Real-world evaluation of an algorithmic machine learning-guided testing approach in stable chest pain: A multinational, multicohort study

Supplemental material

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Supplemental Methods

Clinical Definitions

Clinical Features: In the Yale-New Haven Health system Electronic Health Record (EHR) and UK Biobank (UKB) analyses, we extracted the patient's demographic profile, vital signs, all prescribed medications, laboratory measurements, comorbidities as defined by ICD (International Classification of Diseases)-9 and ICD-10 codes (see **Table S1**), only including information recorded before or on the day of the cardiac test, and ultimately selecting the entry that was closest to the index test. In the PROMISE cohort we included features recorded prior to randomization, as per our prior work (1).

Cardiac Testing: We defined cardiac testing modalities using Current Procedural Terminology (CPT) codes, or relevant fields, as provided in each unique dataset. More specifically:

> **Yale health system cohort:** We defined cardiac testing using the following CPT codes: 75573, 78430, 78431, 78434, 78491, 78492, 75563, 78451, 78452, 78453, 78454, 75572, 75574, 93015, 93016, 93017, 93018, 93350, 93351, 93352; the corresponding codes and entries when then reviewed to ensure that the test reflected a stress test or CCTA performed for coronary anatomy assessment.
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> **UK biobank:** We defined this based on the field #41272, corresponding to hospital/inpatient procedures, including the following codes: U205 (stress echocardiogram), U194 (exercise treadmill test), U102 (CCTA), U106 (myocardial perfusion imaging).

Clinical Outcomes: The primary clinical outcome was the time-to-acute myocardial infarction or death. Acknowledging that non-invasive testing may occasionally be performed in the setting of an acute coronary syndrome work-up, we excluded patients with AMI (acute myocardial infarction) events recorded within 7 days of the index test. In the Yale registry, mortality information was extracted by linking the EHR to the Connecticut death index, whereas AMI was defined as the first appearance of a primary ICD-9 or ICD-10 code during a visit in the emergency department or inpatient admission following the date of the index test (see **Table S1**). In the UK Biobank, data on death or myocardial infarction were directly extracted from pre-processed fields (fields 40000 & 42000, respectively). Cardiovascular mortality was defined based on the primary cause of death by search for ICD codes corresponding to diseases of the circulatory system (I00-I99).

Supplemental Statistical Methods

Propensity score adjustment: Propensity score matching for referral to anatomical versus functional testing was performed by following appropriate statistical and reporting practices (2,3). Within each cohort (Yale health system and UK Biobank), we calculated a propensity score (probability) for undergoing anatomical vs functional-first testing by fitting a multivariable logistic regression model adjusted for all ASSIST components (age at the time of the test, sex, body mass index, history of hypertension, diabetes mellitus, smoking status, antiplatelet, statin or beta-blocker use, total cholesterol and high-density lipoprotein levels) as well as race and ethnic background, ischaemic heart disease history and chronic kidney disease. In accordance with best

practices, all predictors (independent variables) represented baseline features which were available at the time of clinical decision-making. To ensure the inclusion of all observations in our analysis, we chose to include the propensity score for anatomical testing (logistic regression-derived probability of being referred for anatomical vs functional testing) as a covariate in further analyses, such as when exploring the association between undergoing the ASSIST-recommended testing strategy and downstream events in multivariable Cox regression models. This is based on prior work in this space showing that covariate adjustment for propensity score avoids the reduction in observations and precision seen with matching or the undue influence of a small number of observations with inverse probability weighting (3).

Supplemental Tables

Table S1 | Examples of comorbidity definitions based on ICD-9 and ICD-10 codes:

Diagnosis	ICD codes
Hypertension	'I10', 'I11', 'I110', 'I119', 'I12', 'I120', 'I129', 'I13', 'I130', 'I131', 'I132', 'I139', 'I674', 'O10', 'O100', 'O101', 'O102', 'O103', 'O109', 'O11', '401', '4010', '4011', '4019', '402', '4020', '4021', '4029', '403', '4030', '4031', '4039', '404', '4040', '4041', '4049', '6420', '6422', '6427', '6429'
Diabetes mellitus	'E10', 'E100', 'E101', 'E102', 'E103', 'E104', 'E105', 'E106', 'E107', 'E108', 'E109', 'E11', 'E110', 'E111', 'E112', 'E113', 'E114', 'E115', 'E116', 'E117', 'E118', 'E119', 'E12', 'E120', 'E121', 'E122', 'E123', 'E124', 'E125', 'E126', 'E127', 'E128', 'E129', 'E13', 'E130', 'E131', 'E132', 'E133', 'E134', 'E135', 'E136', 'E137', 'E138', 'E139', 'E14', 'E140', 'E141', 'E142', 'E143', 'E144', 'E145', 'E146', 'E147', 'E148', 'E149', 'O240', 'O241', 'O242', 'O243', 'O249', '250', '2500', '25000', '25001', '25009', '2501', '25010', '25011', '25019', '2502', '25020', '25021', '25029', '2503', '2504', '2505', '2506', '2507', '2509', '25090', '25091', '25099', '6480'
Chronic kidney disease	'I12', 'I120', 'I13', 'I130', 'I131', 'I132', 'I139', 'N18', 'N180', 'N181', 'N182', 'N183', 'N184', 'N185', 'N188', 'N189', 'Z49', 'Z490', 'Z491', 'Z492', '403', '4030', '4031', '4039', '404', '4040', '4041', '4049', '585', '5859', '6421', '6462'
Heart failure	'I110', 'I130', 'I132', 'I50', 'I500', 'I501', 'I509', '428','4280','4281','4289'
Acute myocardial infarction	'I21', 'I22', 'I23', 'I240', 'I248', 'I249', '410', '4110', '4111', '4118'
Ischaemic heart disease	'I20', 'I200', 'I208', 'I209', 'I21', 'I210', 'I211', 'I212', 'I213', 'I214', 'I219', 'I21X', 'I22', 'I220', 'I221', 'I228', 'I229', 'I23', 'I230', 'I231', 'I232', 'I233', 'I234', 'I235', 'I236', 'I238', 'I24', 'I240', 'I241', 'I248', 'I249', 'I25', 'I250', 'I251', 'I252', 'I255', 'I256', 'I258', 'I259', 'Z951', 'Z955', '410', '4109', '411', '4119', '412', '4129', '413', '4139', '414', '4140', '4148', '4149'
Peripheral arterial disease	'I702', 'I7020', 'I7021', 'I742', 'I743', 'I744', '4402', '4442'
Stroke	'G45', 'G450', 'G451', 'G452', 'G453', 'G454', 'G458', 'G459', 'I63', 'I630', 'I631', 'I632', 'I633', 'I634', 'I635', 'I638', 'I639', 'I64', 'I65', 'I650', 'I651', 'I652', 'I653', 'I658', 'I659', 'I66', 'I660', 'I661', 'I662', 'I663', 'I664', 'I668', 'I669', 'I672', 'I693', 'I694', '433', '4330', '4331', '4332', '4333', '4338', '4339', '434', '4340', '4341', '4349', '435', '4359', '437', '4370', '4371'

Table S2 | Effect of multivariable and propensity score adjustment on the association between ASSIST-aligned testing and all-cause mortality or acute myocardial infarction.

	Yale health system (HR [95% CI])	UK Biobank (HR [95% CI])
Unadjusted model	0.57 [0.55-0.60], p<0.001	0.59 [0.49-0.71], p<0.001
Multivariable model without propensity score	0.83 [0.79-0.87], p<0.001	0.70 [0.58-0.86], p<0.001
Multivariable model with propensity score adjustment	0.81 [0.77-0.85], p<0.001	0.74 [0.60-0.90], p=0.003

CI: confidence interval; HR: hazard ratio.

Table S3 | Table of characteristics for the PROMISE sub-cohort.

	PROMISE trial
n	4734
Age (years)	59.0 [54.0, 65.0]
Female sex	2426 (51.2)
Hispanic ethnicity	363 (7.7)
Race	
Multi-racial	59 (1.2)
White	3988 (84.2)
Black	502 (10.6)
Asian	138 (2.9)
Indian	36 (0.8)
Hawaiian	11 (0.2)
Hypertension	3064 (64.7)
Diabetes	996 (21.0)
CAD equivalent	1166 (24.6)
Stroke/TIA	164 (3.5)
PAD	81 (1.7)
GFR (mL/min/1.73m2)	77.1 [66.9, 89.2]
Active smoking	840 (17.7)
Former smoking	1575 (33.3)
Total cholesterol (mg/dL)	191.9 [177.0, 213.0]
HDL (mg/dL)	49.5 [43.0, 60.5]
BMI (kg/m2)	29.5 [26.4, 33.9]
Beta-blocker use	1158 (24.6)
Statin use	2151 (45.8)
Antiplatelet use	2256 (48.0)

BMI: body mass index; CAD: coronary artery disease; GFR: glomerular filtration rate; HDL: high-density lipoprotein; PROMISE: PROspective Multicenter Imaging Study for Evaluation of Chest Pain; TIA: transient ischaemic attack.

Supplemental Figures

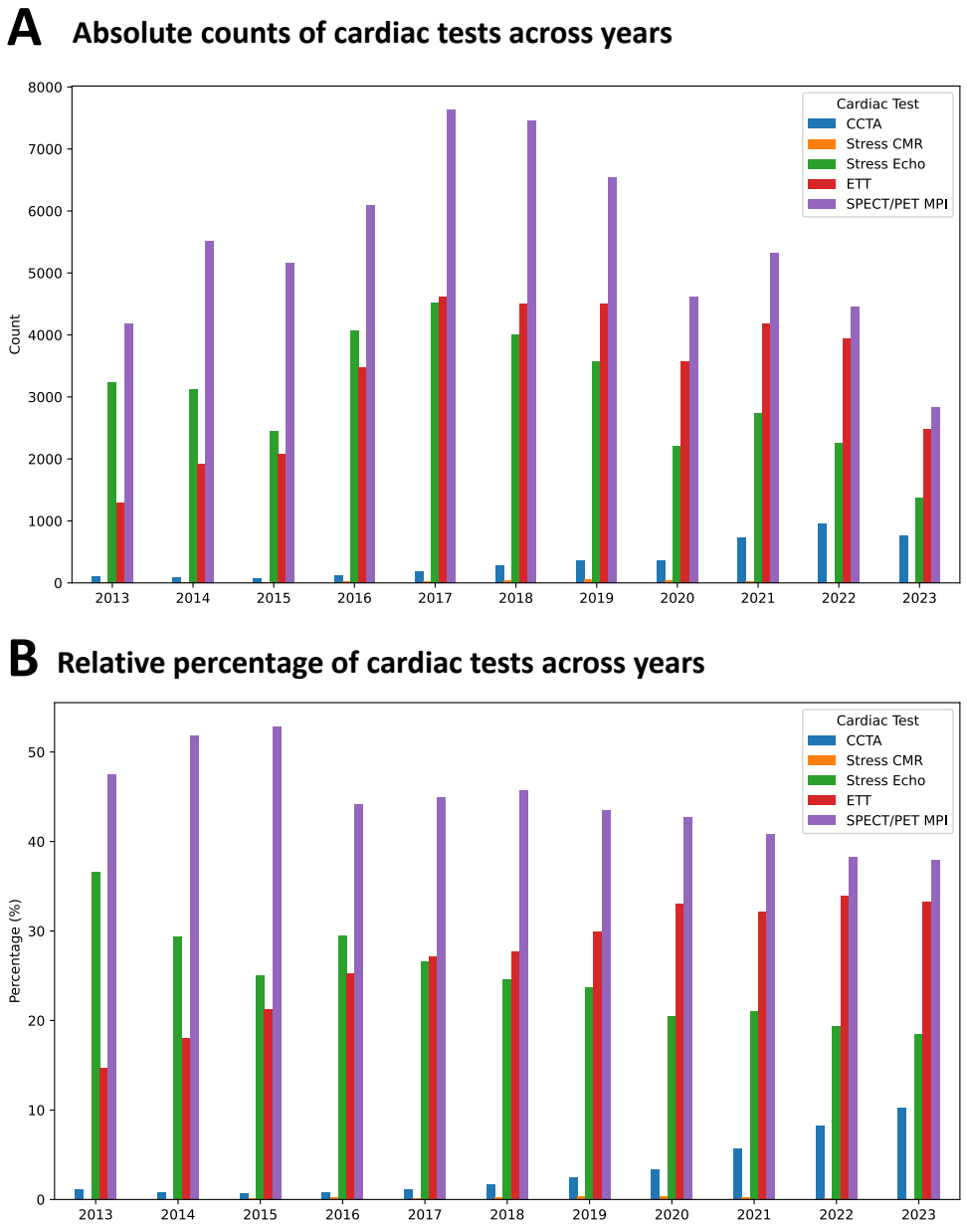

Figure S1 | Counts (A) and relative percentages (B) of anatomical versus functional cardiac investigations per year in the Yale electronic health record. *CCTA: coronary computed tomography angiography; CMR: cardiac magnetic resonance imaging; ETT: exercise treadmill test; MPI: myocardial perfusion imaging; PET: positron emission tomography; SPECT: single-photon emission computed tomography.*

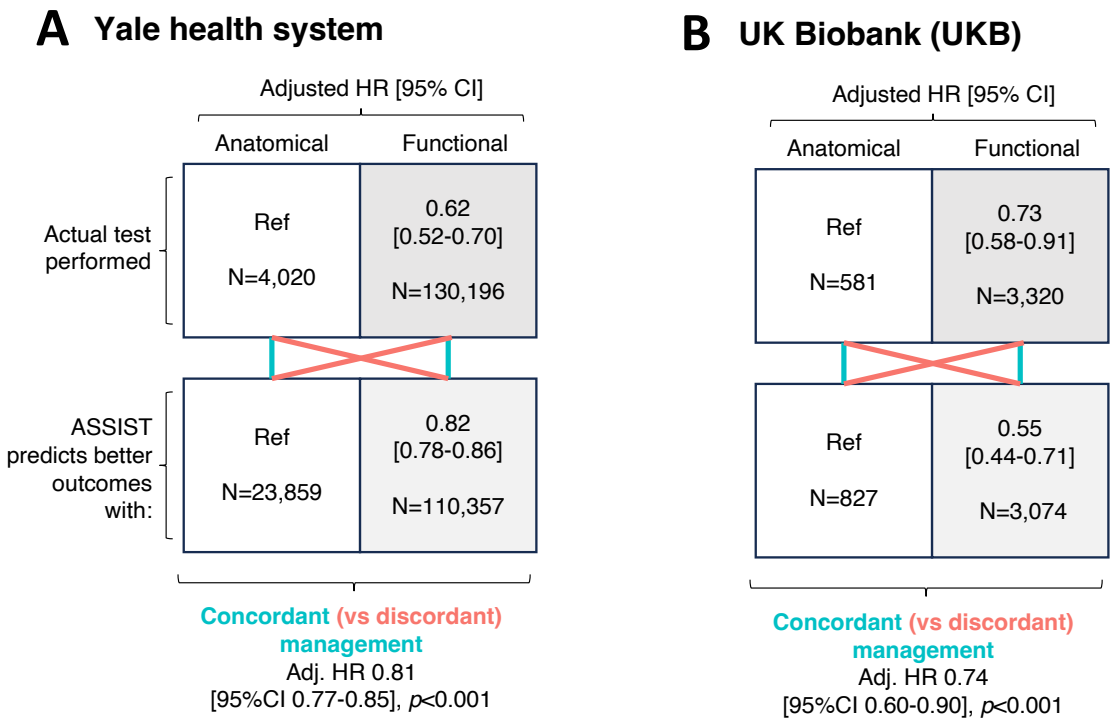

Figure S2 | Adjusted hazard of all-cause mortality or acute myocardial infarction across subgroups of diagnostic testing strategies and ASSIST recommendations. (A) Yale health system cohort, and **(B)** UK Biobank (UKB). *ASSIST: Anatomical vs. Stress teSting decIsion Support Tool; CI: confidence interval; HR: hazard ratio.*

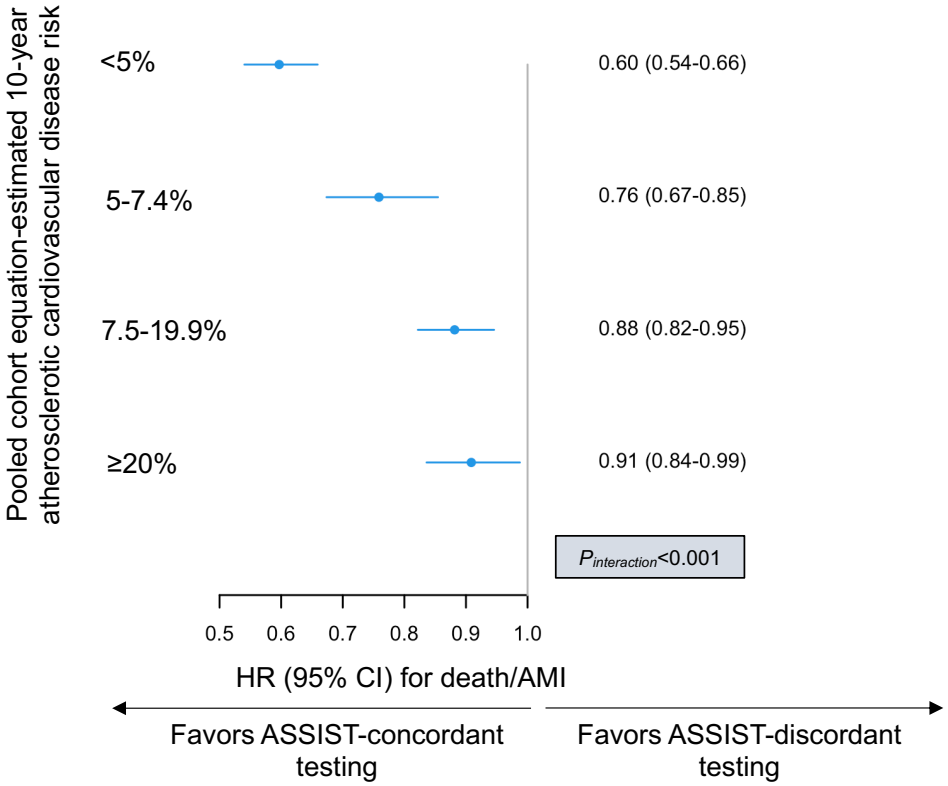

Figure S3 | Subgroup analysis by pooled cohort equation atherosclerotic cardiovascular disease risk the Yale health system cohort. Forest plot showing the adjusted Cox regression-derived hazard ratios and corresponding 95% confidence intervals for the association between ASSIST-aligned (vs discordant) testing and the hazard of all-cause mortality or acute myocardial infarction. A *p* value for interaction is also presented. *AMI: acute myocardial infarction; ASSIST: Anatomical vs. Stress teSting decIsion Support Tool; CI: confidence interval; HR: hazard ratio.*

Supplemental References

1. Oikonomou EK, Van Dijk D, Parise H, Suchard MA, de Lemos J, Antoniades C, et al. A phenomapping-derived tool to personalize the selection of anatomical vs. functional testing in evaluating chest pain (ASSIST). Eur Heart J. 2021 Jul 8;42(26):2536–48.

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