Appendix: Supplemental Figures and Tables

Supplemental Figure 1. Sampling criteria to arrive at final cohorts.

36,354 abdominal CT images from 2013 to 2018

9,588 with at least one year of follow-up, 6 months or more apart

8,139 included images

1,747 with at least five years of follow-up

Stratified random sampling

1449 Excluded images
1060 Prior IHD diagnosis
219 <18 years old at scan
170 Unable to assign a single L3 slice
112 Image artifacts
18 Anatomical factors - e.g. scoliosis-
40 L3 slice not visible - e.g. pelvic scan-

6,530 used for training
1,609 used for testing

1-year IHD outcome

1,401 used for training
346 used for testing

5 year IHD outcome

6,530 used for training
1,609 used for testing

1-year IHD outcome

1,401 used for training
346 used for testing

5 year IHD outcome
1-year IHD Risk

5-year IHD Risk

- FRS
- PCE
- Segmentation only (S)
- PCE + Segmentation (PCE + S)
- Imaging only (I)
- Clinical Only (C)
- Imaging + Clinical Fusion (I+C)
- Imaging + Clinical + Segmentation Fusion (I+C+S)

|                | 1y AUROC (95% CI) | 5y AUROC (95% CI) |
|----------------|-------------------|-------------------|
| FRS            | .74 (.68-.79)     | .71 (.65-.77)     |
| PCE            | .77 (.71-81)      | .73 (.68-79)      |
| Segmentation only (S) | .70 (.65-.76) | .68 (.62-75)      |
| PCE + Segmentation (PCE + S) | .76 (.71-81) | .72 (.66-78)      |
| Imaging only (I) | .76 (.70-81) | .78 (.71-83)      |
| Clinical Only (C) | .80 (.75-84) | .76 (.71-81)      |
| Imaging + Clinical Fusion (I+C) | .81 (.76-.85) | .80 (.74-.85)     |
| Imaging + Clinical + Segmentation Fusion (I+C+S) | .80 (.75-.84) | .81 (.75-.86)     |

1y AUROC P-value

|                | FRS | PCE | S | PCE+S | C | I | I+C | I+C+S |
|----------------|-----|-----|---|-------|---|---|-----|-------|
| FRS            | <.001 | .02 | <.001 | .04 | <.001 | .02 | PCE | -    |
| PCE            | .01  | .18 | .06 | .09  | C | I | I+C | I+C+S |
| S              | .04  | .19 | .95 | C    | I | I+C | I+C+S |
| PCE+S          | .04  | .98 | I  | I+C  | I+C+S |
| I              | .01  | .59 | I  | I+C  | I+C+S |
| I+C            | .16  | I+C | I+C+S |

5y AUROC P-value

|                | FRS | PCE | S | PCE+S | C | I | I+C | I+C+S |
|----------------|-----|-----|---|-------|---|---|-----|-------|
| FRS            | .004 | .03 | .06 | PCE   | - | I | I+C | I+C+S |
| PCE            | .03  | .76 | .12 | PCE+S | - | I | I+C | I+C+S |
| S              | .01  | .09 | .03 | S     | - | I | I+C | I+C+S |
| PCE+S          | .01  | .53 | .14 | PCE+S | - | I | I+C | I+C+S |
| I              | .02  | I+C | I+C+S |
| I+C            | .42  | I+C | I+C+S |
| I+C+S          | .07  | I+C | I+C+S |

1y AUCPR P-value

|                | FRS | PCE | S | PCE+S | C | I | I+C | I+C+S |
|----------------|-----|-----|---|-------|---|---|-----|-------|
| FRS            | .05  | .34 | .30 | .07  | .29 | I | I+C | I+C+S |
| PCE            | .04  | .49 | .76 | .09  | .10 | C | I+C | I+C+S |
| S              | .03  | .53 | .06 | S     | - | I | I+C | I+C+S |
| PCE+S          | .03  | .10 | .01 | S     | - | I | I+C | I+C+S |
| I              | .28  | I+C | I+C+S |
| I+C            | .29  | I+C | I+C+S |
| I+C+S          | .80  | I+C | I+C+S |

5y AUCPR P-value

|                | FRS | PCE | S | PCE+S | C | I | I+C | I+C+S |
|----------------|-----|-----|---|-------|---|---|-----|-------|
| FRS            | .047 | .05 | .05 | PCE   | - | I | I+C | I+C+S |
| PCE            | .048 | .13 | .04 | PCE+S | - | I | I+C | I+C+S |
| S              | .001 | .14 | .04 | S     | - | I | I+C | I+C+S |
| PCE+S          | .001 | .06 | .02 | PCE+S | - | I | I+C | I+C+S |
| I              | .047 | I+C | I+C+S |
| I+C            | .042 | I+C | I+C+S |
| I+C+S          | .07  | I+C | I+C+S |
Supplemental Figure 2. Proposed model performance in comparison to pooled cohort Equations (PCE) and Framingham risk score (FRS) as measured by receiver operating characteristic and precision-recall curves for 1-year (a) and 5-year (b) IHD risk prediction. Shaded areas correspond to 95% confidence intervals. In Figure legend area under receiver operating characteristic and precision-recall curves, the AUROC and AUCPR curves are shown. Below, $P$ values for pair-wise comparisons between models are reported. Confidence intervals (CI) and $P$ values were obtained using the DeLong method for AUROC and the bootstrap method for AUCPR.
Supplemental Figure 3. Segmentation model performance. CV: coefficient of variation, HU: Hounsfield Unit, CSA: cross-sectional area. Center line represents median, box limits upper and lower quartiles, whiskers 1.5x interquartile range, and points outliers.
Supplemental Table 1. Validation performance of alternative training schemes and hyperparameters of predictive models. *,**: hyperparameters selected for 1-year and 5-year IHDI prediction, respectively.

| Model                        | Hyperparameters tested                                                                 | 1y       | 5y       |
|------------------------------|----------------------------------------------------------------------------------------|----------|----------|
| **Segmentation only**        | C: [.001, 0.1, 0.5, 1**,5,10]                                                          | 0.6771   | 0.7038   |
| **Imaging only**             |                                                                                        |          |          |
| **Selected configuration**   | Batch size 8                                                                             |          |          |
|                              | Learning rate [7e-6**,6e-6**]                                                           |          |          |
|                              | Adam optimizer                                                                          |          |          |
|                              | Max epochs 10**                                                                         | 0.7733   | 0.7947   |
|                              | Cross Entropy Loss                                                                      |          |          |
| **Training only final layer**| Batch size 8                                                                             |          |          |
|                              | Learning rate [1e-4,1e-5,1e-6]                                                          |          |          |
|                              | Adam optimizer                                                                          |          |          |
|                              | Max Epochs 15                                                                           | 0.5656   | 0.6523   |
|                              | Cross Entropy Loss                                                                      |          |          |
| **Image augmentations**      | Batch size 8                                                                             |          |          |
|                              | Learning rate [1e-3, 1e-4, 1e-5, 1e-6]                                                  |          |          |
|                              | Adam optimizer                                                                          |          |          |
|                              | Max Epochs 20                                                                           | 0.7089   | 0.7867   |
|                              | Cross Entropy Loss                                                                      |          |          |
|                              | Rotations of up to 3° and pixel shifting of up to 5 pixels during training             |          |          |
| **Focal loss**               | Batch size 8                                                                             |          |          |
|                              | Learning rate [1e-4,1e-5,1e-6]                                                          |          |          |
|                              | Adam optimizer                                                                          |          |          |
|                              | Max Epochs 20                                                                           | 0.7275   | 0.7879   |
|                              | Focal loss (gamma:[2,3,4,5,10] alpha:[.01,.99],[0.05,0.95])                           |          |          |
|                              | Augmentations [Yes/No]                                                                   |          |          |
| **Clinical**                 | colsample_bytree:<2,3,4,5,6,7,8,9,1**                                                  |          |          |
|                              | gamma:{1.5,1.5,,10**}                                                                   |          |          |
|                              | max_depth:{1,2,3,**5.6}                                                                  |          |          |
|                              | min_child_weight:{1,5,**1}                                                              |          |          |
|                              | subsample:{5**,7,8,9,**1}                                                                | 0.7778   | 0.7820   |
|                              | learning_rate:{0.001,.01,.05,**1**,3,1}                                               |          |          |
|                              | scale_pos_weight:{1**,5,10,15,20}                                                       |          |          |
| **PCE + segmentation**       | colsample_bytree:<2,4,6,**1>                                                            |          |          |
|                              | gamma:{1.5,1.5,**10**}                                                                  |          |          |
|                              | max_depth:{1,2,**3},4,5,6                                                               |          |          |
|                              | min_child_weight:{1**,5,1}                                                              | 0.7421   | 0.7366   |
|                              | subsample:{5**,75,1}                                                                    |          |          |
| **Imaging + Clinical Fusion**| C: {0.1**,0.5,1,5,10,20,30,50,100,**,500,1000}                                        | 0.9434   | 0.9215   |
| **Imaging + Clinical + Segmentation Fusion** | C: {0.1,0.5,1,5,10,20,30,50,100**,500,**,1000}                                       | 0.9466   | 0.9241   |
Supplemental Table 2. Variables captured from the electronic medical record and used as covariates of Clinical only model. (See attached file).
Supplemental Table 3. Distribution of demographic variables across the study population. Features relevant to pooled cohort equations risk assessment, as well as body composition metrics derived from segmentation are also included.

| Variable                  | 1-year follow-up | 5-year follow-up |
|---------------------------|------------------|------------------|
|                           | Train            | Test             | Train            | Test             |
|                           | non-IHD (n=6246) | non-IHD (n=1538) | non-IHD (n=1046) | non-IHD (n=284) |
| Age                       | 51.0 (17.1)      | 51.3 (16.7)      | 51.5 (16.4)      | 51.0 (16.9)      |
| Male Sex                  | 39.7             | 40.9             | 36.7             | 51.5             |
| Smoking                   | 6.2              | 6.9              | 5.6              | 6.3              |
| Race/Ethnicity            | 0.0              | 0.0              | 0.0              | 0.0              |
| White                     | 47.7             | 50.3             | 45.1             | 53.1             |
| Black                     | 4.1              | 3.1              | 2.7              | 2.8              |
| Hispanic                  | 21.2             | 20.3             | 18.4             | 21.1             |
| Asian                     | 10.6             | 10.5             | 10.9             | 11.3             |
| Other/Unknown             | 10.6             | 11.3             | 12.9             | 14.5             |
| Treated for hypertension  | 25.0             | 24.8             | 28.0             | 50.4             |
| Diabetes diagnosis        | 13.4             | 26.1             | 13.4             | 25.6             |
| HDL Cholesterol [mg/dL]   | 56.6 (20.4)      | 57.1 (19.7)      | 57.8 (23.3)      | 51.9 (18.0)      |
| Total Cholesterol [mg/dL] | 184.3 (47.3)     | 183.9 (42.2)     | 188.0 (44.4)     | 176.8 (45.1)     |
| Systolic Blood Pressure [mmHg] | 124.0 (17.8) | 125.5 (18.8) | 123.5 (18.2) | 130.5 (21.1) |
| VAT/SAT ratio             | 86.8             | 79.5             | 83.8             | 87.7             |
| Muscle density [HU]       | 43.9 (9.6)       | 43.7 (9.6)       | 44.0 (9.1)       | 38.3 (8.9)       |

Supplemental Table 4. Imaging scanners and protocol details.

| Manufacturer | Scanner Model         | Number of Scans | X-ray Tube Current mean (std) mA | Tube Voltage mode (range) in kV | Reconstruction Kernel (n) | Slice Thickness (mm) |
|--------------|-----------------------|-----------------|----------------------------------|--------------------------------|--------------------------|---------------------|
| GE MEDICAL SYSTEMS | LightSpeed VCT        | 2456            | 460 (187)                        | 120 (80-140)                    | STANDARD (2453), SOFT (3) | 1.25                |
|               | LightSpeed16          | 952             | 284 (117)                        | 120 (100-140)                   | STANDARD (952)            | 1.25                |
|               | Discovery CT750 HD     | 567             | 331 (143)                        | 100 (80-120)                    | SOFT (532), STANDARD (35) | 1.25                |
|               | Revolution CT         | 510             | 385 (143)                        | 100 (80-140)                    | STANDARD (510)            | 1.25                |
|               | LightSpeed Ultra      | 124             | 435 (17)                         | 120 (120-140)                   | SOFT (124)                | 1.25                |
|               | Discovery 690         | 16              | 394 (126)                        | 120 (100-120)                   | STANDARD (9), SOFT (7)    | 1.25                |
|               | Discovery 600         | 12              | 308 (122)                        | 120 (120-120)                   | STANDARD (10), SOFT (2)   | 1.25                |
|               | Discovery 710         | 6               | 388 (82)                         | 100 (100-100)                   | STANDARD (6)              | 1.25                |
| SIEMENS       | SOMATOM Definition Flash | 1693          | 469 (189)                        | 100 (70-140)                    | I26f (1671), I26s (11), B20f (7), I26f (2), I26s (1), Q30f (1) | 1                  |
|               | SOMATOM Definition Edge | 557             | 453 (113)                        | 100 (80-140)                    | I26f (556), I26s (1)      | 1                  |
|               | SOMATOM Definition AS+ | 540            | 441 (119)                        | 100 (80-140)                    | I26f (344), B20f (86), B31f (64), B31s (16), I26s (14), B20s (9), B25f (5), B18f (1), B30f (1) | 1                  |
|               | Sensation 64          | 403             | 360 (97)                         | 120 (80-140)                    | B20f (283), B31f (118), B31s (1) | 1                  |
|               | SOMATOM Force         | 245             | 637 (231)                        | 90 (70-120)                     | Bf32d (238), Bf32d (3), Bf32s (3), Bv36s (1) | 1                  |
|               | SOMATOM Definition    | 58              | 267 (129)                        | 120 (100-120)                   | B31f (53), B18f (5)      | 1                  |
Supplemental Table 5. Performance of proposed classification models using Youden's index as threshold, compared to two clinically relevant thresholds for pooled cohort equations (PCE).

| Model                          | 1-year IHD risk | 5-year IHD risk |
|-------------------------------|-----------------|-----------------|
|                               | Sensitivity [%] | Specificity [%] | PPV [%] | NPV [%] | Sensitivity [%] | Specificity [%] | PPV [%] | NPV [%] |
| PCE (>7.5% threshold)         | 70.4            | 71.1            | 10.1    | 98.1    | 61.2            | 70.5            | 10.1    | 84.8    |
| PCE (>20% threshold)          | 38.0            | 86.9            | 11.8    | 96.8    | 29.4            | 86.6            | 11.8    | 79.0    |
| Segmentation only             | 80.3            | 52.0            | 7.2     | 98.3    | 69.4            | 62.8            | 37.8    | 86.3    |
| Clinical Only                 | 56.3            | 83.0            | 13.3    | 97.6    | 90.6            | 48.7            | 36.5    | 94.1    |
| Imaging Only                  | 80.3            | 59.5            | 8.4     | 98.5    | 64.7            | 77.8            | 48.7    | 87.1    |
| Imaging + Clinical Fusion     | 45.1            | 87.5            | 14.2    | 97.2    | 69.4            | 75.5            | 48.0    | 88.3    |

Supplemental Table 6. Performance of proposed prediction models, along with Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) in different subpopulations of the test set. y/o: years old. (See attached file).