Performance of the Traditional Age, Sex, and Angina Typicality-Based Approach for Estimating Pre-Test Probability of Angiographically Significant Coronary Artery Disease in Patients Undergoing Coronary Computed Tomographic Angiography: Results from the Multinational CONFIRM Registry (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry)

SUPPLEMENTAL MATERIALS

Supplemental Methods 1: Estimating impact of error from missing CAD50 due to nondiagnostic segments and heavy coronary calcification

Supplemental Methods 2: Estimating maximum potential ranges of error in CAD50 prevalence by accounting for the limitations in positive and negative predictive values of coronary CTA

Supplemental Methods 1: Estimating impact of error from missing CAD50 due to nondiagnostic segments and heavy coronary calcification

The meta-analyses of 64-slice coronary CTA accuracy studies by Abdulla, et al. (*Eur Heart J* 2007;28:3042-50, 19 studies in native coronary artery disease) and Sun, et al. (*Eur J Radiol* 2008;67:78-84, 15 studies in native coronary artery disease) both showed a pooled nondiagnostic segment rate of 4%. We believe a 5% nondiagnostic segment rate is representative of the CONFIRM centers, where highly-experienced staff performed and highly-experienced readers interpreted coronary CTAs according to published recommendations (Abbara S, et al. *J Cardiovasc Comput Tomogr* 2009;3:190-204 and Raff, et al. *J Cardiovasc Comput Tomogr* 2009;3:122-136). The worst-case per-patient scenario is therefore 5% of all patients having 1 nondiagnostic segment. This forms the basis for estimating the cumulative number of missed CAD50 patients due to nondiagnostic segments and coronary calcification, using the following 3 steps:

FIRST, we calculated the number of missed CAD50 cases due to nondiagnostic segments by:

1) Assuming all 5% of patients with a nondiagnostic segment had CAD50 in the nondiagnostic segment.
2) Assuming random distribution of nondiagnostic segments. Since CAD50 was found in 1488 of 8106 patients (18.4%) with NonAng, AtypAng, and TypAng, this means that 18.4% of nondiagnostic segments were found in patients already diagnosed with CAD50 in another segment. The remaining 81.6% of segments were then assumed to be in patients who had been "missed" by CTA. The number of such "missed" patients is therefore:

$$(0.816 \times 0.05) \times 8106 \text{ patients} = 331 \text{ patients}$$

In this scenario, 331 patients with NonAng, AtypAng, or TypAng had CAD50 missed by coronary CTA due to a nondiagnostic segment.

SECOND, we calculated number of missed CAD50 cases due to coronary calcification:

1) We first evaluated the distribution of coronary calcium scores available in 11727 patients (83% of the total study population):

score	N	% population	CAD50 prevalence
0	5841	50%	3%
>100	2836	24%	46%
>400	1202	10%	61%
>600	809	7%	65%
>1000	422	4%	70%

Note that 50% of CONFIRM patients had a calcium score of 0. In addition, mean calcium score in these 11727 CONFIRM patients was 146, lower than that reported by ACCURACY (mean score of 284, Budoff, et al. *J Am Coll Cardiol*. 2008;52:1724-1732) and the multi-center, multi-vendor study by Meijboom, et al. (mean score of 213, *J Am Coll Cardiol*. 2008;52:2135-2144). These results suggest that diagnostic difficulties from coronary calcification may have been less common in CONFIRM than in studies designed to test coronary CTA accuracy.

2) Using the table from 1), we selected a calcium score threshold to project CAD50 prevalence using the following steps (the example shown here used calcium score threshold of >1000):
   i) Assume that all patients with calcium score >1000 had CAD50.
   ii) Extend the 4% rate of calcium score >1000 in the table above to the population with NonAng, AtypAng, TypAng (8106 patients)

0.04 x 8106 patients = 324 patients

iii) Assume that 70% of these 324 patients already had CAD50 correctly diagnosed, based on the table shown in 1). This leaves 97 patients in whom CTA "missed" CAD50 due to coronary calcification.

0.3 x 324 patients = 97 patients

THIRD, we assumed no patients had both CAD50 missed due to nondiagnostic segments and CAD50 missed due to coronary calcification:

1) For the example of calcium score >1000, this means a total of 428 patients with CAD50 were missed by coronary CTA.

331 (nondiagnostic) + 97 (calcium scores >1000) = 428

2) We added these 427 patients to the 1488 patients already with CAD50 on CTA and recalculated prevalence. CAD50 prevalence then increased to 23.6%.

(428 + 1488) / (8106) = 0.236.

Hence, in the model built on the assumptions that 5% of the population had randomly distributed nondiagnostic segments, that all patients with nondiagnostic segments had CAD50, that all patients with calcium score >1000 had CAD50, and that no patients had both nondiagnostic segment and calcium score >1000, true CAD50 prevalence in patients with NonAng, AtypAng, or TypAng increased from 18.4% to 23.6%.

3) We repeated the same steps using a calcium score threshold of >600 (7% of total population, CTA miss rate 35%, as shown in Table above). The number of patients with missed CAD50 due to coronary calcium increased to 198 patients, which increased the total number of patients with missed CAD to 529. CAD50 prevalence increased to 24.9%.

(529 + 1488) / (8106) = 0.249.

The calculations shown in this appendix are based on multiple worst-case scenario assumptions. In reality, nondiagnostic segments often do not contain CAD50, calcium scores >600 or >1000 do not universally predict CAD50, and patients with high calcium scores are also more likely to exhibit nondiagnostic segments. Each of these factors would have reduced the number of patients "missed" by coronary CTA. Nevertheless, these calculations show that the large gap between observed and expected CAD50 prevalence in CONFIRM persisted after factoring in worst-case estimates for potential underestimation of CAD50 prevalence due to nondiagnostic segments and coronary calcification.

Supplemental Methods 2: Estimating maximum potential ranges of error in CAD50 prevalence by accounting for the limitations in positive and negative predictive values of coronary CTA

The primary predictive weakness of coronary CTA is "overcalling" – or over-predicting presence of angiographically significant CAD. This was evident in the ACCURACY trial (Budoff, et al. *J Am Coll Cardiol*. 2008;52:1724-1732), where positive predictive value (PPV) of CTA for CAD50 was 64%, in a population with 25% CAD50 prevalence. The reported negative predictive value (NPV) of CTA for CAD50 has consistently been >90% (Abdulla, et al. *Eur Heart J* 2007;28:3042-50, Sun, et al. *Eur J Radiol* 2008;67:78-84, ACCURACY trial, Meijboom, et al. *J Am Coll Cardiol*. 2008;52:2135-2144). Predictive values in these reports included segments with coronary calcification but did not uniformly include segments with nondiagnostic quality, which can reduce both PPV and NPV. To account for this, we reduced the lower limits of tested PPV and NPV and calculated potential "invasive angiography" CAD50 prevalence in scenarios where CTA PPV ranged from 55% to 85% and NPV ranged from 85% to 95%.

In the following example, we calculated potential "invasive angiography" CAD50 prevalence using a PPV of 75% and NPV of 90%.

1) Begin with observed results in CONFIRM:
   8106 total patients with NonAng, AtypAng, or TypAng
   1488 with CAD50, 6618 without CAD50
2) Calculate number of true and false positives using PPV of 75%:
   0.75 x 1488 = 1116 true positives; 0.25 x 1488 = 372 false positives
3) Calculate number of true and false negatives using NPV of 90%:
   0.90 x 6618 = 5956 true negatives; 0.10 x 6618 = 662 false negatives
4) Add the true positives and false negatives to obtain the total number of "invasive angiography" positives:

1116 + 662 = 1778

5) Calculate “invasive angiography” CAD50 prevalence using result from 4)

1778 / 8106 = 0.22

The following table contains results from all PPV/NPV combinations considered:

Modeled Scenarios							
PPV	NPV	True Positive (n)	False Positive (n)	True Negative (n)	False Negative (n)	"Invasive Angiography" Positive (n)	Adjusted CAD50 Prevalence
0.55	0.85	818	670	5625	993	1811	22%
0.55	0.90	818	670	5956	662	1480	18%
0.55	0.95	818	670	6287	331	1149	14%
0.60	0.85	893	595	5625	993	1886	23%
0.60	0.90	893	595	5956	662	1555	19%
0.60	0.95	893	595	6287	331	1224	15%
0.65	0.85	967	521	5625	993	1960	24%
0.65	0.90	967	521	5956	662	1629	20%
0.65	0.95	967	521	6287	331	1298	16%
0.70	0.85	1042	446	5625	993	2034	25%
0.70	0.90	1042	446	5956	662	1703	21%
0.70	0.95	1042	446	6287	331	1373	17%
0.75	0.85	1116	372	5625	993	2109	26%
0.75	0.90	1116	372	5956	662	1778	22%
0.75	0.95	1116	372	6287	331	1447	18%
0.80	0.85	1190	298	5625	993	2183	27%
0.80	0.90	1190	298	5956	662	1852	23%

0.80	0.95	1190	298	6287	331	1521	19%
0.85	0.85	1265	223	5625	993	2258	28%
0.85	0.90	1265	223	5956	662	1927	24%
0.85	0.95	1265	223	6287	331	1596	20%

These calculations showed that the lowest potential “invasive angiography” CAD50 prevalence was 14% (using PPV of 55% and NPV of 95%), and that the highest potential CAD prevalence was 28% (using PPV of 85% and NPV of 85%). Hence, even in the modeled scenario with the greatest underestimation of CAD50 by CTA (PPV of 85% and NPV of 85%), observed CAD50 prevalence still trailed Guideline Probabilities by 23% (28% vs. 51%). We believe a more sensible representation of coronary CTA performance in a real-life population similar to CONFIRM would be a PPV of 75% and a NPV of 90%; this combination yielded an “invasive angiography” prevalence of 22%.