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Prognostic value of coronary CTA vs. exercise treadmill testing: results from the Partners registry

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Aims We sought to compare the complementary prognostic value of exercise treadmill testing (ETT) and coronary computed tomographic angiography (CTA) among patients referred for both exams.

Methods and results We studied 582 patients without known coronary artery disease (CAD) who were clinically referred for ETT and CTA within 6 months. Patients were followed for cardiovascular (CV) death, non-fatal myocardial infarction (MI), or late revascularization (>90 days), stratified by Duke Treadmill Score (DTS) and CAD severity (≥50% stenosis). Mean age was 54 ± 13 years (63% male). In median follow-up of 40 months, there were 3 CV deaths, 7 non-fatal MIs, and 26 late revascularizations. ETT was inconclusive in 23%, positive in 31%, and negative in 46%. CTA demonstrated no CAD in 37%, non-obstructive CAD in 28%, and obstructive CAD in 35%. Among low-risk ETT patients ($n = 326$), there were 3 MI, 10 late revascularizations, and the frequent presence of non-obstructive (32%, $n = 105$) and obstructive CAD (27%, $n = 88$). When present, ETT features (i.e. angina, DTS, ischaemic electrocardiogram changes, and exercise capacity) individually failed to predict CV death/MI after adjustment for Morise score. Conversely, both obstructive CAD [HR 4.9 (1.0–23.3), $P = 0.048$] and CAD extent by segment involvement score >4 [HR 3.9 (1.0–15.2), $P = 0.049$] predicted increased risk for CV death or MI.

Conclusion Patients with a low-risk ETT have an excellent prognosis at 40 months, despite the frequent presence of non-obstructive (32%) and obstructive (27%) CAD. In patients with an intermediate- to high-risk ETT (DTS <5), CTA can provide incremental risk stratification for future CV events.

Keywords exercise testing • coronary computed tomographic angiography • prognosis • major adverse cardiac events • coronary artery disease

Introduction

Exercise treadmill testing (ETT) remains a first-line class I indicated test among patients with suspected stable ischaemic heart disease who are able to exercise with an interpretable electrocardiogram (ECG) by current European Society of Cardiology[1] and United States guidelines.[2] Despite its advantages as an inexpensive and widely available test, ETT alone has limited sensitivity and specificity for identifying obstructive coronary artery disease (CAD) and, consequently, is not recommended in the National Institute for Health and Care Excellence (NICE) guidelines for the assessment of recent onset chest pain.[3] ETT is also potentially unsafe in patients

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with possible unstable angina and has lower diagnostic value in patients who cannot achieve an adequate exercise workload.[4] Coronary computed tomographic angiography (CTA) now provides a safe, accurate, non-invasive method to assess the presence, extent, and severity of CAD and is now incorporated among appropriate use criteria[5,6] and guideline strategies[1,3] for the evaluation of low- to intermediate-risk symptomatic patients.

While ETT and CTA can be used for similar clinical scenarios, few single centre studies have compared the prognostic value offered by these exams.[7–10] As a result, clinicians may pursue either ETT or CTA, with the decision for the initial testing option being influenced by several factors including availability, cost/reimbursement, and local experience. However, when the initial test is inconclusive or when ongoing clinical concern remains due to persistent symptoms, physicians may pursue additional testing.[11,12] Given the need to better understand the complementary value of ETT and CTA, and to understand the yield of test layering, we sought to compare the prognostic value of CTA and ETT among a population clinically referred for both tests.

Methods

Study population

The initial population consisted of 655 consecutive patients who underwent clinically indicated CTA and ETT (with or without stress imaging) between February 2005 and April 2011. ETT and CTA test results were included if performed within a 6-month interval at Brigham and Women's Hospital or Massachusetts General Hospital within the Partners registry.[13] For patients who had multiple tests, only the first available ETT and CTA were used, provided that these tests occurred within 6 months.

We excluded patients with known CAD, defined as prior percutaneous coronary intervention, coronary artery bypass surgery, or myocardial infarction (MI). Patients who underwent coronary revascularization or experienced an acute coronary syndrome between ETT and CTA were excluded, as were patients with unavailable follow-up data, or factors precluding stress ECG interpretation, including: digoxin therapy, ventricular pacing, and left bundle branch block (*Figure 1*). The final cohort consisted of 582 patients, in whom 417 (72%) underwent ETT prior to CTA, with remaining 165 (28%) undergoing CTA prior to ETT.

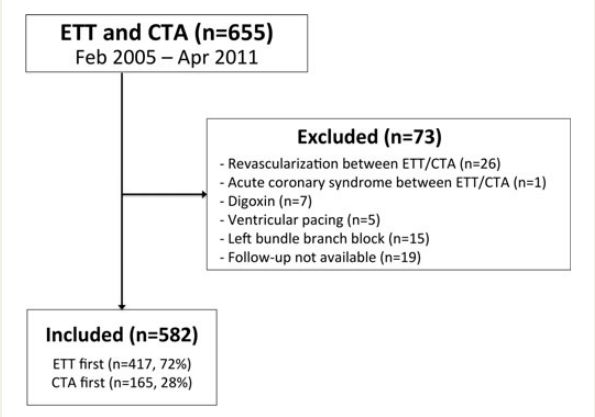


Figure 1 Study design. ETT, exercise treadmill test; CTA, coronary computed tomographic angiography.

Clinical information

Demographics, clinical history, and indications for testing were collected prospectively using a standardized patient interview. Electronic medical records, including all physician notes, were used to identify CAD risk factors (family history of premature CAD, hypertension, dyslipidaemia, smoking, and diabetes) by previously described methods.[13] Pre-test probability of CAD was calculated using the Morise score, stratified by low (0–8), intermediate (9–15), and high risk (>15 points).[14]

Exercise treadmill testing

ETT was performed in all patients using a symptom-limited Bruce protocol according to established guidelines.[15] The target heart rate was defined as 85% of the maximum predicted heart rate (MPHR = 220 − age in years). All ST-segment measurements were performed 80 ms after the J point. The Duke Treadmill Score (DTS) was calculated for each patient as: exercise time (minutes) − (5 × maximal ST-segment depression in millimetres) − (4 × angina index; 0, no angina; 1, non-limiting angina; 2, angina as reason for stopping test).[16] ETT was stratified by low risk (DTS ≥5) vs. intermediate to high risk (DTS <5).

ETT results were categorized as positive, negative, or inconclusive using conventional criteria[15] by an attending cardiologist as part of routine clinical care. Positive tests were defined as upsloping ST depressions ≥1.5 mm, or downsloping or horizontal depressions ≥1.0 mm in at least two leads. Inconclusive ETT included results that may be interpreted as indeterminate and comprised the following categories: (i) negative ECG with reduced sensitivity due to submaximal exercise (<85% MPHR); (ii) positive ECG with reduced specificity due to baseline ECG abnormalities; (iii) positive ECG with reduced specificity due to rapid recovery of ECG changes; (iv) typical angina or inappropriate dyspnoea despite negative ECG findings, and (v) clinically significant rhythm disturbances (any sustained arrhythmia or >3 consecutive beats of ventricular tachycardia).[11]

Coronary CTA

All scans were performed using ≥64-slice multidetector CT scanners according to established guidelines[17] and institutional protocols. Unless contraindicated, all patients were administered variable doses of metoprolol via oral (50–200 mg) or intravenous (5–30 mg) route if the baseline heart rate was >60 bpm, and sublingual nitroglycerin (0.4–0.8 mg) before iodinated contrast image acquisition.

Images were reconstructed in single- or multiphase datasets and interpreted by level III trained cardiologists or radiologists according to current guidelines.[18] Using an 18-segment model, each coronary segment with a >1.5 mm diameter was visualized by axial and multiplanar reformations for the presence of coronary atherosclerotic plaque and stenosis by visual grading defined as: normal (no plaque and no stenosis), non-obstructive (1–49% stenosis), or obstructive CAD (≥50% stenosis). Similar to prior studies, we used an intention-to-diagnose approach, whereby patients with ≥1 uninterpretable segment were categorized as having obstructive CAD.[8,19,20] This approach was selected since excluding uninterpretable segments will falsely increase the diagnostic performance of CTA.[21] Furthermore, in clinical practice, patients with uninterpretable segments have an adverse prognosis[22] and often require further testing to determine the cause of symptoms.

The extent of coronary plaque burden was scored using the segment involvement score (SIS), defined as the sum of the number of segments with any plaque irrespective of the degree of luminal stenosis.[23] Based

on prior data examining the association of disease extent with all-cause mortality, we defined extensive disease as SIS >4.[13] High-risk CAD was defined as ≥50% stenosis involving the left main artery or multivessel obstructive CAD with proximal LAD involvement.[24]

Cardiovascular outcomes

All patient charts were reviewed by two cardiologists blinded to CTA and ETT findings for the adjudication of CV events by previously described methods.[13] Non-fatal MI was defined using universal criteria,[25] and coronary revascularization was recorded as incident percutaneous coronary intervention or coronary artery bypass grafting. Deaths were considered to be of CV origin if the primary cause was acute MI, atherosclerotic coronary disease, congestive heart failure, valvular heart disease, arrhythmic origin, stroke, or sudden death of unknown cause.[26]

The primary outcome was freedom from composite major adverse cardiovascular events (MACE), defined as any CV death, non-fatal MI, or late coronary revascularization (>90 days from CTA). Early revascularizations ≤90 days after CTA ($n = 42/582$, 7%) were censored in the survival analysis to minimize verification bias, consistent with prior research.[27,28] The secondary end point was freedom from CV death or non-fatal MI.

Statistical analysis

Continuous variables with normal distributions are expressed as mean ± standard deviation and were compared with the Student's *t*-test or one-way analysis of variance for multiple group comparisons. Continuous variables with non-normal distributions are expressed as median ± IQR and compared with Wilcoxon rank-sum. Categorical variables are expressed as frequencies (%) and compared by Pearson χ^2 test. To describe the frequency of events according to time since the coronary CTA, we constructed Kaplan–Meier curves, with comparison of event rates by log-rank test. Cox proportional hazard ratios were determined for the primary and secondary outcomes, unadjusted and adjusted for baseline pre-test probability of CAD by Morise score. We compared the ability of CTA, ETT, and Morise score to discriminate patients who experienced MACE from those who had an event-free survival by using receiver operating characteristic curves. Statistical analysis was performed using Stata (Version 12.1, StataCorp., College Station, TX, USA). A two-tailed *P*-value of <0.05 was considered significant. The study was approved by the Partners Healthcare Institutional Review Board and was conducted in accordance with institutional guidelines.

Results

Baseline characteristics

The study population consisted of 582 patients with a mean age of 54 ± 13 years (63% men). Baseline clinical risk factors and CTA findings are shown in *Table 1*, stratified by low-risk ETT (56%) vs. intermediate- to high-risk ETT (44%). Most patients had an intermediate pre-test probability of CAD by the Morise score (58%) and had atypical chest pain (81%). Patients with a low-risk ETT

Table 1 Baseline characteristics

	All patients ($n = 582$)	ETT low risk ($n = 326$)	ETT intermediate to high risk ($n = 256$)	*P*-value
Age, years, mean ± SD	54 ± 13	51 ± 13	59 ± 12	<0.001
Male, *n* (%)	369 (63)	228 (70)	141 (55)	<0.001
Hypertension, *n* (%)	302 (52)	139 (43)	163 (64)	<0.001
Diabetes mellitus, *n* (%)	81 (14)	34 (10)	47 (18)	0.01
Dyslipidaemia, *n* (%)	339 (58)	179 (55)	160 (63)	0.18
Family history early CAD, *n* (%)	296 (51)	160 (54)	136 (46)	0.33
Current smoking, *n* (%)	60 (10)	34 (10)	26 (10)	0.85
Baseline symptoms, *n* (%)				
Typical chest pain	98 (17)	28 (9)	70 (27)	<0.001
Atypical chest pain	469 (81)	286 (88)	183 (71)	
Asymptomatic	15 (3)	12 (4)	3 (1)	
Pre-test probability of CAD[a], *n* (%)				
Low risk	84 (14)	60 (18)	24 (9)	<0.001
Intermediate risk	340 (58)	211 (65)	129 (50)	
High risk	158 (27)	55 (17)	103 (40)	
Coronary CTA, *n* (%)				
Normal	217 (37)	133 (41)	84 (33)	<0.001
<50% stenosis	163 (28)	105 (32)	58 (23)	
≥50% stenosis[c]	202 (35)	88 (27)	114 (45)	
≥1 uninterpretable segment[c]	22 (4)	10 (3)	12 (5)	0.30
High-risk anatomy[b]	78 (13)	25 (8)	53 (21)	<0.001
Segment involvement score >4	175 (30)	76 (23)	99 (39)	<0.001

CAD, coronary artery disease; CTA, computed tomographic angiography; ETT, exercise treadmill test; SD, standard deviation.
[a]By Morise score.
[b]High-risk anatomy defined as left main ≥50% stenosis with multi-vessel obstructive CAD involving the proximal left anterior descending artery.[24]
[c]Includes $n = 22$ with ≥1 uninterpretable segment, of whom $n = 9/22$ had ≥50% stenosis in a remaining segment.

were more likely to be younger and male, with a lower prevalence of hypertension, diabetes, and typical chest pain (all $P \leq 0.01$).

Among all patients, CTA demonstrated normal findings (no plaque and no stenosis) in 37%, non-obstructive CAD in 28%, and obstructive CAD in 35% (*Table 1*). While low-risk ETT patients demonstrated a lower overall CAD burden compared with intermediate- to high-risk ETT patients ($P < 0.001$), approximately one in four low-risk ETT patients demonstrated obstructive CAD, including 8% ($n = 25/326$) with high-risk anatomical findings.

Patient outcomes

During a median follow-up of 40 (IQR: 25–58) months, there were 30 patients with composite MACE, including 26 late revascularizations, 7 non-fatal MI, and 3 CV deaths (6 patients had multiple events). Detailed ETT and CTA results are provided in *Table 2*. Compared with patients without MACE ($n = 552$), those with MACE ($n = 30$) had significantly lower DTS, lower metabolic equivalents of task (METS), and a higher prevalence of typical chest pain during exercise (all $P < 0.05$). Unadjusted, the overall ETT result (positive/inconclusive/negative) demonstrated a non-significant trend for incident MACE prediction ($P = 0.07$), which reached significance following the exclusion of inconclusive ETT patients ($P = 0.02$) and when inconclusive ETT was categorized as positive ($P = 0.02$). By comparison, CTA findings were highly associated with composite MACE. There were no events after a normal CTA ($n = 217$) and a 93% prevalence of obstructive CAD among patients with MACE ($P < 0.001$).

Detailed ETT and CTA findings among patients with CV death ($n = 3$) or non-fatal MI ($n = 7$) are summarized in Supplementary material online, *Table S1*. Among these 10 patients who experienced a hard CV event, 1 had a positive ETT, while the remaining ETT were normal ($n = 4$) or inconclusive ($n = 5$). Nine patients demonstrated evidence of CAD on coronary CTA ($n = 7$ obstructive, $n = 2$ non-obstructive) and one patient had a limited CTA owing to morbid obesity and suboptimal heart rate control. Three out of the seven patients with non-fatal MI were low risk by DTS and had good functional capacity (METS ≥10), including two patients with high-risk CAD on CTA.

Survival analysis

Kaplan–Meier analysis for freedom from composite MACE (CV death, non-fatal MI, or late revascularization) is shown in *Figure 2*. Findings demonstrate excellent prognosis among patients with no or non-obstructive CAD (0–49% stenosis), regardless of ETT risk group. Among patients with low-risk ETT, the presence of obstructive CAD was associated with a decrease in MACE-free survival ($P = 0.002$). Conversely, among patients with obstructive CAD, stratification by ETT risk did not significantly improve composite MACE prediction ($P = 0.22$). When added to the baseline Morise score, the discrimination of composite MACE (CV death, MI, or late revascularization) was significantly improved by CTA (CAD ≥50% stenosis) compared with ETT (DTS <5), with an increase in AUC from 0.72 to 0.85 ($P < 0.001$) (*Figure 3*). The addition of ETT (DTS < 5) to CTA + Morise did not improve discrimination beyond CTA + Morise alone ($P = 0.79$).

When considering only hard events (CV death or MI), patients with a low-risk ETT had an excellent event-free survival ($n = 3/326$, 0.3% annual event rate), regardless of CTA results. When

Table 2 ETT/CTA results by MACE vs. No MACE [CV death, MI, or late (>90 days) revascularization]

		All patients ($n = 582$)	MACE ($n = 30$)[a]	No MACE ($n = 552$)	*P*-value
ETT	DTS, median [IQR]	5.5 [1.5–9.5]	2.5 [−2.5–6.5]	6 [2–10]	0.01
	ETT risk, *n* (%)				
	Low risk (DTS ≥ 5)	326 (56)	10 (33)	316 (57)	0.002
	Intermediate risk (−11 < DTS < 5)	249 (43)	18 (60)	231 (42)	
	High risk (DTS ≤ −11)	7 (1)	2 (7)	5 (1)	
	METS, median [IQR]	10 [7–13]	7.5 [4.5–10.5]	10 [7–13]	0.01
	METS, *n* (%)				
	<7	81 (14)	10 (33)	71 (13)	0.01
	≥7 and <10	146 (25)	7 (23)	139 (25)	
	≥10 and <13	184 (32)	8 (27)	176 (32)	
	≥13	171 (29)	5 (17)	166 (31)	
	Typical chest pain during ETT, *n* (%)	98 (17)	9 (30)	89 (16)	0.048
	ETT result, *n* (%)				
	Negative	269 (46)	8 (27)	261 (47)	0.07
	Inconclusive	132 (23)	8 (27)	124 (23)	
	Positive	181 (31)	14 (47)	167 (30)	
CTA	Normal, *n* (%)	217 (37)	0 (0)	217 (39)	<0.001
	<50% stenosis, *n* (%)	163 (28)	2 (7)	161 (29)	
	≥50% stenosis, *n* (%)	202 (35)	28 (93)	174 (32)	
	High-risk anatomy[b]	78 (13)	17 (57)	61 (11)	<0.001
	Segment Involvement Score >4	175 (30)	23 (77)	152 (28)	<0.001

CTA, computed tomographic angiography; ETT, exercise treadmill test; IQR, inter-quartile range; METS, metabolic equivalents of task.
[a]MACE [cardiovascular (CV) death, non-fatal myocardial infarction (MI), or late (>90 days) revascularization].
[b]Defined as left main ≥50% stenosis or multi-vessel obstructive CAD involving the proximal left anterior descending artery.[24]

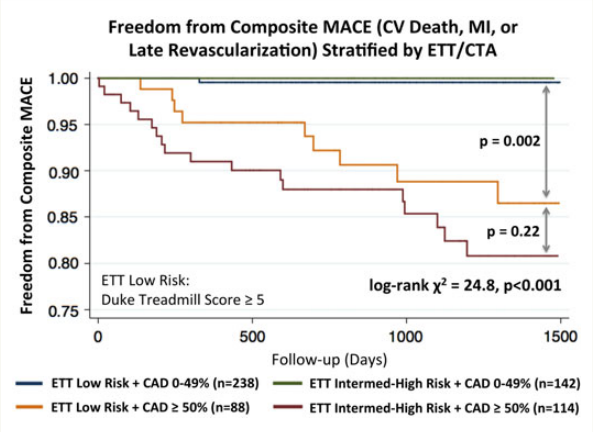


Figure 2 Unadjusted freedom from composite MACE [CV Death, non-fatal MI, or late (>90 day) revascularization]. Low-risk ETT defined as DTS ≥5 compared with ETT intermediate to high risk (DTS <5). CAD stratified by CTA-identified stenosis. CAD, coronary artery disease; CTA, coronary computed tomographic angiography; CV, cardiovascular; ETT, exercise treadmill test; MACE, major adverse cardiac events; MI, myocardial infarction.

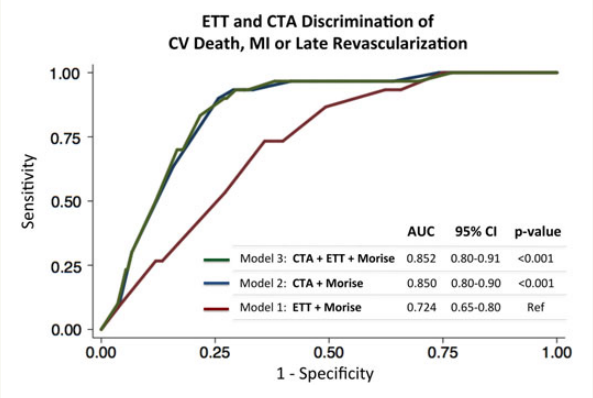


Figure 3 ETT and CTA discrimination of composite MACE [CV death, non-fatal MI, or late (>90 days) revascularization]. Receiver operating curves demonstrate a significant improvement in discrimination of composite MACE (CV death, MI, or late revascularization) with Model 2 (CTA stenosis ≥50% + Morise score) and Model 3 (CTA stenosis ≥50% + DTS < 5 + Morise score) compared with Model 1 (DTS < 5 + Morise score) ($P < 0.001$ for both). When ETT was added to Model 2, DTS < 5 did not improve discrimination for MACE beyond CTA + Morise score (Model 2 vs. Model 3, $P = 0.79$). AUC, area under the curve; CI, confidence interval; CTA, computed tomographic angiography; CV, cardiovascular; ETT, exercise treadmill testing; MI, myocardial infarction.

considering the entire cohort, the addition of CAD ≥50% to intermediate- to high-risk ETT was associated with improved risk stratification for survival free from CV death or MI ($P = 0.02$) (*Figure 4*). However, due to an overall small number of hard events

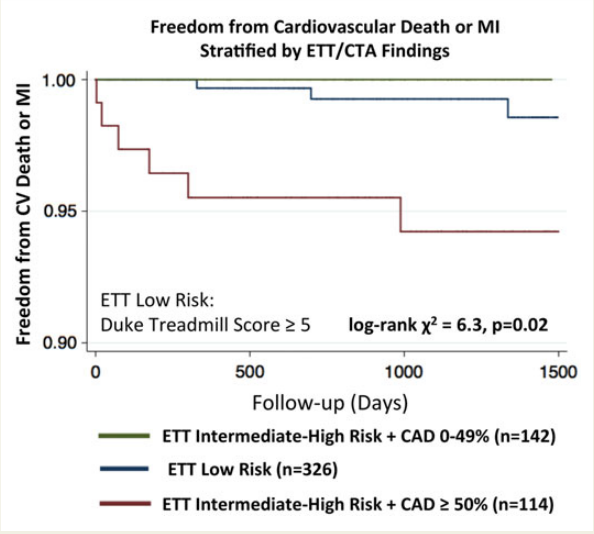


Figure 4 Freedom from CV death or MI. Demonstrates good overall prognosis for patients with a low-risk ETT (DTS ≥ 5) regardless of CAD burden. In patients with an intermediate- to high-risk ETT (DTS < 5), CTA demonstrates a strong trend for incremental risk stratification to predict future hard events (CV death/MI). CAD, coronary artery disease; CTA, computed tomographic angiography; CV, cardiovascular; ETT, exercise treadmill test; MI, myocardial infarction.

($n = 10$), this analysis was underpowered to detect any differences between patient subgroups.

Predictors of major adverse cardiac events

Cox regression analysis for the prediction of composite MACE is presented in Supplementary material online, *Figure S1*. Unadjusted, the presence of ≥50% stenosis and SIS >4 were the strongest predictors of MACE (both $P < 0.001$). ETT predictors of MACE included: METS <7, DTS <5, and a positive stress ECG (unadjusted $P < 0.05$). Following adjustment for baseline Morise score, only ≥50% stenosis and SIS >4 remained significant predictors of composite MACE (both $P < 0.001$).

For the prediction of CV death or non-fatal MI, only obstructive CAD and extensive plaque (SIS >4) were associated with future events, both unadjusted and following adjustment for baseline Morise score (all $P < 0.05$) (*Figure 5*).

Yield of ETT after initial CTA

Among patients who initially underwent CTA followed by ETT ($n = 165$), we examined the ETT findings stratified by CAD severity to estimate the 'yield' of further ETT testing (*Figure 6*). In this group, those with no CAD or non-obstructive plaque had a low rate of positive ETT (<10%). As expected, the rate of a positive ETT was significantly increased in patients with ≥50% stenosis compared with those with no/non-obstructive CAD (32 vs. 7%, $P < 0.001$). While high-risk CAD had the greatest yield of positive ETT findings, 19% of these high-risk CAD patients had a normal ETT.

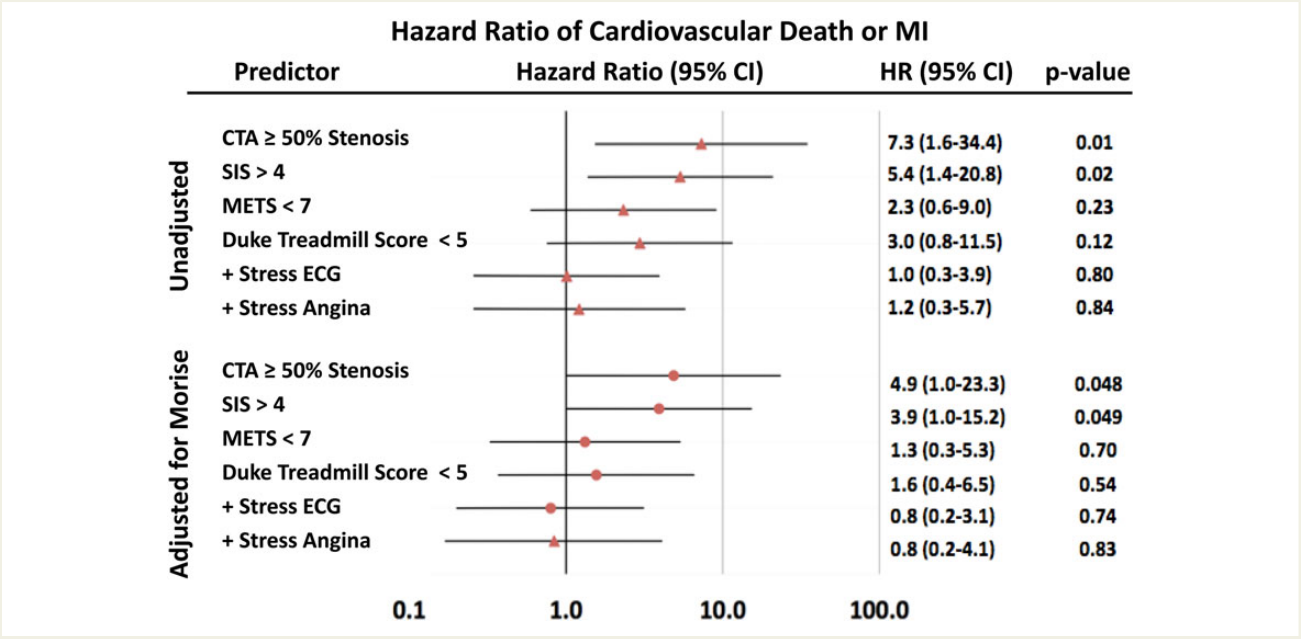


Figure 5 Hazard ratio of CV death or MI. Note that only CTA predictors (≥50% stenosis and SIS > 4) maintain significant association with increased risk of CV death/MI unadjusted and adjusted for baseline Morise score.

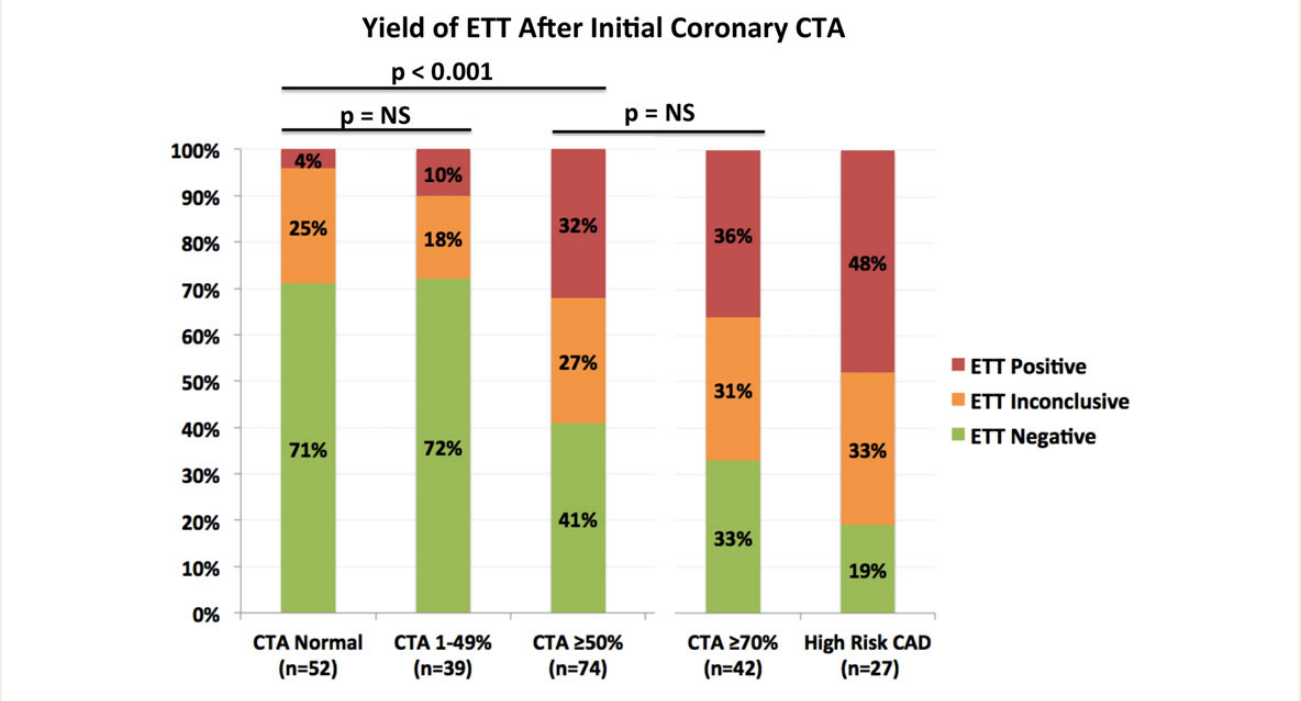


Figure 6 Yield of ETT after initial coronary CTA. Note that the rate of positive ETT increases among patients with obstructive CAD (both ≥50 and ≥70% stenosis) compared with no/non-obstructive CAD. Importantly, the rate of negative ETT is high (41%) among patients with ≥50% stenosis, and 19% in patients with high-risk CAD (defined as left main ≥ 50% stenosis or multi-vessel obstructive CAD involving the proximal left anterior descending artery[24]). CAD, coronary artery disease; CTA, computed tomographic angiography; ETT, exercise treadmill test. NS, not significant.

Yield of CTA after initial ETT

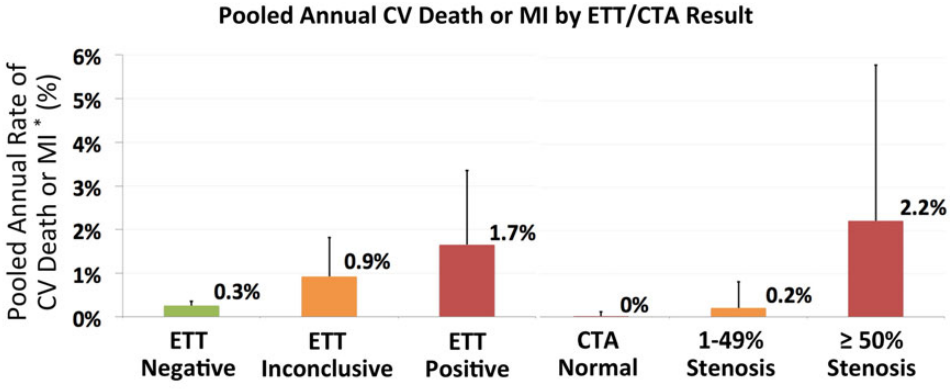
When patients underwent ETT followed by CTA, those with an intermediate- to high-risk ETT demonstrated a higher burden of CAD compared with those with a low-risk ETT ($P < 0.001$) (see Supplementary material online, *Figure S2*). Importantly, among those with a normal ETT, CTA-identified obstructive CAD in 22% and non-obstructive CAD in 40%. Additionally, there was no significant difference between CAD severity among patients with an inconclusive ETT compared with those with a positive ETT ($P = 0.69$).

Discussion

In this study, we evaluated the complementary prognostic value of ETT and CTA among patients who were clinically referred for both exams and found that: (i) patients with low-risk ETT results have an excellent prognosis at 40 months despite a common prevalence of non-obstructive (32%) and obstructive CAD (27%); and (ii) in patients with an intermediate- to high-risk ETT, CTA can provide incremental risk stratification for future adverse CV events.

Although both ETT and CTA are suitable testing options for low- to intermediate-risk symptomatic patients, there are advantages and disadvantages to both strategies. ETT can provide an important assessment of a patient's functional capacity as well as identify the heart rate, blood pressure, and symptomatic response to exercise. Further ETT is an inexpensive and widely available test with no radiation or contrast exposure. However, ETT has a limited specificity and sensitivity to detect obstructive CAD.[1,29] By comparison, CTA offers a high negative predictive value to exclude obstructive CAD, but it has several potential limitations including small risks associated with contrast and radiation exposure, higher initial cost, and the potential to increase coronary revascularizations.[29,30] In some patients, CTA may offer a particular advantage to detect incidental findings and non-cardiac causes for a patient's symptoms (e.g. hiatal hernia, aortic syndromes, and pulmonary embolism). In a large systematic review of 19 studies and 15 877 patients undergoing CTA, the prevalence of major non-cardiac findings requiring further evaluation or immediate intervention was 16% (95% CI: 14–20%).[31] While further investigation is needed to understand the cost-effectiveness of test layering for incidental findings, available evidence has demonstrated both strengths and limitations of CTA for this purpose.[32]

Among prior studies examining the prognostic value of ETT and CTA, Pontone *et al.*[8] demonstrated a similar association of obstructive CAD with future risk of CV death or MI. When pooling their results and other studies providing >2-year follow-up[7,9] with results from our present analysis, CTA-identified obstructive CAD demonstrates the highest risk of CV death/MI across CAD strata and beyond ETT findings (*Figure 7*; see Supplementary material online, *Table S2*). Reassuringly, patients with a negative ETT and normal CTA or non-obstructive CAD have very low risk for hard MACE across studies, with a low rate of CV death/MI (~1%/year) in patients with an inconclusive ETT. Accounting for variable



	n	Age, years	Follow-up, years	ETT Positive (%)	CTA ≥ 50% Stenosis (%)	Annual CV Death or MI, (%/year)
Partners Registry	582	55 ± 13	3.4 ± 1.7	31%	35%	0.5%
Dedic et al [7]	424	56 ± 10	2.6 [2.1-3.2]	20%	33%	0.9%
Cho et al [9]	2,977	58 ± 10	3.3^ [2.3-4.6]	12%	14%	0.1%
Pontone et al [8]	681	61 ± 10	3.7 ± 1	61%	40%	2.9%
Pooled Weighted	4,664	58 ± 10	3.3 ± 1.5	22%	22%	0.7%

Figure 7 Annual rate of CV death or non-fatal MI stratified by ETT/CTA result: pooled analysis of studies. *Included current analysis (Partners registry) and studies with >2-year outcomes among patients undergoing both ETT and CTA.[7–9] Values in table are reported as mean ± SD or interquartile range, and *n* (%), unless otherwise noted. ^Median value. Figure error bars represent upper limit of reported rates. Note: Pontone *et al.*[8] excluded inconclusive ETT patients and Cho *et al.*[9] excluded patients in whom ETT was 'inadequate', defined as patient inability to reach ETT reference standard for age, sex, and weight. CTA, coronary computed tomographic angiography; CV, cardiovascular; ETT, exercise treadmill test; MI, myocardial infarction.

outcomes between these studies (CV death/MI incidence range: 0.1–2.9%/year), notable differences exist among the methods and populations studied despite a common factor that all patients were eligible for both ETT and CTA. For example, Pontone *et al.* had a markedly higher rate of CV death/MI compared with our findings (2.9 vs. 0.5%/year), among an older population (mean age: 61 vs. 54 years) that excluded inconclusive ETT patients, and demonstrated a higher rate of obstructive CAD (40 vs. 35%) and positive ETT findings (61 vs. 31%). Conversely, Cho *et al.* found a lower rate of CV death/MI (0.1%/year), but excluded 'inadequate' ETT patients, defined as a patient's 'inability to reach ETT reference standard', finding both a lower incidence of obstructive CAD (14%) and positive ETT studies (12%).[8]

Our results suggest that when considering further testing following ETT, those who have an intermediate- to high-risk ETT (DTS <5) are more likely to have obstructive CAD and would be more likely to have disease identified upon further testing. Beyond the identification of obstructive CAD, CTA offers a particular advantage to detect non-obstructive plaque and identify patients who may warrant preventive therapies when functional testing is normal. In this study, CTA identified coronary atherosclerosis in 59% of low-risk ETT patients. These findings are important as recent findings have shown a potential role for CTA to guide preventive therapies and improve CAD risk factor control.[33,34] Additionally, observational data have suggested improved CV death/MI event-free survival among patients with extensive non-obstructive plaque (SIS >4) taking statin therapy compared with no statin use over 3-year follow-up ($P = 0.01$).[34] Further studies are required to determine whether the potential benefit of treating such patients offsets the increased cost associated with long-term medication use and the cost of CTA vs. ETT.

Recognizing that inconclusive ETT results are common[11] and account for nearly 25% of patients in the present study, a question arises as to the value of performing CTA after an inconclusive ETT. In our study, the rate of obstructive CAD was identical among inconclusive ETT and positive ETT patients (37% in both groups). Supporting the potential role of CTA testing following inconclusive ETT results, de Azevedo *et al.*[10] studied 529 patients with an inconclusive ETT undergoing CTA and found an increased risk of all-cause death and non-fatal MI in patients with obstructive CAD (HR 3.15, 95% CI 1.3–7.9, $P = 0.01$).

Limitations

Our study has several important limitations. Given the retrospective and observational design, treatment decisions were at the discretion of the referring physicians—which could have been influenced by CTA and/or ETT findings—and may have influenced event rates. As such, direct causation of CTA and ETT findings on outcomes cannot be determined, and prospective randomized data are needed to examine the independent impact of these tests on patient care.[35] While studies have demonstrated the potential for CTA to trigger revascularization, we censored early interventions ($\leq$90 days) to minimize verification bias as prior findings from the Partners registry, and others have demonstrated that late revascularization occurs mainly due to the progression of CAD.[13] Thus, ETT and CTA may have triggered early revascularizations with potential to influence outcomes—and our results should be interpreted with caution. As expected for a low- to intermediate-risk cohort, hard event rates (CV death/MI) were low and thus limited our ability to detect differences in patient subgroups. Finally, our study has selection bias as patients who underwent both CTA and ETT are more likely to have an abnormal or inconclusive finding on the initial test to 'trigger' the second test. Consequently, the burden of CAD was higher in this cohort than the burden observed among all patients referred for coronary CTA in our centres.[13] However, this is the exact same population in which physicians are often faced with the decision regarding whether to obtain additional testing, and thus, our findings regarding the complementary value of these tests are highly applicable in this setting.

Conclusion

Patients with a low-risk ETT have an excellent prognosis at 40 months ($\sim$0.3% annual CV death or MI) despite the frequent presence of non-obstructive (32%) and obstructive (27%) CAD. In patients with an intermediate- to high-risk ETT (DTS <5), CTA provides incremental risk stratification for future adverse CV events.

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Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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