# Supplementary Information for Enhancing the diagnosis of functionally relevant coronary artery disease with machine learning

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**Supplementary Table 1** | Parameter grid for conventional machine learning models. Full maximum depth means nodes are expanded until all leaves are pure. Source data are provided as a Source Data file. To evaluate the classification performance of conventional, linear, and non-linear machine learning models trained on static clinical features alone, we performed grid searches for a logistic regression model, a decision tree classifier, a support vector machine, and a random forest classifier. The best model for each grid search was chosen based on the area under the precision-recall curve. The AUPRC of the results of the grid searches are shown in Supplementary Table 2. We selected the random forest for further investigation due to its superior performance on the validation cohort.

| Model | Parameter | Values |
|---|---|---|
| Support Vector Machine | Kernel | {linear, polynomial, RBF, sigmoid} |
| | C | {1E-2, 0.1, 1, 10} |
| | Degree for polynomial kernel | {1,2, 3} |
| | Gamma | {1E-6, 3.2E-2, ⅛, 1000} |
| | Coefficient for polynomial and sigmoid kernel | {0, 0.4, 0.7, 1} |
| | Shrinking | {true, false} |
| | Tolerance for stopping criterion | {1E-4, 1E-3, 1E-2} |
| Logistic Regression | Penalty | {none, l1, l2, elastic net} |
| | C | {1E-2, 0.1, 1, 5, 10} |
| | Tolerance | {1E-4, 1E-3, 1E-2} |
| | Class weight | {balanced, none} |
| | Fit intercept | {true, false} |
| Decision Tree | Splitter | {best, random} |
| | Criterion | {gini, entropy} |
| | Maximum depth | {2, 5, 10, 20, 50, full} |
| | Minimum samples split | {1, 2, 5, 10, 15} |
| Random Forest | Number trees | {25, 50, 100} |
| | Maximum number of features | {2, 5, 8} |
| | Maximum depth | {full, 5, 10} |
| | Minimum impurity increase | {1E-5, 1E-4, 1E-3} |

**Supplementary Table 2** | Results of the grid searches for the statistical machine learning approaches. Parameters were selected based on the best validation performance. Source data are provided as a Source Data file.

| Model | Validation AUPRC |
|---|---|
| Support Vector Machine | $0.38 \pm 0.05$ |
| Logistic Regression | $0.49 \pm 0.03$ |
| Decision Tree | $0.57 \pm 0.08$ |
| **Random Forest** | $\mathbf{0.61 \pm 0.04}$ |

**Supplementary Table 3** | **Architectural details.** Convolutional layers are written as [input dimension, output dimension, kernel size, stride]Conv, linear layers as [input dimension, output dimension]Lin. BN: Batch norm, ReLU: Rectified Linear Unit, DO: Dropout. Max pooling is written as MP(kernel size; stride). add denotes the addition of the output of the $MP_{1\times1}$ layer and the preceding convolutional layer. Source data are provided as a Source Data file.

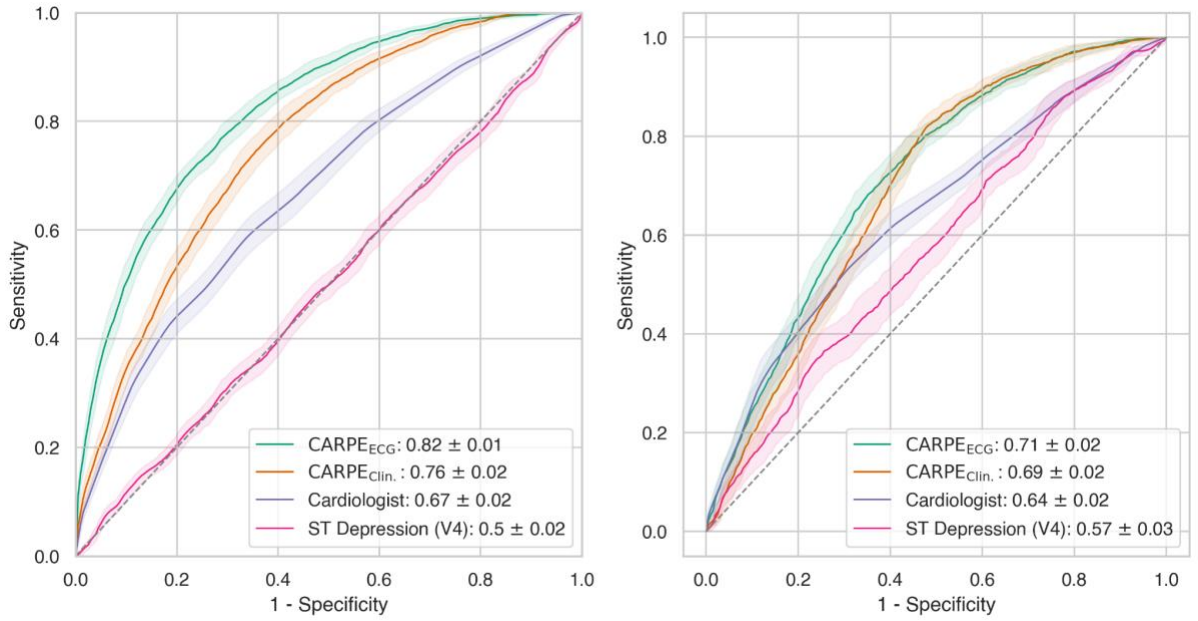
| Task | Layer Name | Parameters |
|---|---|---|
| N/A | $MP_{1\times1}$ | [MP(4, 4), $[64, 128, 1, 1]_{Conv}$] |
| N/A | BR | [BN, ReLU] |
| N/A | BRD | [BR, DO(0.8)] |
| N/A | $Conv_{init}$ | $[[1, 64, 20, 1]_{Conv}$, BR] |
| N/A | $Res_1$ | $[[64, 128, 20, 1]_{Conv}$, BRD, $[128, 128, 20, 4]_{Conv}$, add, BRD] |
| N/A | $Res_2$ | $[[128, 196, 20, 1]_{Conv}$, BRD, $[196, 196, 20, 4]_{Conv}$, add, BRD] |
| N/A | $Res_3$ | $[[196, 256, 20, 1]_{Conv}$, BRD, $[256, 256, 20, 4]_{Conv}$, add, BRD] |
| | $Res_4$ | $[[320, 320, 20, 1]_{Conv}$, BRD, $[320, 320, 20, 5]_{Conv}$, add, BRD] |
| N/A | $Res_5$ | $[[320, 160, 20, 1]_{Conv}$, BRD, $[160, 160, 20, 4]_{Conv}$, add, BRD] |
| Embedding ECG | $h_{res}$ | [$Conv_{init}$, Res1, Res2, Res3, Res4, Res5, BR] |
| fCAD Prediction | $g_{lin}$ | $[[672, 32]_{Lin}$, ReLU, DO(0.5), $[32, 1]_{Lin}$] |
| MPSSRS Prediction | $g_{lin}$ | $[[672, 32]_{Lin}$; ReLU, DO(0.4), $[32, 1]_{Lin}$] |
| MPSSSS Prediction | $g_{lin}$ | $[[672, 32]_{Lin}$; ReLU, DO(0.4), [32, 1]Lin] |
| Stress Type Prediction | $g_{lin}$ | $[[672, 32]_{Lin}$; ReLU, DO(0.4), $[32, 5]_{Lin}$] |
| Embedding Clinical Features | $h_{lin}$ | $[[8, 16]_{Lin}$, ReLU, BN, $[16, 32]_{Lin}$, ReLU, BN, DO(0.5)] |

**Supplementary Table 4** | **Multi-task regularisation grid.** Parameter grid to determine multi-task regularisation parameters. $\eta_{best}$ refers to the best learning rate from the first selection step. Source data are provided as a Source Data file.

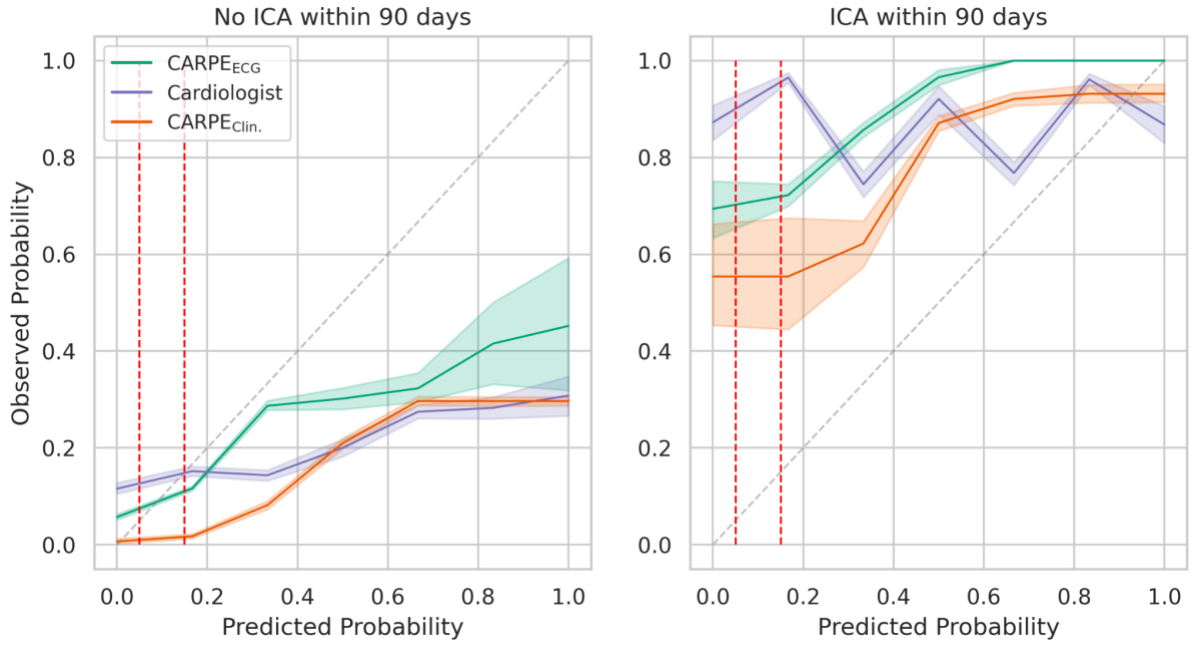
| Parameter | Values |
|---|---|
| $\lambda_{MPSSRS}$ | {0.00, 0.25, 0.50, 0.75, 1.00} |
| $\lambda_{MPSSSS}$ | {0.00, 0.25, 0.50, 0.75, 1.00} |
| $\lambda_{Stress}$ | {0.00, 0.25, 0.50, 0.75, 1.00} |
| $\eta$ | $\{2\eta_{best}, \eta_{best}, \frac{\eta_{best}}{2}\}$ |

**Supplementary Table 5** | **Multi-task regularisation results.** Impact of regularisation strength on mean AUPRC (%) on the validation sets over all splits and learning rates. Uncertainty is shown as standard deviation. None refers to training without any regularisation, Best to the configuration with highest mean AUPRC over all five validation splits. Highest mean AUPRC over all validation sets is reached on lead V6 with $\lambda_{MPSSRS} = \lambda_{MPSSSS} = 0.5$, and $\lambda_{Stress} = 0.75$. Source data are provided as a Source Data file.

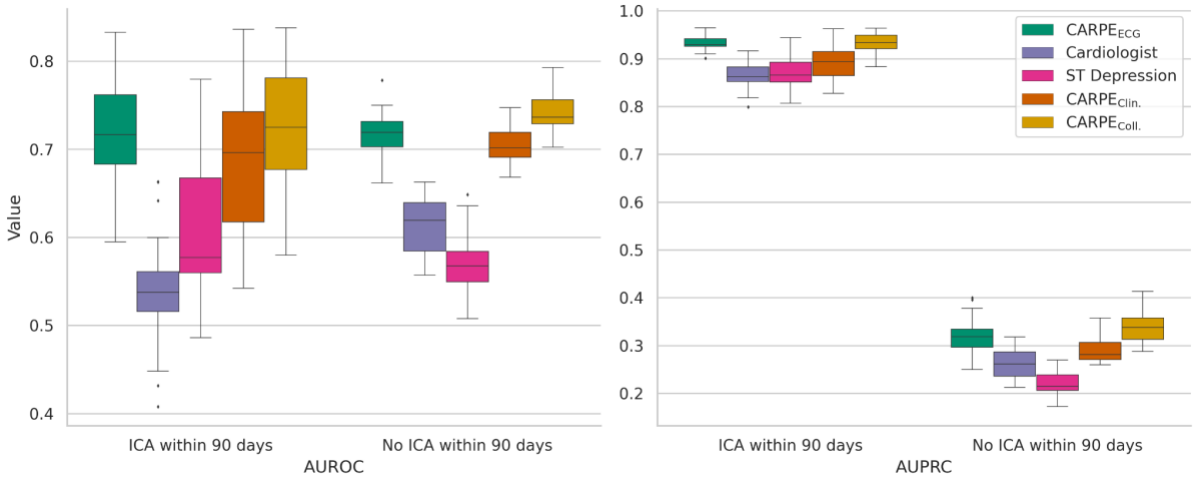
| Regularisation Strength | | Lead aVR | V1 | V6 |
|---|---|---|---|---|
| $\lambda_{MPSSRS}$ | 0.00 | 54.71 ± 1.73 | 52.47 ± 1.01 | 55.94 ± 1.26 |
| | 0.25 | 55.55 ±0.87 | 52.99 ± 0.45 | 56.57 ± 0.60 |
| | 0.50 | 55.59 ±0.86 | 52.93 ± 0.46 | 56.70 ± 0.50 |
| | 0.75 | 55.56 ±0.86 | 52.93 ± 0.48 | 56.81 ± 0.45 |
| | 1.00 | 55.26 ±1.07 | 52.85 ± 0.48 | 56.80 ± 0.47 |
| $\lambda_{MPSSSS}$ | 0.00 | 53.91 ±1.36 | 52.07 ± 1.01 | 55.86 ± 1.18 |
| | 0.25 | 55.56 ±0.88 | 53.03 ± 0.40 | 56.82 ± 0.53 |
| | 0.50 | 55.82 ±0.75 | 53.10 ± 0.39 | 56.90 ± 0.48 |
| | 0.75 | 55.71 ±0.77 | 53.04 ± 0.38 | 56.68 ± 0.48 |
| | 1.00 | 55.66 ±0.77 | 52.93 ± 0.40 | 56.54 ± 0.54 |
| $\lambda_{Stress}$ | 0.00 | 54.82 ±1.05 | 52.64 ±0.64 | 56.10 ± 0.76 |
| | 0.25 | 55.37 ±1.12 | 52.77 ±0.61 | 56.45 ± 0.73 |
| | 0.50 | 55.36 ±1.16 | 52.88 ± 0.63 | 56.70 ± 0.62 |
| | 0.75 | 55.54 ±1.17 | 52.89 ±0.62 | 56.74 ± 0.85 |
| | 1.00 | 55.57 ±1.23 | 52.98 ±0.67 | 56.82 ± 0.75 |
| None | | 51.21 ±0.17 | 50.73 ±0.58 | 53.80 ± 0.21 |
| Best | | | | 57.23 ± 0.68 |



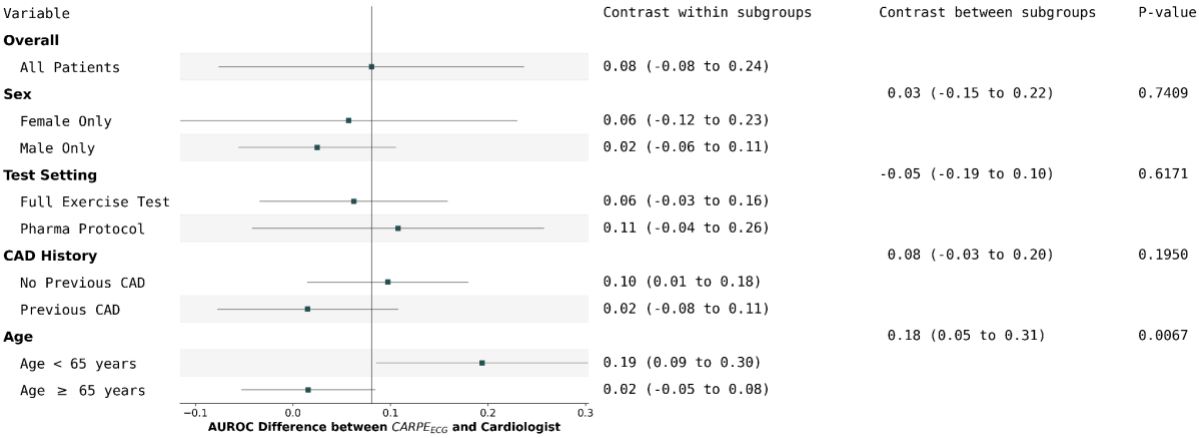

**Supplementary Figure 1** | **Overfitting Assessment:** Receiver operating characteristics curves of the treating physician's clinical assessment prediction (Cardiologist), CARPE$_{ECG}$, CARPE$_{Clin.}$, and ST depression in the training (right) and held-out test cohorts (left). Numbers in legend are area under the curve and their standard deviations. While there is a performance drop from training to test data in all approaches except for the ST depression approach, it is most prominent in CARPE$_{ECG}$.



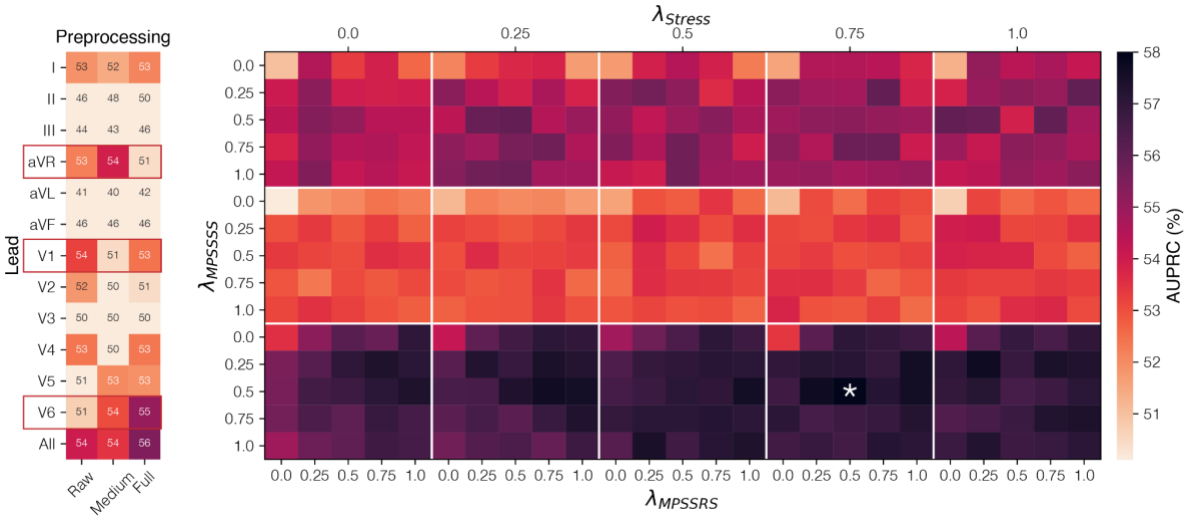

**Supplementary Figure 2** | Calibration plot of patients with and without ICA within 90 days of ECG stress test. Red dotted line marking decision thresholds at 5% and 15%. Source data are provided as a Source Data file.




**Supplementary Figure 3** | Predictive performance (AUROC and AUPRC) for patients with and without ICA. Source data are provided as a Source Data file.




**Supplementary Figure 4 |** Interaction analysis showing the statistical interaction of four subgroups. The "Age" variable is the only feature exhibiting a statistical effect. Rectangles show means; bars show the 95% confidence intervals. Source data are provided as a Source Data file. Source data are provided as a Source Data file.




**Supplementary Figure 5** | **Preprocessing and lead selection.** Performance heatmaps for lead, preprocessing, and regularisation parameter selection. Prevalence: 34%. Left: Best AUPRC among three learning rates per lead and preprocessing pipeline. The best three leads are highlighted with a red rectangle. Right: Results of the grid search to find the best regularisation parameters. Large rows (separated by white horizontal lines) represent the three best-performing leads (aVR, V1, and V6, respectively). Large columns (separated by white vertical lines) represent five settings for $\lambda_{Stress}$ (upper x-axis), small columns and rows respective regularisation values for $\lambda_{MPSSRS}$ and $\lambda_{MPSSSS}$. The best regularisation combination is marked with a white asterisk. Source data are provided as a Source Data file.

**Supplementary Table 6 | Diagnostic Performance Subcohort Analysis.** Performance analysis on different cohorts, i.e. (1) all patients, (2) patients that completed the stress test on the bicycle, (3) patients on a pharmacological protocol, (4) patients without CAD history, (5) patients with a history of CAD, (6/7) female/male patients, (8) patients younger than 65 years, and (9) patients that are 65 years or older. Prevalence values are provided as they represent the AUPRC a random classifier would reach. Asterisks indicate a statistically significant effect of the respective computational approach compared to the performance of the cardiologist. Diamonds indicate a statistically significant effect compared to $CARPE_{ECG}$.p-values are computed using a one-sided Kolmogorov-Smirnov test. Multiple hypotheses are corrected for using Bonferroni correction. Number of stars/diamonds signal strength of statistical effect: One symbol: p<0.05/correction factor, two symbols: p<0.01/correction factor, three symbols: p<0.001/correction factor. The correction factor equals the number of subgroups (ten) multiplied by the number of comparisons (three for the comparison with the cardiologist, one for the comparison with $CARPE_{ECG}$). Source data are provided as a Source Data file.

| Cohort | Method | AUROC ± STD | AUPRC ± STD |
|---|---|---|---|
| All Patients, (n=803) Prevalence: 28.3% | $CARPE_{ECG}$ | 0.71 ± 0.02*** , p=4.0e-13 | 0.46 ± 0.03* , p=9.6e-04 |
| | Cardiologist | 0.64 ± 0.02 | 0.42 ± 0.03 |
| | ST Depression (lead V4) | 0.58 ± 0.02, p=1.0 | 0.34 ± 0.02, p=1.0 |
| | $CARPE_{Clin.}$ | 0.70 ± 0.02***, p=1.6e-10 | 0.42 ± 0.02, p=5.33e-01 |
| | $CARPE_{Coll.}$ | **0.74 ± 0.03◊◊◊, p=7.9e-07** | **0.49 ± 0.03◊◊◊ , p=7.9e-07** |
| Full Exercise Testing, (n=482) Prevalence: 24.5% | $CARPE_{ECG}$ | 0.74 ± 0.03*** , p=7.9e-07 | 0.47 ± 0.03, p=0.00281 |
| | Cardiologist | 0.68 ± 0.03 | 0.42 ± 0.04 |
| | ST Depression (lead V4) | 0.58 ± 0.04, p=1.0 | 0.31 ± 0.03, p=1.0 |
| | $CARPE_{Clin.}$ | 0.73 ± 0.03** , p=8.1e-05 | 0.41 ± 0.04, p=0.7021 |
| | $CARPE_{Coll.}$ | **0.77 ± 0.03,** p=7.42e-03 | **0.52 ± 0.04◊◊◊**, p=4.2e-06 |
| Pharmacological Testing, (n=100) Prevalence: 33.0% | $CARPE_{ECG}$ | 0.69 ± 0.07** , p=8.1e-05 | 0.47 ± 0.01, p=0.0178 |
| | Cardiologist | 0.58 ± 0.07 | 0.40 ± 0.06 |
| | ST Depression (lead II) | 0.56 ± 0.07, p=0.9615 | 0.39 ± 0.06, p=0.8547 |
| | $CARPE_{Clin.}$ | 0.65 ± 0.07, p=0.0178 | 0.42 ± 0.06, p=0.1428 |
| | $CARPE_{Coll.}$ | **0.70 ± 0.07,** p=0.3728 | **0.50 ± 0.10,** p=0.1428 |
| No prior history of CAD, (n=446) Prevalence: 20.6% | $CARPE_{ECG}$ | 0.73 ± 0.03***, p=9.7e-12 | 0.38 ± 0.04***, p=4.2e-06 |
| | Cardiologist | 0.63 ± 0.04 | 0.33 ± 0.03 |
| | ST Depression (lead V4) | 0.52 ± 0.03, p=1.0 | 0.24 ± 0.03, p=1.0 |
| | $CARPE_{Clin.}$ | 0.73 ± 0.04***, p=9.7e-12 | 0.37 ± 0.05, p=0.0028 |
| | $CARPE_{Coll.}$ | **0.75 ± 0.04**, p=7.42e-03 | **0.44 ± 0.05◊◊**, p=8.1e-05 |
| | CADConsortium | 0.65 ± 0.03, p=7.78e-02 | 0.32 ± 0.04, p=0.8547 |
| | ESC2019 | 0.68 ± 0.04**, p=2.95e-04 | 0.32 ± 0.03, p=0.8547 |
| Prior history of CAD, (n=357) Prevalence: 37.8% | $CARPE_{ECG}$ | 0.64 ± 0.03, p=0.2405 | 0.51 ± 0.04, p=0.3728 |
| | Cardiologist | 0.63 ± 0.04 | 0.49 ± 0.04 |
| | ST Depression (lead V4) | 0.63 ± 0.04, p=0.7021 | 0.48 ± 0.04, p=0.8547 |
| | $CARPE_{Clin.}$ | 0.58 ± 0.03, p=1.0 | 0.44 ± 0.03, p=1.0 |
| | $CARPE_{Coll.}$ | **0.68 ± 0.03,** p=0.0178 | **0.53 ± 0.04,** p=0.0779 |
| Female Only, (n=272) Prevalence: 12.9% | $CARPE_{ECG}$ | **0.69 ± 0.06,** p=0.0028 | 0.26 ± 0.06, p=0.3728 |
| | Cardiologist | 0.63 ± 0.07 | 0.24 ± 0.06 |
| | ST Depression (lead V4) | 0.50 ± 0.04, p=1.0 | 0.13 ± 0.02, p=1.0 |
| | $CARPE_{Clin.}$ | 0.68 ± 0.07, p=0.0074 | 0.25 ± 0.07, p=0.5326 |
| | $CARPE_{Coll.}$ | **0.69 ± 0.06,** p=0.5326 | **0.29 ± 0.06,** p=0.2405 |
| Male Only, (n=531) Prevalence: 36.2% | $CARPE_{ECG}$ | 0.67 ± 0.03, p=0.0074 | 0.50 ± 0.04, p=0.1428 |
| | Cardiologist | 0.64 ± 0.03 | 0.49 ± 0.04 |
| | ST Depression | 0.57 ± 0.04, p=1.0 | 0.41 ± 0.03, p=1.0 |
| | $CARPE_{Clin.}$ | 0.60 ± 0.04, p=1.0 | 0.43 ± 0.03, p=1.0 |
| | $CARPE_{Coll.}$ | **0.69 ± 0.03,** p=0.0178 | **0.53 ± 0.04,** p=0.0390 |
| Age < 65 years, (n=292) Prevalence: 20.5% | $CARPE_{ECG}$ | 0.78 ± 0.04***, p=7.9e-15 | 0.45 ± 0.06***, p=9.7e-12 |
| | Cardiologist | 0.59 ± 0.05 | 0.30 ± 0.04 |
| | ST Depression | 0.59 ± 0.05, p=0.7021 | 0.28 ± 0.05, p=0.8547 |
| | $CARPE_{Clin.}$ | 0.74 ± 0.04***, p=4.0e-13 | 0.39 ± 0.05***, p=1.3e-07 |
| | $CARPE_{Coll.}$ | **0.79 ± 0.04,** p=0.2405 | **0.47 ± 0.05,** p=0.3728 |
| Age ≥ 65 years, (n=511) Prevalence: 32.7% | $CARPE_{ECG}$ | 0.66 ± 0.03, p=0.1428 | 0.46 ± 0.04, p=0.8547 |
| | Cardiologist | 0.65 ± 0.02 | 0.47 ± 0.03 |
| | ST Depression | 0.58 ± 0.02, p=1.0 | 0.40 ± 0.03, p=1.0 |
| | $CARPE_{Clin.}$ | 0.64 ± 0.03, p=0.8547 | 0.41 ± 0.03, p=1.0 |
| | $CARPE_{Coll.}$ | **0.69 ± 0.02◊◊◊**, p=8.1e-05 | **0.49 ± 0.04,** p=0.0178 |
| Age < 65 years and full exercise test, (n=214) Prevalence: 16.8% | $CARPE_{ECG}$ | 0.78 ± 0.04***, p=9.7e-12 | 0.40 ± 0.06***, p=7.9e-07 |
| | Cardiologist | 0.62 ± 0.06 | 0.27 ± 0.06 |
| | ST Depression | 0.66 ± 0.06, p=7.79e-02 | 0.28 ± 0.06, p=0.0241 |
| | **$CARPE_{Clin.}$** | 0.76 ± 0.04***, p=1.6e-10 | 0.33 ± 0.05**, p=3.0e-04 |
| | $CARPE_{Coll.}$ | **0.79 ± 0.04**, p=0.1428 | **0.43 ± 0.07**, p=0.2405 |

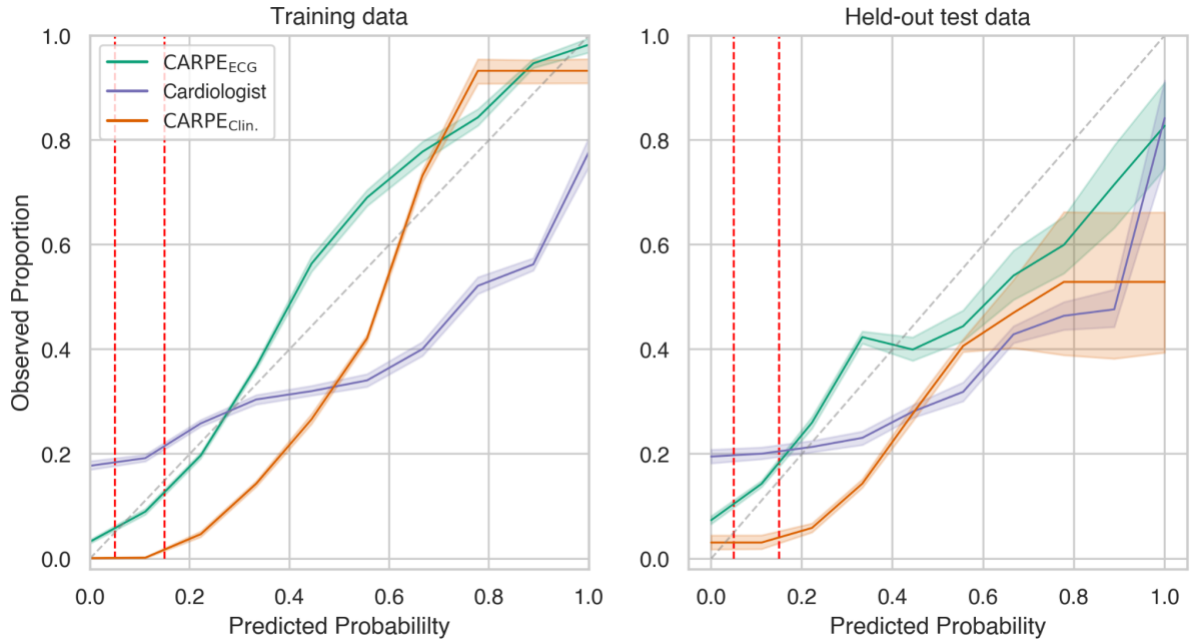
**Supplementary Table 7 | Diagnostic Performance on External Validation.** Area under receiver operator characteristic and precision recall curve on the internal (held-out) data set and the external validation set. Values in parentheses are computed on an upsampled data set to match the prevalence of the internal validation of 24.5% such that AUPRC values are comparable. Source data are provided as a Source Data file.

| | Internal Validation (exercise stress only) fCAD prevalence: 24.5% | | External Validation fCAD prevalence: 7.5% | |
|---|---|---|---|---|
| | AUPRC ± STD | AUROC ± STD | AUPRC ± STD | AUROC ± STD |
| $CARPE_{Clin.}$ | 0.41 ± 0.04 | 0.73 ± 0.03 | 0.19 ± 0.01<br>(0.47 ± 0.03) | 0.75 ± 0.004<br>(0.75 ± 0.02) |
| **$CARPE_{ECG}$** | **0.47 ± 0.03** | **0.74 ± 0.03** | **0.28 ± 0.02**<br>**(0.58 ± 0.03)** | **0.80 ± 0.01**<br>**(0.80 ± 0.01)** |

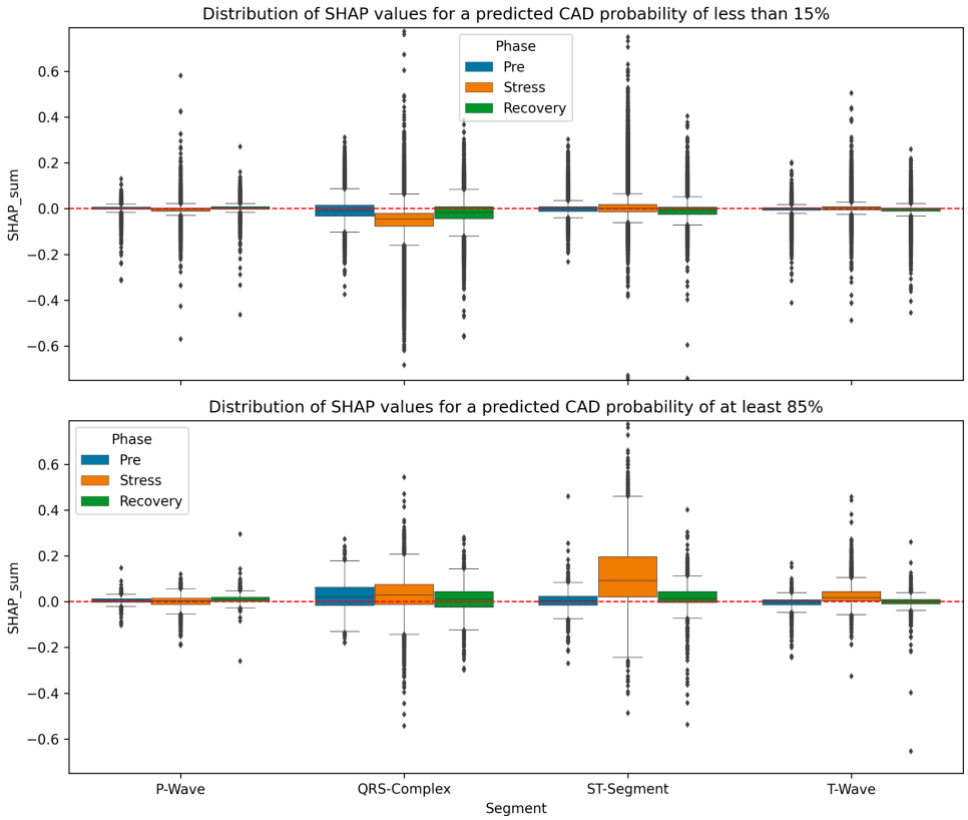
**Supplementary Table 8 | Additional Performance Metrics.** Positive predictive value (PPV), specificity, F1 score, and accuracy score at the three decision thresholds recommended in international guidelines for different subcohorts. The score distribution may lead to results with zero standard deviation. Highest mean values are highlighted in bold. Source data are provided as a Source Data file.

| | Method | PPV ± STD | Specificity ± STD | F1 Score ± STD | Accuracy ± STD |
|---|---|---|---|---|---|
| **Threshold <5% for rule-out** | | | | | |
| All patients (n=803) Prevalence: 28.3% | $CARPE_{Coll.}$ | 0.29 ± 0.003 | 0.07 ± 0.012 | 0.45 ± 0.004 | 0.33 ± 0.009 |
| | $CARPE_{ECG}$ | **0.31 ± 0.005** | **0.14 ± 0.020** | **0.47 ± 0.006** | **0.38 ± 0.014** |
| | $CARPE_{Clin.}$ | 0.28 ± 0.000 | 0.00 ± 0.000 | 0.44 ± 0.000 | 0.28 ± 0.000 |
| | Cardiologist | 0.29 ± 0.003 | 0.05 ± 0.011 | 0.45 ± 0.004 | 0.32 ± 0.008 |
| No prior CAD (n=446) Prevalence: 20.6% | $CARPE_{Coll.}$ | 0.22 ± 0.005 | 0.11 ± 0.017 | 0.36 ± 0.007 | 0.29 ± 0.015 |
| | $CARPE_{ECG}$ | **0.24 ± 0.007** | **0.21 ± 0.025** | **0.38 ± 0.011** | **0.37 ± 0.021** |
| | $CARPE_{Clin.}$ | 0.21 ± 0.000 | 0.00 ± 0.000 | 0.34 ± 0.000 | 0.21 ± 0.000 |
| | Cardiologist | 0.21 ± 0.003 | 0.05 ± 0.013 | 0.34 ± 0.005 | 0.24 ± 0.010 |
| Prior CAD (n=357) Prevalence: 37.8% | $CARPE_{Coll.}$ | 0.38 ± 0.000 | 0.00 ± 0.000 | 0.55 ± 0.000 | 0.38 ± 0.000 |
| | $CARPE_{ECG}$ | 0.38 ± 0.001 | 0.002 ± 0.003 | 0.55 ± 0.001 | 0.38 ± 0.002 |
| | $CARPE_{Clin.}$ | 0.38 ± 0.000 | 0.00 ± 0.000 | 0.55 ± 0.000 | 0.38 ± 0.000 |
| | Cardiologist | **0.38 ± 0.005** | **0.05 ± 0.018** | **0.55 ± 0.006** | **0.40 ± 0.011** |
| Female Only, (n=272) Prevalence: 12.9% | $CARPE_{Coll.}$ | 0.13 ± 0.008 | 0.14 ± 0.025 | 0.23 ± 0.013 | 0.24 ± 0.023 |
| | $CARPE_{ECG}$ | **0.15 ± 0.009** | **0.24 ± 0.031** | **0.26 ± 0.015** | **0.33 ± 0.030** |
| | $CARPE_{Clin.}$ | 0.12 ± 0.000 | 0.00 ± 0.000 | 0.22 ± 0.000 | 0.12 ± 0.000 |
| | Cardiologist | 0.12 ± 0.006 | 0.03 ± 0.012 | 0.21 ± 0.010 | 0.14 ± 0.001 |
| Male Only, (n=531) Prevalence: 36.2% | $CARPE_{Coll.}$ | 0.36 ± 0.001 | 0.01 ± 0.006 | 0.53 ± 0.001 | 0.37 ± 0.004 |
| | $CARPE_{ECG}$ | **0.37 ± 0.004** | 0.05 ± 0.011 | **0.54 ± 0.005** | 0.39 ± 0.008 |
| | $CARPE_{Clin.}$ | 0.36 ± 0.000 | 0.00 ± 0.000 | 0.53 ± 0.000 | 0.36 ± 0.000 |
| | Cardiologist | **0.37 ± 0.004** | **0.07 ± 0.015** | **0.54 ± 0.005** | **0.40 ± 0.010** |
| Age < 65 years, (n=292) Prevalence: 20.5% | $CARPE_{Coll.}$ | 0.22 ± 0.006 | 0.10 ± 0.029 | 0.36 ± 0.008 | 0.28 ± 0.023 |
| | $CARPE_{ECG}$ | **0.24 ± 0.009** | **0.21 ± 0.033** | **0.39 ± 0.013** | **0.37 ± 0.028** |
| | $CARPE_{Clin.}$ | 0.20 ± 0.001 | 0.00 ± 0.000 | 0.34 ± 0.000 | 0.20 ± 0.002 |
| | Cardiologist | 0.21 ± 0.004 | 0.06 ± 0.012 | 0.34 ± 0.007 | 0.25 ± 0.011 |
| Age < 65 years and full exercise test, (n=214) Prevalence: 16.8% | $CARPE_{Coll.}$ | 0.18 ± 0.005 | 0.13 ± 0.030 | 0.31 ± 0.008 | 0.28 ± 0.025 |
| | $CARPE_{ECG}$ | **0.21 ± 0.011** | **0.26 ± 0.040** | **0.34 ± 0.017** | **0.38 ± 0.035** |
| | $CARPE_{Clin.}$ | 0.16 ± 0.000 | 0.00 ± 0.000 | 0.28 ± 0.000 | 0.16 ± 0.000 |
| | Cardiologist | 0.17 ± 0.006 | 0.09 ± 0.020 | 0.30 ± 0.009 | 0.23 ± 0.018 |
| **Threshold <10% for rule-out** | | | | | |
| All patients (n=803) Prevalence: 28.3% | $CARPE_{Coll.}$ | **0.34 ± 0.006** | 0.27 ± 0.020 | **0.50 ± 0.007** | 0.46 ± 0.014 |
| | $CARPE_{ECG}$ | **0.34 ± 0.006** | **0.28 ± 0.017** | 0.50 ± 0.008 | **0.46 ± 0.013** |
| | $CARPE_{Clin.}$ | 0.28 ± 0.000 | 0.00 ± 0.000 | 0.44 ± 0.000 | 0.28 ± 0.000 |
| | Cardiologist | 0.29 ± 0.003 | 0.07 ± 0.011 | 0.45 ± 0.004 | 0.32 ± 0.008 |
| No prior CAD (n=446) Prevalence: 20.6% | $CARPE_{Coll.}$ | **0.29 ± 0.012** | 0.42 ± 0.026 | **0.43 ± 0.017** | 0.52 ± 0.022 |
| | $CARPE_{ECG}$ | **0.29 ± 0.015** | **0.44 ± 0.030** | **0.43 ± 0.021** | **0.53 ± 0.026** |
| | $CARPE_{Clin.}$ | 0.21 ± 0.000 | 0.00 ± 0.000 | 0.34 ± 0.000 | 0.21 ± 0.000 |
| | Cardiologist | 0.21 ± 0.004 | 0.07 ± 0.015 | 0.34 ± 0.007 | 0.25 ± 0.012 |
| Prior CAD (n=357) Prevalence: 37.8% | $CARPE_{Coll.}$ | 0.38 ± 0.002 | 0.01 ± 0.009 | 0.55 ± 0.002 | 0.38 ± 0.005 |
| | $CARPE_{ECG}$ | 0.38 ± 0.003 | 0.02 ± 0.010 | 0.55 ± 0.004 | 0.38 ± 0.007 |
| | $CARPE_{Clin.}$ | 0.38 ± 0.000 | 0.00 ± 0.000 | 0.55 ± 0.000 | 0.38 ± 0.000 |
| | Cardiologist | **0.39 ± 0.005** | **0.07 ± 0.018** | **0.55 ± 0.007** | **0.41 ± 0.012** |
| Female Only, (n=272) | $CARPE_{Coll.}$ | **0.18 ± 0.019** | **0.48 ± 0.034** | **0.29 ± 0.031** | **0.52 ± 0.033** |
| | $CARPE_{ECG}$ | **0.18 ± 0.02** | 0.46 ± 0.036 | **0.29 ± 0.032** | 0.50 ± 0.036 |
| | $CARPE_{Clin.}$ | 0.12 ± 0.000 | 0.00 ± 0.000 | 0.22 ± 0.000 | 0.12 ± 0.000 |

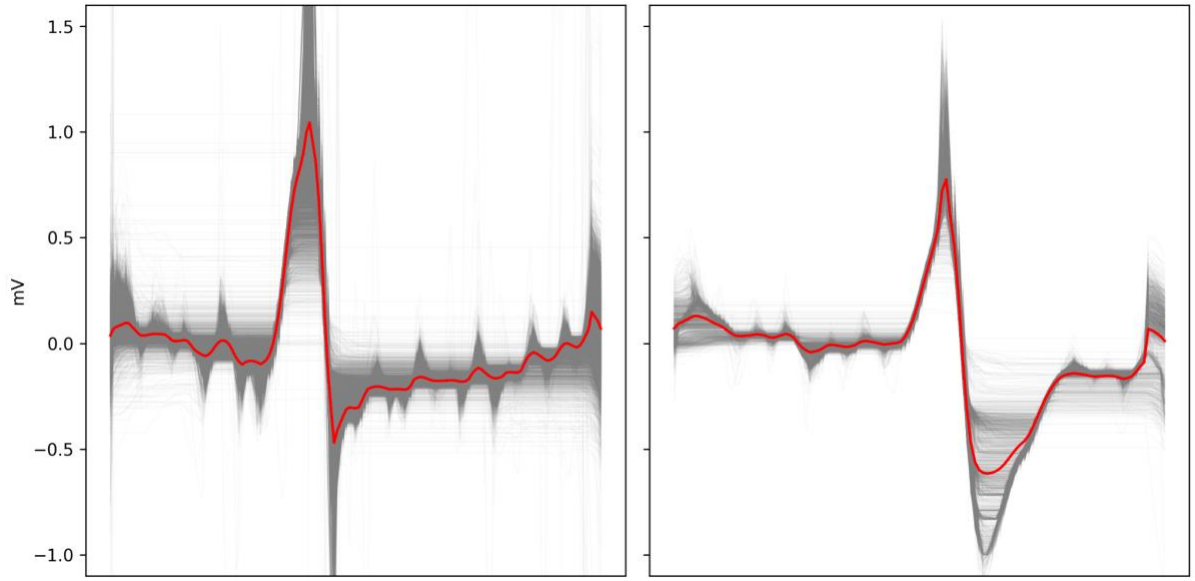
| | | | | | |
|---|---|---|---|---|---|
| Prevalence: 12.9% | Cardiologist | 0.12 ± 0.006 | 0.03 ± 0.012 | 0.21 ± 0.010 | 0.14 ± 0.010 |
| Male Only, (n=531) Prevalence: 36.2% | $CARPE_{Coll.}$ | 0.38 ± 0.006 | 0.11 ± 0.017 | 0.55 ± 0.007 | 0.42 ± 0.012 |
| | $CARPE_{ECG}$ | **0.39 ± 0.007** | **0.14 ± 0.018** | **0.56 ± 0.009** | **0.44 ± 0.014** |
| | $CARPE_{Clin.}$ | 0.36 ± 0.000 | 0.00 ± 0.000 | 0.53 ± 0.000 | 0.36 ± 0.000 |
| | Cardiologist | 0.38 ± 0.005 | 0.08 ± 0.017 | 0.54 ± 0.006 | 0.40 ± 0.012 |
| Age < 65 years, (n=292) Prevalence: 20.5% | $CARPE_{Coll.}$ | 0.27 ± 0.011 | 0.36 ± 0.035 | 0.43 ± 0.014 | 0.48 ± 0.027 |
| | $CARPE_{ECG}$ | **0.28 ± 0.011** | **0.37 ± 0.035** | **0.43 ± 0.014** | **0.49 ± 0.027** |
| | $CARPE_{Clin.}$ | 0.20 ± 0.000 | 0.00 ± 0.000 | 0.34 ± 0.000 | 0.20 ± 0.002 |
| | Cardiologist | 0.21 ± 0.005 | 0.08 ± 0.014 | 0.34 ± 0.008 | 0.25 ± 0.011 |
| Age < 65 years and full exercise test, (n=214) Prevalence: 16.8% | $CARPE_{Coll.}$ | 0.24 ± 0.019 | 0.43 ± 0.048 | 0.39 ± 0.027 | 0.51 ± 0.043 |
| | $CARPE_{ECG}$ | **0.26 ± 0.020** | **0.47 ± 0.043** | **0.40 ± 0.028** | **0.55 ± 0.038** |
| | $CARPE_{Clin.}$ | 0.16 ± 0.000 | 0.00 ± 0.000 | 0.28 ± 0.000 | 0.16 ± 0.00 |
| | Cardiologist | 0.18 ± 0.006 | 0.11 ± 0.025 | 0.30 ± 0.009 | 0.25 ± 0.021 |
| **Threshold <15% for rule-out** | | | | | |
| All patients (n=803) Prevalence: 28.3% | $CARPE_{Coll.}$ | **0.37 ± 0.007** | 0.41 ± 0.021 | **0.53 ± 0.009** | **0.55 ± 0.013** |
| | $CARPE_{ECG}$ | 0.37 ± 0.008 | **0.39 ± 0.020** | 0.52 ± 0.009 | 0.53 ± 0.013 |
| | $CARPE_{Clin.}$ | 0.28 ± 0.001 | 0.01 ± 0.004 | 0.44 ± 0.001 | 0.29 ± 0.003 |
| | Cardiologist | 0.31 ± 0.008 | 0.25 ± 0.015 | 0.46 ± 0.012 | 0.42 ± 0.014 |
| No prior CAD (n=446) Prevalence: 20.6% | $CARPE_{Coll.}$ | **0.34 ± 0.024** | **0.63 ± 0.026** | **0.47 ± 0.035** | **0.65 ± 0.023** |
| | $CARPE_{ECG}$ | 0.32 ± 0.023 | 0.59 ± 0.025 | 0.45 ± 0.033 | 0.62 ± 0.024 |
| | $CARPE_{Clin.}$ | 0.21 ± 0.001 | 0.12 ± 0.007 | 0.34 ± 0.002 | 0.22 ± 0.005 |
| | Cardiologist | 0.23 ± 0.010 | 0.27 ± 0.024 | 0.36 ± 0.015 | 0.39 ± 0.018 |
| Prior CAD (n=357) Prevalence: 37.8% | $CARPE_{Coll.}$ | 0.39 ± 0.006 | 0.06 ± 0.018 | **0.56 ± 0.007** | 0.41 ± 0.013 |
| | $CARPE_{ECG}$ | 0.39 ± 0.006 | 0.15 ± 0.062 | **0.56 ± 0.007** | 0.41 ± 0.014 |
| | $CARPE_{Clin.}$ | 0.38 ± 0.000 | 0.00 ± 0.000 | 0.55 ± 0.000 | 0.38 ± 0.000 |
| | Cardiologist | **0.40 ± 0.013** | **0.23 ± 0.030** | 0.55 ± 0.017 | **0.47 ± 0.023** |
| Female Only, (n=272) Prevalence: 12.9% | $CARPE_{Coll.}$ | **0.21 ± 0.040** | **0.69 ± 0.043** | **0.30 ± 0.056** | **0.67 ± 0.044** |
| | $CARPE_{ECG}$ | 0.19 ± 0.029 | 0.60 ± 0.039 | 0.29 ± 0.044 | 0.60 ± 0.040 |
| | $CARPE_{Clin.}$ | 0.13 ± 0.001 | 0.02 ± 0.012 | 0.23 ± 0.002 | 0.14 ± 0.011 |
| | Cardiologist | 0.14 ± 0.014 | 0.26 ± 0.038 | 0.23 ± 0.024 | 0.33 ± 0.035 |
| Male Only, (n=531) Prevalence: 36.2% | $CARPE_{Coll.}$ | 0.40 ± 0.007 | 0.21 ± 0.022 | **0.57 ± 0.009** | 0.48 ± 0.014 |
| | $CARPE_{ECG}$ | **0.41 ± 0.009** | **0.24 ± 0.019** | **0.57 ± 0.012** | **0.49 ± 0.016** |
| | $CARPE_{Clin.}$ | 0.36 ± 0.000 | 0.00 ± 0.000 | 0.53 ± 0.000 | 0.36 ± 0.000 |
| | Cardiologist | 0.39 ± 0.009 | 0.24 ± 0.020 | 0.54 ± 0.012 | 0.47 ± 0.015 |
| Age < 65 years, (n=292) Prevalence: 20.5% | $CARPE_{Coll.}$ | 0.31 ± 0.022 | **0.50 ± 0.038** | 0.45 ± 0.029 | 0.58 ± 0.032 |
| | $CARPE_{ECG}$ | **0.31 ± 0.018** | 0.49 ± 0.039 | **0.47 ± 0.022** | **0.58 ± 0.029** |
| | $CARPE_{Clin.}$ | 0.20 ± 0.001 | 0.02 ± 0.006 | 0.34 ± 0.001 | 0.21 ± 0.005 |
| | Cardiologist | 0.23 ± 0.018 | 0.30 ± 0.033 | 0.36 ± 0.028 | 0.41 ± 0.033 |
| Age < 65 years and full exercise test, (n=214) Prevalence: 16.8% | $CARPE_{Coll.}$ | 0.28 ± 0.034 | **0.60 ± 0.044** | 0.42 ± 0.047 | 0.63 ± 0.043 |
| | $CARPE_{ECG}$ | **0.30 ± 0.029** | 0.59 ± 0.045 | **0.44 ± 0.038** | **0.64 ± 0.040** |
| | $CARPE_{Clin.}$ | 0.17 ± 0.001 | 0.02 ± 0.020 | 0.29 ± 0.002 | 0.18 ± 0.009 |
| | Cardiologist | 0.21 ± 0.013 | 0.35 ± 0.034 | 0.34 ± 0.021 | 0.44 ± 0.030 |



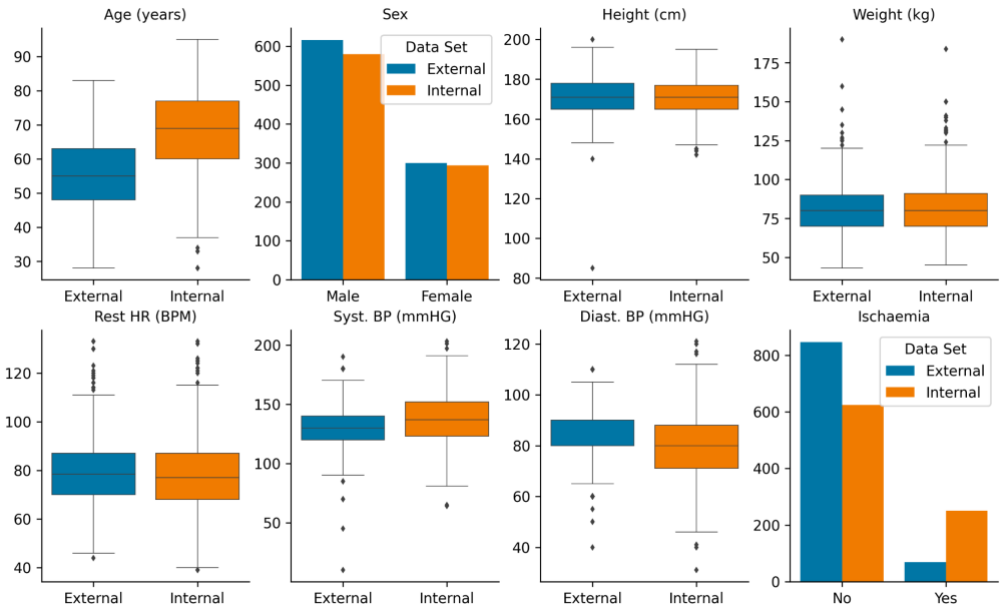

**Supplementary Figure 6** | **Calibration Plot.** Calibration behaviour of CARPE$_{ECG}$, Cardiologist, and CARPE$_{Clin.}$ on both training and held-out test set. A perfectly calibrated classifier is shown in grey. Envelopes show 95% confidence intervals. Advocated decision thresholds are shown as dashed red vertical lines. Source data are provided as a Source Data file.




**Supplementary Figure 7** | **SHAP Analysis of EKG Segments.** Aggregated SHAP values stratified by stress phase and segment in populations of low (upper plot) and high (lower plot) predicted CAD risk. Deviations from zero indicate higher contributions to the predicted risk score. On average, ST-segments from the stress phase are most relevant for higher risk scores, and QRS complexes from the stress phase for the prediction of lower scores. Source data are provided as a Source Data file.




**Supplementary Figure 8** | **SHAP Analysis of ECG Segments.** ECG waves whose QRS-complexes contribute to the prediction of absence of CAD (left) and whose ST-Segments contribute to the prediction of the presence of CAD (right). All extracted ECG waves are aligned using dynamic time warping and are shown in gray. The average wave is shown in red. There is slowed ventricular activation and distinct ST-segment depression in the mean wave associated with high SHAP values (right) as compared to patients for which a low CAD-risk was predicted (left).

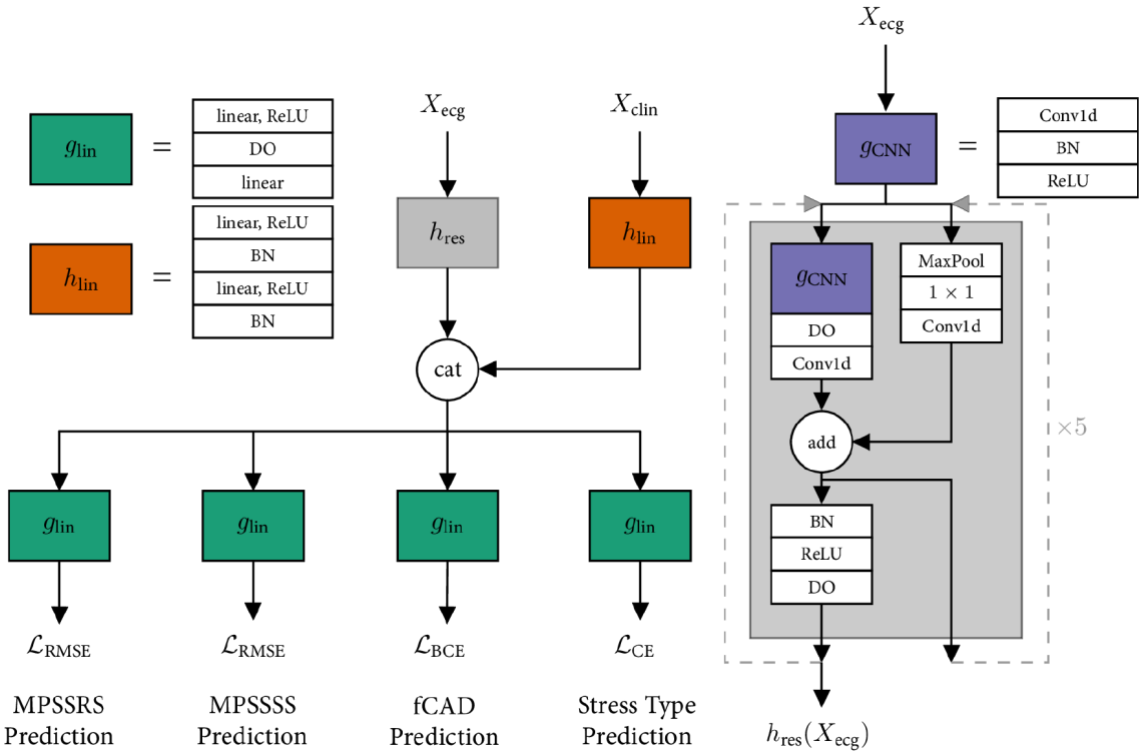



**Supplementary Figure 9** | **Variable Distributions.** Comparing relevant clinical variables from the internal with the external data set. While most variables follow a similar distribution in both data sets, the ages of both study populations differ significantly. In addition, the prevalence of CAD in the external data set is significantly lower than in our internal data set. The bottom and top edges of the boxplots correspond to the 25th (Q1) and the 75th (Q3) percentile, respectively. The horizontal line in the center is the median value. Whiskers capture data in the 1.5x interquartile ranges beyond and below Q1 and Q3. Outliers are visualized as diamonds.

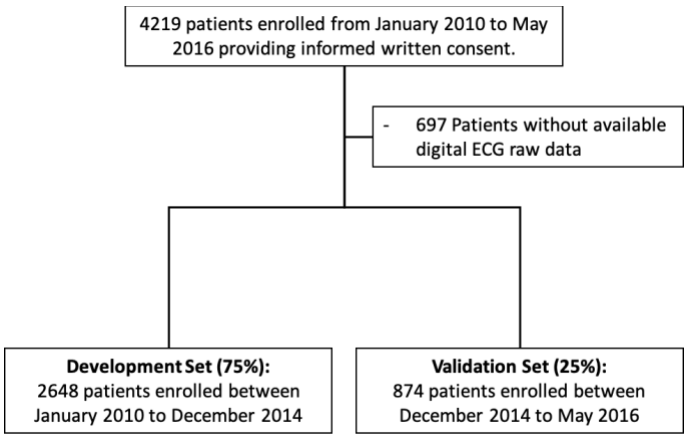
**Supplementary Table 9 |** Demographic and clinical characteristics of patients in development and held-out test set. Source data are provided as a Source Data file.

| **Characteristic** | Development set (n=2648) | Held-out test set (n=874) |
|---|---|---|
| Median age (SD), years | 66.7 (11.1) | 68.2 (11.4) |
| Female, % (n) | 849 (32) | 294 (34) |
| Median body mass index [IQR], kg/m2 | 27.3 [24.5, 30.8] | 27.2 [24.2, 30.4] |
| Ever smoking, % (n) | 1588 (60) | 554 (63) |
| Hypertension, % (n) | 2166 (82) | 694 (79) |
| Dyslipidemia, % (n) | 1902 (72) | 633 (72) |
| Diabetes, % (n) | 684 (26) | 205 (23) |
| Heart failure, % (n) | 75 (3) | 19 (2) |
| Atrial Fibrillation, % (n) | 388 (15) | 144 (16) |
| Pacemaker, % (n) | 149 (6) | 59 (7) |
| **CAD history, % (n)** | 1264 (48) | 393 (45) |
| Prior myocardial infarction, % (n) | 782 (30) | 235 (27) |
| Coronary artery bypass grafting, % (n) | 354 (13) | 126 (14) |
| PCI, % (n) | 973 (37) | 300 (34) |
| **Medications** | | |
| ACE inhibitor, % (n) | 837 (32) | 267 (31) |
| Angiotensin-receptor antagonists, % (n) | 838 (32) | 280 (32) |
| Aspirin, % (n) | 1643 (62) | 515 (59) |
| β-Blocker, % (n) | 1507 (57) | 450 (51) |
| Calcium antagonist, % (n) | 611 (23) | 187 (21) |
| Statins, % (n) | 1558 (59) | 520 (59) |
| Nitroglycerine, % (n) | 280 (11) | 62 (7) |
| **Stress testing** | | |
| Pure exercise stress testing, % (n) | 1417 (54) | 517 (59) |
| Pre stress testing VAS [IQR], % | 40.0 [30.0, 60.0] | 35.0 [20.0, 50.0] |
| Post stress testing VAS [IQR], % | 40.0 [20.0, 70.0] | 30.0 [20.0, 60.0] |
| Resting heart rate (SD), bpm | 75.6 (15.0) | 78.3 (14.4) |
| Resting systolic blood pressure (SD), mmHg | 133.8 (22.6) | 137.4 (20.5) |
| Resting diastolic blood pressure (SD), mmHg | 80.4 (13.6) | 79.7 (12.6) |
| **Functionally relevant CAD, % (n)** | 909 (34) | 250 (29) |

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; IQR - interquartile range; PCI = percutaneous coronary intervention.




**Supplementary Figure 10** | **Neural Network Architecture.** Left: Composition of our multi-task architecture. Each task obtains its own loss function *L*. RMSE: Root Mean Squared Error, BCE: Binary Cross Entropy, CE: Cross Entropy. Linear blocks are composed of linear (feedforward) layers with Rectified Linear Units (ReLU) as activation function, dropout (DO), and batch normalisation (BN). Right: Residual neural network $\mathbf{h}_{res}$ with ECG signal $\boldsymbol{X}_{ecg}$ as input. cat denotes the concatenation of the embeddings of the ECG signal $\mathbf{X}_{ecg}$ and the clinical data $\mathbf{X}_{clin}$. DO: Dropout, BN: Batch normalisation. Conv1d: 1-dimensional convolutional neural network layer.




**Supplementary Figure 11** | **Data Split.** After excluding all patients without available digital ECG raw data, a temporal split was performed.

**Supplementary Table 10** | Parameter grid for ST-segment depression baseline. Source data are provided as a Source Data file.

| Parameter | Values |
|---|---|
| Difference computation | {ST_Stress - ST_Pre, ST_Rec - ST_Pre} |
| Difference aggregation | {mean, median, min, max} |
| I_PR | {20ms, 40ms, 100ms} |