

## SUPPLEMENTARY APPENDIX

### **Diagnostic and prognostic benefits of CTCA using the 2016 NICE guidance within a randomised trial**

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# Methods

## Study Population

Participants were recruited from 12 cardiology chest pain clinics across Scotland and those randomised to the intervention arm underwent CTCA imaging at one of 3 sites in addition to routine clinical assessment. The main exclusion criteria related inability to undergo CTCA due to renal failure (estimated glomerular filtration rate  $<30$  mL/min), major allergy to iodinated contrast media, or known pregnancy. Recruitment began November 18, 2010 and follow-up of clinical events is ongoing with planned reporting of five-year outcomes in early 2018. The study was performed in accordance with the Declaration of Helsinki and with research ethics committee approval.

Pre-test probability of coronary disease was estimated according to the 2010 NICE guidelines (1) and 10-year cardiovascular risk was calculated with the ASSIGN score, a validated Scottish cardiovascular risk score that incorporates social deprivation (2).

## Computed tomography coronary angiography

Participants underwent coronary artery calcium scoring and CTCA using either a 64-detector row scanner (Brilliance 64, Philips Medical Systems, Netherlands, and Biograph mCT, Siemens, Germany) or a 320-detector row scanner (Aquilion One, Toshiba Medical Systems, Nasushiobara, Japan). Computed tomography images were analysed by 2 trained observers with excellent reproducibility (3) and differences in categorisation were resolved by consensus. A complete description of the image analysis procedure has been previously published (4, 5). For the purposes of this study, prognostically important coronary heart

disease was defined as either of the following:  $\geq 50\%$  stenosis in the left main stem, or  $\geq 70\%$  stenosis in all three major epicardial vessels (6).

### **(1) Clinical classification of chest pain symptoms**

|                        |   |
|------------------------|---|
| Typical angina         | Meets all three of the following characteristics: <ul style="list-style-type: none"><li>• constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms</li><li>• precipitated by physical exertion</li><li>• relieved by rest or GTN within about 5 minutes</li></ul> |
| Atypical angina        | Meets two of these characteristics  |
| Non-anginal chest pain | Meets only one or none of these characteristics   |

### **(2) Resting ECG interpretation**

|              |   |
|--------------|---|
| Abnormal ECG | Any of the following changes: <ul style="list-style-type: none"><li>• pathological Q waves</li><li>• LBBB</li><li>• ST-segment and T wave abnormalities</li></ul> |
| Normal ECG   | None of the above changes   |

### **(3) NICE 2016 diagnostic cohort**

|                 |  |
|-----------------|--|
| Possible angina | Meets any of the following criteria: <ul style="list-style-type: none"><li>• Typical or atypical angina</li><li>• Non-anginal chest pain and an ABNORMAL resting ECG</li></ul> |
| Non-anginal     | Non-anginal chest pain and a NORMAL resting ECG  |

Supplementary Table 1: Classification of diagnostic cohorts according to the revised NICE guideline.

GTN, glyceryl trinitrate; ECG, electrocardiogram; NICE, national institute for health and care excellence.

|                                  | Estimated PTP of CHD (NICE 2010) |            |            |            |            | NICE Classification (2016) |                 |
|----------------------------------|----------------------------------|------------|------------|------------|------------|----------------------------|-----------------|
|                                  | <10%                             | 10-29%     | 30-59%     | 60-89%     | >90%       | Non-anginal                | Possible Angina |
| <b>n</b>                         | 170                              | 292        | 425        | 414        | 318        | 592                        | 1027            |
| <b>CTCA findings</b>             |                                  |            |            |            |            |                            |                 |
| <b>Normal</b>                    | 116 (69.0)                       | 161 (55.3) | 197 (46.6) | 119 (29.1) | 41 (12.9)  | 295 (50.0)                 | 339 (33.3)      |
| <b>Non-obstructive (&lt;70%)</b> | 48 (28.6)                        | 101 (34.7) | 179 (42.3) | 180 (44.0) | 108 (34.0) | 239 (40.5)                 | 377 (37.0)      |
| <b>Obstructive (≥70%)</b>        | 4 (2.4)                          | 29 (10.0)  | 47 (11.1)  | 110 (26.9) | 169 (53.1) | 56 (9.5)                   | 303 (29.7)      |

Supplementary Table 2: CTCA findings according to previous or revised diagnostic classification cohorts.

PTP, pre-test probability; CHD, coronary heart disease; NICE, national institute of health and care excellence; CTCA, computed tomography coronary angiography.

| <b>Female</b> |            |             |                 |
|---------------|------------|-------------|-----------------|
|               |            | Non-anginal | Possible angina |
| Age           | < 60 years | 3.4%        | 11.7%           |
|               | ≥ 60 years | 6.7%        | 21.2%           |
| <b>Male</b>   |            |             |                 |
|               |            | Non-anginal | Possible angina |
| Age           | < 60 years | 11.1%       | 31.8%           |
|               | ≥ 60 years | 20.2%       | 48.6%           |

Supplementary Table 3: Predicted risk of CHD within each diagnostic cohort according to age and gender. CHD, coronary heart disease.

| <b>Sex</b> | <b>Mean age (years)</b> | <b>Diagnostic certainty (%)</b> | <b>Rate of fatal or non-fatal MI (per person year)</b> |
|------------|-------------------------|---------------------------------|--|
| Female     | 57.0                    | 24.8                            | 0.4  |
| Male       | 56.3                    | 28.1                            | 1.2  |

Supplementary Table 4: Average rate of the primary diagnostic and prognostic endpoints for the study population. MI, myocardial infarction.

|   | <b>Non-anginal</b> | <b>Possible Angina</b> |
|---|--------------------|------------------------|
| <b>n</b>  | 1447               | 2323                   |
| <b>Non-coronary cardiac findings, %</b>           | 133 (22.5)         | 312 (30.3)             |
| <b>Aortic valve calcification, %</b>              | 29 (2.0)           | 99 (4.3)               |
| <b>Mitral valve calcification, %</b>              | 5 (0.3)            | 22 (0.9)               |
| <b>Dilated left ventricle, %</b>                  | 11 (0.8)           | 17 (0.7)               |
| <b>Dilated right ventricle, %</b>                 | 8 (0.6)            | 4 (0.2)                |
| <b>Dilated left atrium, %</b>                     | 16 (1.1)           | 45 (1.9)               |
| <b>Dilated right atrium, %</b>                    | 4 (0.3)            | 7 (0.3)                |
| <b>Left ventricular wall thinning, %</b>          | 2 (0.1)            | 12 (0.5)               |
| <b>Left ventricular hypertrophy, %</b>            | 15 (1.0)           | 51 (2.2)               |
| <b>Hypertrophic obstructive cardiomyopathy, %</b> | 2 (0.1)            | 2 (0.1)                |
| <b>Pericardial disease, %</b>                     | 0 (0.0)            | 2 (0.1)                |
| <b>Pulmonary hypertension, %</b>                  | 0 (0.0)            | 1 (0.0)                |
| <b>Other, %</b>                                   | 71 (4.9)           | 143 (6.2)              |
| <b>Non-cardiac findings, %</b>                    | 187 (31.5)         | 427 (41.5)             |
| <b>Pulmonary mass, %</b>                          | 45 (3.1)           | 122 (5.3)              |
| <b>Mediastinal mass, %</b>                        | 1 (0.1)            | 4 (0.2)                |
| <b>Lymphadenopathy, %</b>                         | 4 (0.3)            | 7 (0.3)                |
| <b>Pulmonary embolism, %</b>                      | 1 (0.1)            | 4 (0.2)                |
| <b>Parenchymal lung disease, %</b>                | 70 (4.8)           | 184 (7.9)              |
| <b>Emphysema, %</b>                               | 45 (3.1)           | 95 (4.1)               |
| <b>Pulmonary fibrosis, %</b>                      | 1 (0.1)            | 6 (0.3)                |
| <b>Other parenchymal disease, %</b>               | 27 (1.9)           | 90 (3.9)               |
| <b>Pleural disease, %</b>                         | 7 (0.5)            | 21 (0.9)               |
| <b>Hiatus hernia, %</b>                           | 43 (3.0)           | 79 (3.4)               |
| <b>Liver pathology, %</b>                         | 20 (1.4)           | 19 (0.8)               |
| <b>Other, %</b>                                   | 36 (2.5)           | 88 (3.8)               |

Supplementary Table 5: Non-coronary findings on CTCA according to diagnostic cohort.

Data are value (%). CTCA, computed tomography coronary angiography.

## Supplementary 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 Guideline 95. London: NICE; 2010.
2. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish heart health extended cohort (SHHEC). *Heart*. 2007;93(2):172-6.
3. Williams MC, Golay SK, Hunter A, Weir-McCall JR, Mlynska L, Dweck MR, Uren NG, Reid JH, Lewis SC, Berry C, van Beek EJ, Roditi G, Newby DE, Mirsadraee S. Observer variability in the assessment of CT coronary angiography and coronary artery calcium score: substudy of the Scottish computed tomography of the heart (SCOT-HEART) trial. *Open Heart*. 2015;2(1):e000234.
4. The SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *The Lancet*. 2015;385(9985):2383-91.
5. The SCOT-HEART investigators. Role of multidetector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, The Scottish computed tomography of the heart (SCOT-HEART) trial: study protocol for randomized controlled trial. *Trials*. 2012;13:184.
6. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *The Lancet*. 1994;344(8922):563-70.