Coll Cardiol 2009, 54(25):2409-2422.

26. Amemiya S, Takao H: Computed tomographic coronary angiography for diagnosing stable coronary artery disease: a cost-utility and cost-effectiveness analysis. Circ J 2009, 73(7):1263-1270.

27. Genders TS, Meijboom WB, Meijs MF, Schuijf JD, Mollet NR, Weustink AC, Pugliese F, Bax JJ, Cramer MJ, Krestin GP, de Feyter PJ, Hunink MG: CT coronary angiography in patients suspected of having coronary artery disease: decision making from various perspectives in the face of uncertainty. Radiology 2009, 253(3):734-744.

28. Darlington M, Gueret P, Laissy JP, Pierucci AF, Maoulida H, Quelen C, Niarra R, Chatellier G, Durand-Zaleski I: Cost-effectiveness of computed tomography coronary angiography versus conventional invasive coronary angiography. Eur J Health Econ 2015, 16(6):647-55.

29. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH: Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010, 55(25):2816-2821.

30. New generation cardiac CT scanners (Aquilion ONE, Brilliance iCT, Discovery CT750 HD and Somatom Definition Flash) for cardiac imaging in people with suspected or known coronary artery disease in whom imaging is difficult with earlier generation CT scanners NICE diagnostics guidance 3. London: NICE; 2012 https://www.nice.org.uk/guidance/dg3/resources/new-generation-cardiac-ct-scanners-aquilion-one-brilliance-ict-discovery-ct750-hd-and-somatom-definition-flash-for-cardiac-imaging-in-people-with-suspected-or-known-coronary-artery-disease-in-whom-im-29270622661 .Accessed 09, 2012

31. Severens JL, Brunenberg DE, Fenwick EA, O'Brien B, Joore MA. Cost-effectiveness acceptability curves and a reluctance to lose. Pharmacoeconomics. 2005;23(12):1207-14.

32. Welte R, Feenstra T, Jager H, Leidl R: A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics 2004, 22(13):857-876.

33. Department of Health. NHS Reference costs 2010/11. Collection Guidance. London: Department of Health; 2010 [[www.dh.gov.uk/en/Publicationsandstatistics/](http://www.dh.gov.uk/en/Publicationsandstatistics/)Publications/PublicationsPolicyAndGuidance/DH\_122803]

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1: Intermediate outcomes | | |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
|  |  | Proportion correct classification | Misclassification | | Test mortality | Test morbidity | Mortality revascularization | Morbidity revascularizationa |
|  |  | FPs | FNs |
|  | |  |  |  |  |  |  |  |
| *Suspected CAD population* | |  |  |  |  |  |  |  |
|  | ICA - only | 1 | - | - | 0.00073 | 0.00064 | 0.00027 | 0.00047 |
|  | NGCCT - ICA | 0.9903 | - | 0.0097 | 0.00019 | 0.00018 | 0.00026 | 0.00044 |
|  | NGCCT - only | 0.8934 | 0.0969 | 0.0097 | - | - | 0.00039 | 0.00067 |
|  | |  |  |  |  |  |  |  |
| *Known CAD population* | |  |  |  |  |  |  |  |
|  | ICA - only | 1 | - | - | 0.0007 | 0.0006 | 0.0030 | 0.0051 |
|  | NGCCT - ICA | 0.9818 | - | 0.0182 | 0.0001 | 0.0003 | 0.0028 | 0.0048 |
|  | NGCCT - only | 0.9042 | 0.0775 | 0.0182 | - | - | 0.0034 | 0.0058 |
|  |  |  |  |  |  |  |  |  |
| a Stroke or MI due to the procedure | | | | | |  |  |  |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2: Cost effectiveness of NGCCT for the suspected CAD population | | | | | | | | | | | |
| *Suspected CAD population* | | Relative proportionsa | **Costs** | | | **QALYs** | | |  |  |  |
|  |  | **Mean (£)** | **sd** | **range (2.5%-97.5%)** | **Mean** | **sd** | **range (2.5%-97.5%)** | **ΔCosts** | **ΔQALYs** | **ICER (£/QALY)** |
| **Overall** | |  |  |  |  |  |  |  |  |  |  |
|  | NGCCT - only |  | 5808 | 573 | 4683-6901 | 10.588 | 0.109 | 10.377-10.806 |  |  |  |
|  | NGCCT - ICA |  | 5950 | 589 | 4825-7068 | 10.590 | 0.109 | 10.371-10.808 | 142 | 0.002 | 71,000 |
|  | ICA - only |  | 6534 | 572 | 5415-7642 | 10.597 | 0.107 | 10.385-10.797 | 584 | 0.007 | 83,429 |
| Obese | | 16.25% |  |  |  |  |  |  |  |  |  |
|  | NGCCT - ICA | 6297 | 1237 | 4055-8976 | 10.508 | 0.167 | 10.173-10.829 |  |  |  |
|  | NGCCT - only | 6106 | 1202 | 3917-8695 | 10.508 | 0.167 | 10.159-10.824 | -191 | 0 | Dominates NGCCT - ICA |
|  | ICA - only | 6968 | 1217 | 4743-9629 | 10.519 | 0.163 | 10.183-10.830 | 862 | 0.011 | 81,318 |
| Arrhythmias | | 11.75% |  |  |  |  |  |  |  |  |  |
|  | NGCCT - ICA | 6227 | 1190 | 4052-8706 | 9.419 | 0.171 | 9.073-9.748 |  |  |  |
|  | NGCCT - only | 6077 | 1161 | 3943-8494 | 9.42 | 0.171 | 9.073-9.740 | -150 | 0 | Dominates NGCCT - ICA |
|  | ICA - only | 6785 | 1205 | 4603-9367 | 9.448 | 0.166 | 9.112-9.761 | 708 | 0.029 | 24,645 |
| Heart rate > 65 bpm | | 29.25% |  |  |  |  |  |  |  |  |  |
|  | NGCCT - only | 6595 | 1256 | 4314-9287 | 10.967 | 0.156 | 10.642-11.258 |  |  |  |
|  | NGCCT - ICA | 6758 | 1289 | 4419-9511 | 10.968 | 0.157 | 10.651-11.266 | 162 | 0.001 | 312,047 |
|  | ICA - only | 7342 | 1263 | 5027-10041 | 10.969 | 0.155 | 10.660-11.255 | 584 | 0.001 | 440,057 |
| Coronary calcium level >400 | | 27.50% |  |  |  |  |  |  |  |  |  |
|  | NGCCT - only | 5962 | 1168 | 3872-8456 | 10.201 | 0.169 | 9.855-10.520 |  |  |  |
|  | NGCCT - ICA | 6142 | 1248 | 3973-8794 | 10.202 | 0.169 | 9.851-10.530 | 180 | 0.001 | 205,536 |
|  | ICA - only | 6801 | 1189 | 4711-9361 | 10.21 | 0.167 | 9.871-10.531 | 659 | 0.008 | 80,446 |
| Intolerance β-Blocker | | 15.25% |  |  |  |  |  |  |  |  |  |
|  | NGCCT – ICA | 6430 | 1320 | 4082-9209 | 11.54 | 0.151 | 11.235-11.830 |  |  |  |
|  | ICA – only | 7016 | 1242 | 4767-9576 | 11.541 | 0.148 | 11.242-11.824 | 586 | 0.001 | 972,803 |
|  | NGCCT – only | 6279 | 1240 | 4058-8850 | 11.542 | 0.151 | 11.234-11.828 | -736 | 0.001 | Dominant |
| a Expert opinion | |  |  |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 3: Cost effectiveness of NGCCT for the known CAD population | | | | | | | | | | | |
| *Known CAD population* | | Relative proportionsa | **Costs** | | | **QALYs** | | |  |  |  |
| **Mean (£)** | **sd** | **range (2.5%-97.5%)** | **Mean** | **sd** | **range (2.5%-97.5%)** | **ΔCosts** | **ΔQALYs** | **ICER (£/QALY)** |
| **Overall** | |  |  |  |  |  |  |  |  |  |  |
|  | ICA - only |  | 28,234 | 502 | 27,262-29,240 | 9.516 | 0.288 | 8.959-10.066 |  |  |  |
|  | NGCCT - ICA |  | 27,785 | 531 | 26,785-28,786 | 9.537 | 0.283 | 8.986-10.081 | -449 | 0.022 | Dominates ICA - only |
|  | NGCCT - only |  | 28,228 | 498 | 27,269-29,217 | 9.538 | 0.286 | 8.986-10.081 | 443 | 0.001 | 726,230 |
| Obese | | 10% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 29,694 | 928 | 27,973-31,562 | 8.857 | 0.464 | 7.823-9.674 |  |  |  |
|  | NGCCT - only | 29,254 | 924 | 27,538-31,130 | 8.869 | 0.477 | 7.800-9.707 | -439 | 0.012 | Dominates ICA - only |
|  | NGCCT - ICA | 29,177 | 920 | 27,465-31,024 | 8.872 | 0.46 | 7.891-9.700 | -77 | 0.003 | Dominant |
| Arrhythmias | | 7.33% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 27,428 | 908 | 25,625-29,232 | 6.545 | 0.504 | 5.507-7.480 |  |  |  |
|  | NGCCT - ICA | 27,084 | 916 | 25,316-28,912 | 6.588 | 0.503 | 5.552-7.523 | -344 | 0.043 | Dominates ICA - only |
|  | NGCCT - only | 27,726 | 971 | 25,833-29,660 | 6.595 | 0.499 | 5.565-7.507 | 642 | 0.007 | 90,683 |
| Heart rate > 65 bpm | | 27.33% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 30,434 | 1169 | 28,219-32,764 | 11.223 | 0.381 | 10.400-11.894 |  |  |  |
|  | NGCCT - only | 30,477 | 1190 | 28,226-32,927 | 11.233 | 0.377 | 10.424-11.906 | 43 | 0.011 | 4021 |
|  | NGCCT - ICA | 30,080 | 1184 | 27,853-32,486 | 11.242 | 0.378 | 10.429-11.903 | -397 | 0.009 | Dominant |
| Coronary calcium level >400 | | 25.67% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 31,145 | 1079 | 29,054-33,300 | 9.271 | 0.538 | 8.155-10.216 |  |  |  |
|  | NGCCT - only | 30,839 | 1103 | 28,753-33,092 | 9.301 | 0.533 | 8.201-10.288 | -306 | 0.03 | Dominates ICA - only |
|  | NGCCT - ICA | 30,661 | 1075 | 28,643-32,861 | 9.306 | 0.539 | 8.138-10.259 | -178 | 0.005 | Dominant |
| Intolerance β-blockers | | 9.33% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 29,339 | 986 | 27,478-31,345 | 10.016 | 0.392 | 9.188-10.720 |  |  |  |
|  | NGCCT - only | 29,354 | 1004 | 27,446-31,377 | 10.039 | 0.392 | 9.206-10.746 | 14 | 0.024 | 610 |
|  | NGCCT - ICA | 28,972 | 988 | 27,121-30,976 | 10.042 | 0.394 | 9.185-10.740 | -381 | 0.003 | Dominant |
| Previous stent | | 11% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 28,450 | 842 | 26,828-30,082 | 8.724 | 0.364 | 7.944-9.370 |  |  |  |
|  | NGCCT - ICA | 28,056 | 855 | 26,413-29,690 | 8.737 | 0.358 | 7.960-9.371 | -394 | 0.013 | Dominates ICA - only |
|  | NGCCT - only | 28,672 | 888 | 26,972-30,406 | 8.744 | 0.354 | 7.986-9.381 | 617 | 0.007 | 93,526 |
| Previous CABG | | 9.33% |  |  |  |  |  |  |  |  |  |
|  | ICA - only | 28,466 | 844 | 26,852-30,152 | 8.719 | 0.363 | 7.935-9.374 |  |  |  |
|  | NGCCT - ICA | 28,088 | 859 | 26,458-29,797 | 8.725 | 0.36 | 7.963-9.389 | -378 | 0.006 | Dominates ICA - only |
|  | NGCCT - only | 28,554 | 1028 | 26,682-30,723 | 8.725 | 0.359 | 7.956-9.382 | 466 | 0 | 2,943,850 |
| a Expert opinion | |  |  |  |  |  |  |  |  |  |  |

**Figure legends**

Figure 1: Diagnostic model for suspected CAD population

CAD: coronary artery disease; ICA: invasive coronary angiography; NGCCT: new generation coronary computed tomography; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; DPM: disease progression model

Figure 2: Diagnostic model for known CAD population

CAD: coronary artery disease; ICA: invasive coronary angiography; NGCCT: new generation coronary computed tomography; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; DPM: disease progression model

Figure 3: Disease progression model\*

\*Adapted from Briggs et al. 2007 [8]

MI: myocardial infarction; CA: cardiac arrest; CV: cardiovascular; Eq: equation

Figure 4: Life-death model structure used for stroke model and GPM

GPM: general population model

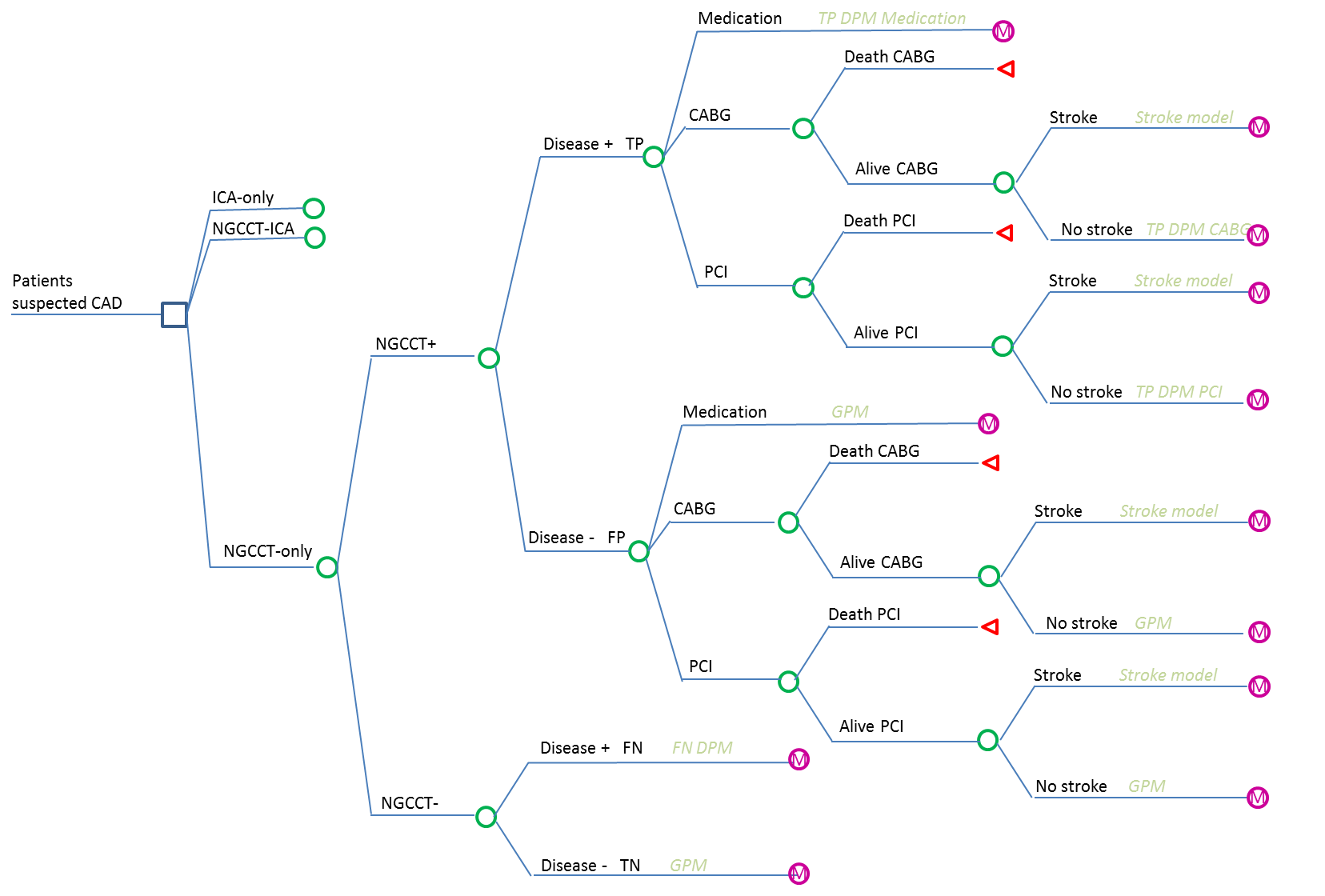
Figure 5: York radiation model

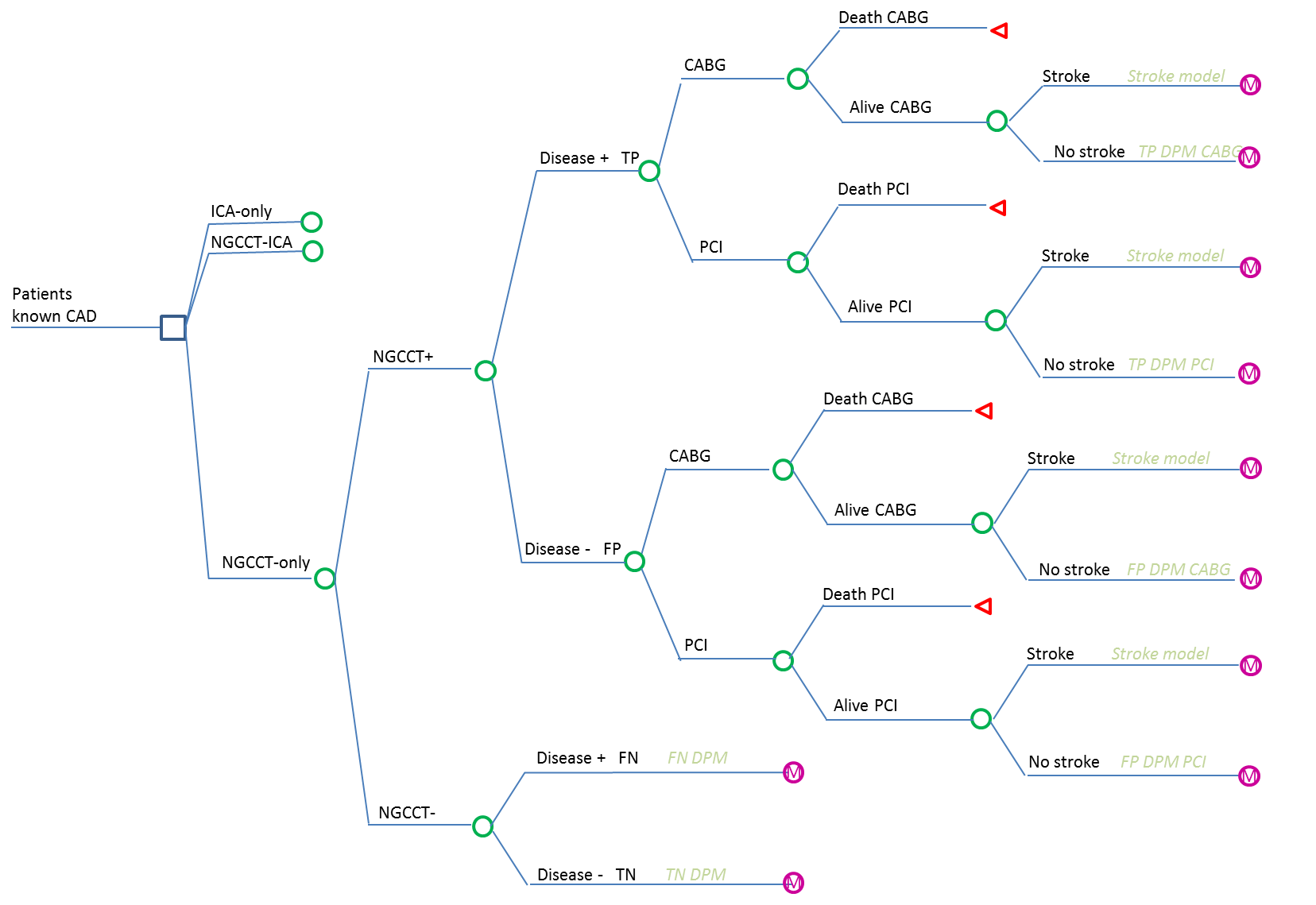
QALY: quality adjusted life years

Figure 6: Acceptability curves for suspected and known CAD populations

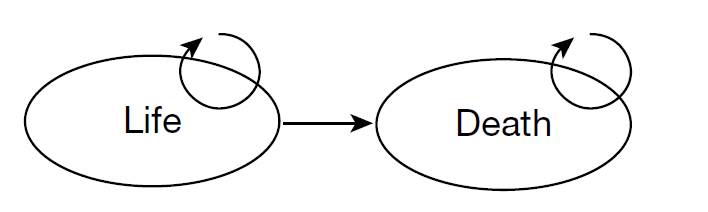
CAD: coronary artery disease; QALY: quality adjusted life years; ICA: invasive coronary angiography; NGCCT: new generation coronary computed tomography

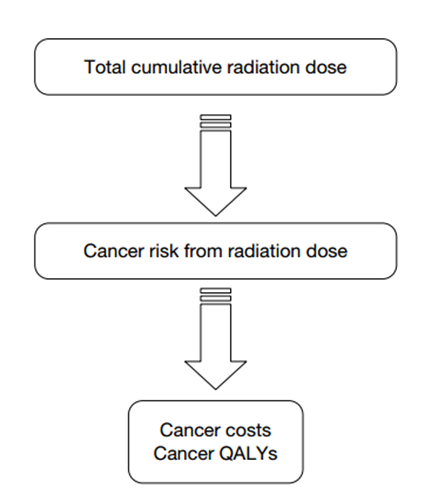
|  |  |  |  |
| --- | --- | --- | --- |
| Table S1: Input parameters and costs | |  |  |
|  |  |  |  |
|  |  | Value | Source |
| Prevalence | |  |  |
|  | Suspected CAD population | 0.200 (0.1 - 0.29) | [1] |
|  | Known CAD population | 0.395 | [7] |
|  |  |  |  |
| Accuracy estimates | |  |  |
|  | *Sensitivity* |  |  |
|  | ICA: 'gold' standard | 1 | Assumption [2] |
|  | NGCCT | 0.904 - 0.977a | [6] |
|  | *Specificity* |  |  |
|  | ICA: 'gold' standard | 1 | Assumption [2] |
|  | NGCCT | 0.816 - 0.921a | [6] |
|  |  |  |  |
| Complications ICA | |  |  |
|  | Mortality rate | 0.0007 | [11] |
|  | Cerebrovascular accident rate | 0.0006 | [11] |
|  | Myocardial infarction rate | 0.00003 | [11] |
| Complications PCI | |  |  |
|  | Mortality rate | 0.0029 | [14] |
|  | Cerebrovascular accident rate | 0.0005 | [14] |
|  | Myocardial infarction rate | 0.0005 | [14] |
| Complications CABG | |  |  |
|  | Mortality rate | 0.018 | [15] |
|  | Cerebrovascular accident rate | 0.016 | [12] |
|  | Myocardial infarction rate | 0.024 | [12, 13] |
|  |  |  |  |
| Costs per procedure | |  |  |
|  | ICA | 1003 | [33] |
|  | NGCCT | 169 | [6] |
|  | Coronary artery bypass graft | 8280 | [33] |
|  | Percutaneous coronary intervention | 3633 | [33] |
|  | Coronary artery bypass graft + ICA | 9242 | [33] |
|  | Percutaneous coronary intervention + ICA | 4196 | [33] |
|  |  |  |  |
| Cost per event | |  |  |
|  | Non-fatal event (MI or cardiac arrest) | 11805 | [8] |
|  | Cardiovascular fatal event | 3641 | [8] |
|  | Non-cardiovascular fatal event | 1241 | [8] |
|  | Non-fatal event history | 986b | [8] |
|  | Background costs | regressionc | [8] |
|  |  |  |  |
|  | Stroke first year | 9429b | [17] |
|  | Stroke subsequent years | 4894b | [17] |
|  |  |  |  |
|  | Radiation induced cancer | 12389 – 22712d | [9] |
|  | a Range for all subgroups |  |  |
|  | b Per cycle |  |  |
|  | c Depending on age, the existence of cardiovascular diseases, diabetes mellitus, medication usage, clearance and symptomatic disease | | |
|  | d Depending on type of cancer |  |  |





H:\bmg\somatom\tweede revisie\figure 3- DPM.tif





H:\bmg\somatom\tweede revisie\figure 6 - CEACs Somatom.tif