Combination of computed tomography angiography with coronary artery calcium score for improved diagnosis of coronary artery disease: a collaborative meta-analysis of stable chest pain patients referred for invasive coronary angiography

**Electronic Supplementary Material** 

## **APPENDIX RESULTS**

## **Appendix Figure 1: Flowchart**



Overall, 2315 patients with complete data on age, gender, chest pain type, and CAC score from 29 studies were included from the CoMe-CCT dataset (7813 patients from 76 studies)



Appendix Figure 2: Calibration plot of the CAC-plus-CTA model and CTA-alone model

## Appendix Figure 3: Forest plot of the CTA-alone model.

	Experim	nental	Co	ontrol		
Study	Events	Total	Events	Total	Odds Ratio 0	95%-CI
Leschka_2005	27	27	0	17	1925.0	00 [36.496; 101535.308]
Alkadhi_2010	28	33	2	61	165.2	00 [30.168; 904.649]
Alkadhi_2008	58	70	1	80	381.8	33 [48.281; 3019.780]
Leschka_2008_1	39	47	0	33	311.3	53 [17.320; 5597.112]
Bettencourt 2009	21	36	1	29	39.2	00 [4.792; 320.699]
Dewy_2009	11	12	0	17	268.3	33 [10.037; 7173.695]
Diederichsen_2009	28	39	0	50	250.3	04 [14.214; 4407.638]
Diederichsen_unpublished	19	42	0	6	10.7	87 [0.571; 203.730]
Garcia_2006	48	84	17	114	7.6	08 [3.883; 14.905]
Halvorsen_2008	34	45	2	34	49.4	55 [10.165; 240.600]
Martuscelli_2004	41	47	2	17	51.2	50 [9.306; 282.255]
Meijboom_2006	12	13	4	17	39.0	00 [3.804; 399.855]
Meijboom_2007	57	65	0	60	818.5	29 [46.182; 14507.600]
Meijboom_2008	40	51	6	25	11.5	15 [3.702; 35.817]
Mendoza_Rodriguez_2009	18	24	0	57	327.3	08 [17.587; 6091.560]
Bonmassari_2006	12	16	2	17	22.5	00 [3.505; 144.445]
Ovrehus_2010_1	26	40	3	60	35.2	86 [9.328; 133.473]
Ovrehus_2010_2	38	46	1	58	270.7	50 [32.531; 2253.382]
Shabestari_2007	82	90	4	19	38.4	37 [10.264; 143.947]
Ugolini_2009	6	11	1	9	9.6	00 [0.876; 105.166]
Sun_2013	27	31	0	6	79.4	44 [3.784; 1667.824]
Kajander_2010	40	45	2	52	200.0	00 [36.841; 1085.753]
Husmann_2010	15	17	0	13	167.4	00 [7.371; 3801.640]
Scheffel_2006	30	31	2	29	405.0	00 [34.736; 4722.080]
Chen_2011	48	53	2	22	96.0	00 [17.177; 536.539]
Leschka_2008_2	6	6	1	16	134.3	33 [4.813; 3749.569]
Herzog_2009	26	29	2	37	151.6	67 [23.616; 974.036]
Gueret_2013	101	203	14	107	6.5	78 [3.519; 12.296]
Random effects model		1253		1062		33 [35.911; 114.179]
Heterogeneity: $I^2 = 70\%$ , $\tau^2 =$	1.2972, p	< 0.01	l			

0.001 0.1 1 10 1000 Odds Ratio (95% CI)

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## Appendix Figure 4: Forest plot of the CAC-plus-CTA model.

	Experim	nental	Co	ontrol			
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-Cl
Leschka 2005	27	27	0	17	1	925.000	[36 496: 101535 308]
Alkadhi 2010	28	33	2	61		165.200	[30,168: 904,649]
Alkadhi 2008	58	70	1	80		381.833	[48.281: 3019.780]
Leschka 2008 1	39	47	0	33	<u> </u>	311.353	[17.320; 5597.112]
Bettencourt 2009	21	36	1	29		39,200	[4,792; 320,699]
Dewy 2009	11	12	0	17		268.333	[10.037; 7173.695]
Diederichsen_2009	28	39	0	50		250.304	[14.214; 4407.638]
Diederichsen_unpublished	19	42	0	6	- <u></u>	10.787	[0.571; 203.730]
Garcia_2006	48	84	17	114		7.608	[3.883; 14.905]
Halvorsen_2008	34	45	2	34		49.455	[10.165; 240.600]
Martuscelli_2004	41	47	2	17		51.250	[9.306; 282.255]
Meijboom_2006	12	13	4	17		39.000	[ 3.804; 399.855]
Meijboom_2007	57	65	0	60		818.529	[46.182; 14507.600]
Meijboom_2008	40	51	6	25		11.515	[ 3.702; 35.817]
Mendoza_Rodriguez_2009	18	24	0	57		327.308	[17.587; 6091.560]
Bonmassari_2006	12	16	2	17		22.500	[ 3.505; 144.445]
Ovrehus_2010_1	26	40	3	60	-	35.286	[9.328; 133.473]
Ovrehus_2010_2	38	46	1	58		270.750	[32.531; 2253.382]
Shabestari_2007	82	90	4	19		38.437	[10.264; 143.947]
Ugolini_2009	6	11	1	9		9.600	[0.876; 105.166]
Sun_2013	27	31	0	6		79.444	[ 3.784; 1667.824]
Kajander_2010	40	45	2	52		200.000	[36.841; 1085.753]
Husmann_2010	15	17	0	13		167.400	[7.371; 3801.640]
Scheffel_2006	30	31	2	29		405.000	[34.736; 4722.080]
Chen_2011	48	53	2	22		96.000	[17.177; 536.539]
Leschka_2008_2	6	6	1	16		134.333	[4.813; 3749.569]
Herzog_2009	26	29	2	37		151.667	[23.616; 974.036]
Gueret_2013	101	203	14	107	+	6.578	[3.519; 12.296]
Random effects model		1253		1062		64.033	[35.911; 114.179]
Heterogeneity: $I^2 = 70\%$ , $\tau^2 =$	1.2972, p	< 0.01					
					0.001 0.1 1 10 1000		
					Odds Ratio (95% CI)		

Performance Measure	Original Model	Bootstrap Sample	Original Sample	Optimism	Bootstrap corrected
CTA-alone model					
AUC <sup>a</sup>	80.2%	80.4%	80.4%	0.0000	80.2%
Brier Score <sup>b</sup>	0.149	0.149	0.149	0.0002	0.149
Scaled Brier Score <sup>c</sup>	0.4	0.4	0.4	0.00	0.4
Discrimination Slope <sup>d</sup>	0.400	0.397	0.396	0.000	0.399
Calibration Slope <sup>e</sup>	0.994	0.982	0.994	-0.0117	1.006
CAC-plus-CTA mode	1				
AUC <sup>a</sup>	87.2%	87.2%	87.1%	-0.00002	87.2%
Brier Score <sup>b</sup>	0.132	0.132	0.132	0.000	0.132
Scaled Brier Score <sup>c</sup>	0.47	0.47	0.47	0.0001	0.47
Discrimination Slope <sup>d</sup>	0.455	0.454	0.455	-0.0013	0.456
Calibration Slope <sup>e</sup>	0.984	0.971	0.985	-0.0136	0.998

Appendix Table 1. Internal validation for CAC-plus-CTA model and CTA-alone model

<sup>a</sup> AUC: area under the receiver-operating-characteristic curve as a concordance statistics <sup>b</sup> Brier score: measuring the accuracy of probabilistic predictions by quantifying the prediction error. A perfect model has a zero Brier score

<sup>c</sup> Scaled Brier score: is scaled by its maximum score and accounts for the outcome (CAD) prevalence. A perfect model has a score of 1

<sup>d</sup> Discrimination slope: is the difference in mean of predicted probabilities between disease (CAD) and no disease (no CAD)

<sup>e</sup> Calibration slope: measures the agreement between the actual outcome and predicted probabilities.

Appendix Table 2. Diagnostic Performance of CAC-plus-CTA and CTA-alone model								
	CAC plus CTA	CTA alone	p-value*					
	n/total n (% [95% CI*])	n/total n (% [95% CI*])						
Diagnostic accuracy	1895 / 2315 (81.9% [81.7-82.0])	1840 / 2315 (79.5% [79.4-79.7])	<0.0001					
Sensitivity	846/1007 (83.9% [81.6-86.2])	867 / 1007 (86.1% [84.0-88.2])	<0.021					
Specificity	1050 / 1308 (80.3% [78.1-82.4])	973/1308 (74.4% [72.0-86.8])	< 0.0001					
Positive predictive value	846 / 1103 (76.6% [74.1-79.1])	867/1202 (72.1% [69.6-74.7])	< 0.0001					
Negative predictive value	1050/ 1212 (86.6% [84.7-88.5])	973/1113 (87.4% [85.5-89.4])	0.257					

Appendix Table 3. Estimates of the mixed-effect logistic regression model of CTA-alone								
and CAC-plus-CTA models (n=2315)								
· · · · · · · · · · · · · · · · · · ·	Estimate (S.E.)	p value	Odds Ratio (95% CI)					
CTA-alone model								
CTA	2.91 (0.116)	< 0.001	18.3 (14.63 to 23.03)					
Model constant	-1.897 (0.124)	—	—					
Random intercept (72) <sup>b</sup>	0.167(0.411)							
BIC	2256.9							
logLik	-1116.8							
CAC-plus-CTA model								
Log CAC score <sup>c</sup>	0.362 (0.026)	< 0.001	1.44 (1.37 to 1.51)					
СТА	2.67 (0.123)	< 0.001	14.51 (11.42 to 18.54)					
Model constant	-3.257 (0.183)		—					
Random intercept ( $\tau$ 2) <sup>b</sup>	0.272 (0.522)							
BIC	2028.4							
logLik	-998.7							
BIC: Bayesian information criterion								
<sup>a</sup> Typical angina is defined as: retrosternal chest discomfort, precipitation by exertion, and								

prompt relief (within 30 s-10 min) by rest or nitroglycerin. Patients in whom two, one, or none of these three criteria were found were classified as having atypical angina, nonanginal chest discomfort, and other chest discomfort, respectively.

<sup>b</sup>Variance component estimate ( $\tau$ 2) for random intercept

<sup>c</sup>Log CAC score was used to overcome its nonnormality.

CAC cut-off value =  $e^{(\beta_{CTA}/\beta_{\log CAC})} = 1715$ 

Appendix Table 4. Likelihood ratio test comparing the CTA-alone and CAC-plus-CTA								
models (n=2315)								
	BIC	logI ik	Dovionoo	<b>V</b> 2	n voluo			

	BIC	logLik	Deviance	X <sup>2</sup>	p value
CTA alone	2256.9	-1116.8	2233.7		
CAC plus CTA	2028.4	-998.7	1997.4	236.25	< 0.001