Title: Optimizing Diagnostic Resource Use in Suspected Chronic coronary Syndrome: Pre-Test Probability and Acoustic CAD rule-out in the FILTER-SCAD Trial

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Abstract (250/250 words)

Background and aim

The FILTER-SCAD trial combined pre-test-probability (PTP) and the FDA-cleared CAD-Score System to guide and improve deferred testing in suspected chronic coronary syndrome (CCS). However, adherence to the recommended strategy was low, with fewer than one-fourth of patients deferred. This study evaluates the potential of a PTP- and CAD-score-based deferral strategy on diagnostic resource consumption and clinical outcomes.

Methods

This observational post-hoc analysis included 1002 patients from the FILTER-SCAD intervention arm. Deferred testing was recommended for PTP ≤5% and/or CAD-score ≤20. We calculated the number of potentially deferred tests and clinical outcomes, including significant coronary artery disease and major adverse cardiac events (MACE).

Results

A deferred testing strategy could nearly double the number of safely deferred tests, reducing overall diagnostic test (n=1043) volume by 275 tests (26%). Deferral based on PTP ≤5% alone would avoid unnecessary testing in 13.5% of patients, with an additional 31.3% deferrable based on CAD-score ≤20 (using the 2024 ESC risk factor–weighted likelihood increased deferral from 38.8% to 51.4%). Among the 135 low-likelihood patients (PTP ≤5%), 43.7% underwent testing, with only one (0.7%) positive test result, no invasive coronary angiographies, and no MACE. Among patients with CAD-score ≤20 tested (n=209), 2.1% had positive test results, 1.9% were revascularized and there were two MACE. Conversely, 11.4% of the 596 higher likelihood patients (PTP >5%) were revascularized, and 20 patients experienced a MACE.

Conclusion

A strategy incorporating PTP and CAD-score can safely reduce unnecessary testing in low-likelihood CCS patients, optimizing resource use without compromising outcomes.

Key words

Chronic coronary syndrome; heart sound; pre-test probability; risk stratification; deferred testing; rule-out strategy.

Abbreviations

CAD Coronary artery disease

CCS Chronic coronary syndrome

ESC European Society of Cardiology

ICA invasive coronary angiography

MACE Major adverse cardiac event

PTP Pre-test probability

RF-CL Risk factor weighted clinical likelihood

UAP Unstable angina pectoris

Introduction

Overuse of diagnostic testing in patients with angina pectoris is well recognized, leading to unnecessary use of resources, inappropriate radiation exposure, and incidental findings that may trigger further testing (1–6). New strategies are needed to better direct the diagnostic efforts toward patients at greater risk of obstructive coronary artery disease (CAD) and away from patients undergoing unnecessary diagnostic tests.

Guidelines recommend deferred testing in patients with a low likelihood of CAD, as determined by pre-test probability (PTP) scores, given the excellent prognosis (7,8). The CADScor® System (Acarix AB, Sweden), an FDA-cleared, low-cost and simple-to-use acoustic-based rule-out tool, has shown promise in safely reducing unnecessary testing in low-risk patients while maintaining favourable outcomes (9). The FILTER-SCAD trial tested the use of the CAD-score alongside

current guidelines for test deferral, including PTP estimation based on age sex and type of angina according to the European Society of Cardiology (ESC) 2019 guidelines, which were applicable at the time of the study, in a real-world clinical setting to guide test deferral in consecutive patients with suspected chronic coronary syndrome (CCS) (10). However, the strategy was not successfully implemented – many patients were still referred for diagnostic testing despite low PTP (≤ 5%) and/or low CAD-score (≤ 20), resulting in a deferral rate of only 23.4% among patients with low likelihood. In these patients, the prevalence of significant CAD was low, and very few major adverse cardiac events (MACE) occurred during follow-up.

This study examines the potential resource savings and clinical impact of adhering to a deferred testing strategy based on low likelihood of CAD defined as PTP ≤5% and/or low CAD-score ≤20. We focus on excess diagnostic testing, detailed test outcomes, and MACE among the 1002 patients with suspected CCS, randomised to the intervention arm in the FILTER-SCAD study. Following completion of the study, the 2024 ESC guidelines were published (8). These recommend the use of a risk factor–weighted clinical likelihood (RF-CL), which combines the original three PTP variables with the number of risk factors. Therefore, RF-CL in combination with the CAD-score was tested in the supplementary analyses of this study.

Methods

Study design and population

We conducted a detailed observational post-hoc analysis of the intervention arm of the multicentre randomised FILTER-SCAD implementation trial (Supplementary Figure 1). This

analysis included all patients randomised to the CAD-score intervention arm in an intention-to-treat manner, meaning a test deferral in all patients with a low guidelines-recommended PTP ≤ 5% and/or a low CAD-score ≤20 (Figure 1).

The FILTER-SCAD trial design and main results are described in detail elsewhere (9,10). In short, the study evaluated the implementation of a novel FDA-cleared, low-cost, simple to use acoustic-based tool for ruling out CAD, when used in addition to the ESC Guidelines 2019 recommended strategy (7). The study included patients aged ≥30 years with new-onset symptoms of suspected CCS, referred for outpatient diagnostic cardiac evaluation at five Danish and one Swedish hospital. Exclusion criteria were non-invasive or invasive examinations for stable CAD within six months of randomisation, known CAD or inability to perform a CAD-score measurement. Patients were followed for 12 months for the primary efficacy endpoint of cumulative numbers of diagnostic tests and the secondary safety endpoint of MACE. Additional secondary endpoint were quality of life and angina symptoms.

Study procedures

All patients underwent up to four CAD-score measurement attempts, PTP estimation, and a standard diagnostic evaluation, including medical history and cardiovascular risk assessment, blood test and echocardiography. PTP was based on age, sex and symptom characteristics according to the ESC 2019 Guidelines (7).

The CAD-score is a non-invasive acoustic-based risk score for obstructive CAD, which has proven good rule-out capabilities for obstructive CAD (11–15). To use the CADScor System the patient lays in a supine position with the microphone part of the device affixed via an adhesive patch on the chest at the fourth intercostal space. The device records heart sound for three

minutes, and automatically calculates a CAD-score for risk stratification by combining the recorded heart sounds with the patients' sex, age and whether they have hypertension or not (11,12). A CAD-score ≤20 indicates low likelihood of obstructive CAD, supporting a deferred testing strategy (12).

This study examines the diagnostic and prognostic implications of following a low PTP and low CAD-score-based deferral algorithm in the intervention arm of the FILTER-SCAD study (10). In the simulated flow, all patients with low CAD-score ≤20 and those with a low PTP ≤5 follow a deferred testing strategy. In patients without a CAD-score, the testing strategy was guided by PTP alone, meaning that all patients with a PTP >5 and CAD-score NA were categorized as referred for diagnostic testing as were all patients with CAD-score >20 and/or PTP > 5 (Figure 1).

In addition, we performed a supplementary analysis combining the current 2024 ESC Guidelines recommended strategy using the RF-CL with the CAD-score.

Implementation strategy

The FILTER-SCAD trial included standardized training of all study personnel in ESC 2019 PTP recommendations, the CAD-score, and a clinical decision sheet for the treatment. Physicians were required to state reasons for deviations, but the decision to defer or test was left at the clinician's discretion.

End points

In the FILTER-SCAD trial, the cumulative number of diagnostic tests included all non-invasive and invasive diagnostic tests one year after randomisation. Diagnostic tests included cardiac computed tomography angiography, myocardial perfusion imaging, exercise ECG, stress

echocardiography, cardiac magnetic resonance imaging and invasive coronary angiography (ICA). MACE included death, myocardial infarction, hospitalisation for unstable angina pectoris (UAP), heart failure, or ischemic stroke, and major complications from cardiovascular procedures up to one year after randomisation. Other outcomes were downstream tests, results of diagnostic tests, revascularization, and obstructive CAD. Obstructive CAD was defined as stenosis ≥70% or FFR <0.80, or revascularization, which was the definition used in the main study (FILTER-SCAD).

In the present study, data are presented with the impact of deferring testing based on low PTP alone and the further impact of adding a CAD-score.

Statistics

A descriptive analysis of patients with CAD-score measurement by PTP and CAD-score group was conducted. Continuous data are presented as mean (SD) or median (IQR). Categorical variables are presented as count (percentage), compared by using $\chi 2$ test. All statistical tests were performed with the Statistical Software R version 4.1.0 (16). The risk factor weighted clinical likelihood (RF-CL) was calculated from the original standard formular by Winther et al. (17)

Ethics

The FILTER-SCAD trial was approved by the Danish Medical Agency (2019024326), the Danish National Committee on Health Research Ethics (H-19012579), and the Swedish Ethical Review Authority (Dnr 2019-04252). The trial is registered on ClinicalTrial.gov with the ID number: NCT04121949.

Results

Study population

All 1002 patients assigned to CAD-score measurement and PTP estimation in the FILTER-SCAD Trial were included in the present analysis (Supplementary figure 1). Low CAD-score ≤20 was observed in 37.3% (n=374) of all patients (Figure 1), and in 31.3% (n=271) of the 86.5% (n=867) patients with a PTP >5% (Figure 1 and 2). CAD-score was successfully obtained in 94.5% (n=947) of the population.

Baseline characteristics are shown in Table 1. Overall, the mean age was 62 (SD 12) years and 44.3% were male. The mean number of risk factors was 1.7, including hypertension, hyperlipidaemia, diabetes mellitus, family history of CAD and current or past tobacco use. The median PTP was 14% (IQR 9.3-26.6%). Patients with PTP ≤5% had fewer risk factors and less often presented with typical angina than in patients with PTP >5-15% and PTP>15%; 1.2 vs. 1.6 vs. 1.8 mean numbers of risk factors and 3.1% vs. 11.6% vs. 43.8% with typical angina.

Diagnostic testing and consequences/outcomes

Overall, 40.5 % (n=406) of all patients of the FILTER-SCAD intervention arm had a PTP ≤5% and/or a CAD score ≤20, indicating deferral of further testing (Figure 2). However, only 23.4% (n=234) were actually deferred, while the remaining 76.6% (n=768) underwent a total of 1043 tests;898 non-invasive tests (NIT) and 145 ICA (Table 2). Of these, 275 tests (263 NIT and 12 ICA) were performed in patients with low PTP and/or low CAD-score. Overall, obstructive CAD was diagnosed in just 94 patients (9.4%), with almost all (97%) having a CAD-score >20 and/or PTP >15%. Only 77 patients (7.7%) required revascularization. During the one-year follow-up, 22 MACE were recorded (Table 2).

Among the 135 patients with PTP ≤5%, 43.7% (n=59) were tested with 65 diagnostic tests performed. Only one patient (0.7 %) had a positive test, and no ICAs were performed. There was no MACE during follow-up.

Of the 374 patients with CAD-score ≤20, 55.9% (n=209) were tested with 248 diagnostic tests. In the subgroup of 271 patients with a PTP >5%, 62.8% (n=173) were tested, undergoing 210 diagnostic tests (198 NIT and 12 ICA) (Table 2).

Among patients with a CAD-score ≤20, only 8 (2.1%) were diagnosed with obstructive CAD and 7 (1.9%) required revascularization – distributed as 1.1% in those with a PTP of 5-15% and 5.7% in those with a PTP>15%. Only two patients with a low CAD-score (<20), both with a PTP>15% and both revascularized, experienced a MACE. In contrast, among the 596 patients with a PTP >5 and a CAD-score ≥20 or NA, 70 (11.4%) were revascularized and 20 (3.4%) patients experienced a MACE (Figure 1).

The seven patients with CAD-score ≤20, who were revascularized, including the two patients with a MACE (one non-fatal MI and one hospitalization for UAP) are individually described in Supplementary Table 1. They had a mean age of 57.9 (SD 6.01) years, were predominantly males (71.4%) and had a mean burden of CV risk factors of only 0.71 (SD 0.07). Two patients underwent CABG and only one patient had 3VD. This patient had known hyperlipidaemia and peripheral arterial or cerebrovascular disease and received antiplatelet medication prior to the study.

A supplementary analysis (Supplementary Figure 2) found that 38.8% (n = 389) of the population had a low RF-CL ≤5% corresponding to a deferred testing strategy. Among the remaining 613 patients with RF-CL >5%, 126 (20.6%) had low CAD-score ≤20. Reclassifying

these 20.6% to low likelihood of CAD would potentially increase the number of deferred patients with 32.5% meaning that a deferred testing strategy may be applied in 51.4% of the population.

Discussion

In this post-hoc analysis of the interventional arm of FILTER-SCAD, we confirmed the favourable prognosis and the overall low diagnostic yield observed in the trial population (9). Importantly, our findings suggest that up to 40% of all patients – nearly twice as many as were deferred – could have safely avoided further testing, potentially reducing the total number of tests by one-fourth. This potential gain was demonstrated in two key ways: Firstly, by deferring the 13.5% of patients with a low PTP (≤5%), who had an excellent prognosis and no significant CAD. Secondly, by deferral of the additional 31.3% of patients with a low CAD-score (≤20), in whom only two non-fatal events occurred during follow-up, and in whom the need for revascularization was low (2.6%).

The results reinforce existing evidence that low likelihood CCS patients have a favourable prognosis and that implementing a CAD-score could substantially improve deferred testing strategies (1,4,5). Previous studies of patients referred for cardiac-CTA found that a CAD-score may increase rule-out by 20%-33% (14,18). In line with these findings, 31.3% of our patients with PTP >5% were reclassified to low likelihood by a CAD-score ≤20 in our unselected all-comer cohort.

However, despite clear opportunities for safe test deferral, excessive testing remains common in clinical practice (1)(1). Even in the FILTER-SCAD trial, where a structured approach based on low PTP and low CAD-score was implemented, many patients underwent unnecessary diagnostic procedures. Multiple factors may contribute to this, including physicians' and patients'

fear of missing prognostic lesions. However, the fact that cardiovascular risk factors associated with increased likelihood of CAD were not considered in the 2019 ESC testing strategy may have led to over-testing. The latest 2024 ESC Guidelines address this by incorporating risk factors in the RF-CL model, which enhances risk stratification (8). We calculated the RF-CL for our cohort and found that further testing may be deferred in threefold more patients if RF-CL ≤5% was used instead of the former PTP ≤5% cut-off (38.8% vs. 13.3%). Still, by adding the CAD-score to RF-CL in the remaining patients had the potential to increase the deferral rate by one third downgrading one out of five with RF-CL >5%, meaning that a deferred testing strategy may be applied in half of the total population. When stratified by RF-CL according to the ranges provided by the ESC 2024 guidelines (≤5%, >5–15%, and >15%), CAD-score showed the greatest reclassification potential (26% of patients) in the intermediate RF-CL range (5–15%), consistent with guideline recommendations to adjust likelihood. In patients with RF-CL >15%, CAD-score ≤20 still led to substantial, however fewer reclassifications (12.7%). These results highlight CAD-score's utility for fine-tuning risk assessment in patients with both intermediate and higher RF-CL. This highlights the incremental value of CAD-score in refining clinical decision-making also in combination with the RF-CL and, especially in patients with intermediate RF-CL >5-15% as an alternative to other supplementary tests (e.g. exercise ECG) (19). Because many patients with a low CAD-score had multiple CV risk factors, combining these tools might further optimise future patient evaluation.

Further research is needed to evaluate the combined impact of the RF-CL model and CAD-score (9,20), along with health-economic assessments to determine cost-effectiveness.

It should be taken into account that excessive testing not only carries procedure-related risks, incidental findings leading to additional investigations and patient anxiety, and inappropriate

healthcare resource consumption, but also contributes to CO_2 emission globally (21). Substantial resources are allocated to generate solid clinical evidence and update national and international guidelines for optimal clinical work and patient care. However, effective implementation in clinical practice lags behind, highlighting the need for new implementation strategies – probably involving expertise beyond the healthcare sector.

Our study strongly supports the safe deferral of testing in all patients with low PTP, in nearly half of those with intermediate PTP guided by a low CAD-score, and potentially even in patients with a high PTP and a low CAD-score. In selected patients, clinical follow-up may be a reasonable approach to identify patients with persistent or worsening symptoms who may still require further testing despite a low PTP or low CAD-score.

Angina symptoms often improve spontaneously over time, as shown in previous studies (22), and our data also suggested a decreasing symptom burden during follow-up. Further analysis may help identify predictors of symptom remission and provide insights into its extent and underlying mechanisms.

Strength and limitations

This study adds valuable data on all-comer patients referred for cardiac evaluation for new-onset chest pain. However, the study has several limitations. First, this is an observational post-hoc analysis, and no causative conclusions can be made. Second, the results cannot be extrapolated to patients with pacemaker, cardioverter defibrillator, or implanted donor heart, as they were excluded from the study population. Third, the cohort only includes Scandinavian, primarily Danish patients and the result may therefore not be extrapolated to other cohorts with other ethnicities. Moreover, the main study (FILTER-SCAD) was conducted when PTP was recommended as first-line evaluation of patients with new-onset chest pain by the 2019 ESC

Guidelines(7). Current guidelines recommend an updated risk factor weighted clinical likelihood (RF-CL) model for initial assessment of this patient group. However, the 2019 guidelines also recommended an estimation of the patient's overall clinical likelihood based on risk factors without any specific algorithm for this. This was taken into account in the current study and in the main study, as the treating physician could cross the patient over from one PTP risk group to another based on the PTP and the estimated overall clinical likelihood. Moreover, we provided a supplementary analysis calculating RF-CL for the cohort, which showed that CAD-score still had a potential to increase the deferral rate; adding the CAD-score increased the proportion of patients with deferred testing from 38.8% to 51.4%, as one in five patients with high RF-CL (≥5%) had a low CAD-score and could be reclassified to low likelihood (Supplementary Figure 2).

The definition of obstructive CAD (stenosis ≥70% or FFR <0.80, or revascularization) is a fusion of European and North American standards. However, this was the definition used in the main study FILTER-SCAD (9), and we used it in this sub study for consistency.

Conclusion

A strategy implementing deferred testing in patients at low likelihood of obstructive CAD, as assessed by 2019 ESC PTP ≤5% and/or CAD-score ≤20, will allow 40% of safe deferred testing corresponding to a potential doubling compared to current clinical practice. Additionally, when combining the 2024 ESC RF-CL and CAD-score patient evaluation strategy as much as half of all patients may be deferred.

Contributorship statement

LB, SG, EP, and KWSH conceptualised and designed this post hoc sub study. LHB, KWSH, EP, and SG obtained funding for the FILTER-SCAD trial. LHB performed the data analysis. LHB and SG drafted the manuscript. All authors contributed to the interpretation of the results, critically revised the manuscript, and approved the final version.

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Disclosures of interest

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Data availability statement

Data cannot be shared for ethical/privacy reasons.

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Figure legends

Figure 1

Figure 1 shows a simulation of the diagnostic flow if all patients with as recommended in the protocol; deferred testing strategy was recommended in patients with low CAD-score ≤20 and patients with CAD-score >20 should be offered a diagnostic test. In patients where CAD-score measurements are NA the diagnostic work-up followed the protocol for the control group and the pre-test probability (PTP) score; in patients with PTP ≤5% a deferred testing strategy was recommended, in patients with PTP 6-15% a diagnostic test could be done depending on the overall clinical likelihood, and in patients with PTP >15% a diagnostic test was recommended. "Tests saved" refers to tests performed (in the FILTER-SCAD study) that might have been deferred if a low PTP/low CAD-score guided algorithm had been followed. "Overlooked disease" refers to obstructive CAD, revascularizations and diseased vessels among patients, who underwent diagnostic testing, despite a low PTP and/or low CAD-score and MACE among all patients with a low PTP and/or a low CAD-score.

Figure 2

Figure 2 shows the potential down-classification of risk from intermediate to low when adding a CAD-score. When adding a CAD-score to the patients with PTP >5%, the number of patients with a deferred testing strategy increased from 13.5% to 40.5%.

Tables

Table 1: Baseline characteristics by PTP and CAD-score group

Patient characteristic	PTP ≤ 5%			PTP > 5-15%			PTP > 15%		
	CADs ≤ 20 (n = 103)	CADs > 20 (n = 28)	CAD-score NA (n= 4)	CADs ≤ 20 (n = 183)	CADs > 20 (n = 206)	CAD-score NA (n=20)	CADs ≤ 20 (n = 88)	CADs > 20 (n = 339)	CAD-score NA (n=31)
Mean (SD) age, y	45.8 (9.2)	52.0 (7.4)	43.5 (2.5)	57.1 (10.3)	65.3 (10.7)	62.1 (11.8)	61.51 (8.9)	68.6 (8.98)	67.7 (8.96)
Males, no. (%)	21 (20.4)	10 (35.7)	2 (5)	31 (16.9)	46 (22.3)	5 (25)	57 (64.8)	248 (73.2)	24 (77.4)
Ethnicity									
White	100 (97.1)	27 (96.4)	4 (100)	175 (95.6)	198 (96.1)	20 (100)	85 (96.6)	336 (99.4)	30 (96.8)
Other	3 (2.9)	1 (3.6)	0 (0)	8 (4.3)	8 (3.9)	0 (0)	3 (3.4)	2 (0.6)	1 (3.2)
CV risk factors									
Hypertension, no. (%)	12 (11.7)	17 (60.7)	0 (0)	19 (10.4)	144 (69.9)	12 (60)	5 (5.7)	215 (63.4)	15 (48.4)
Hyperlipidaemia (lipid lowering drugs)	15 (14.6)	8 (28.6)	0 (0)	36 (19.7)	75 (36.4)	9 (45)	16 (18.2)	126 (37.2)	14 (45.2)
Family history of CAD	27 (26.2)	7 (25.0)	1 (25)	50 (27.3)	49 (23.8)	7 (36.8)	22 (25.0)	61 (18.0)	7 (22.6)
Current or past tobacco use	54 (52.4)	12 (42.9)	3 (75)	110 (60.1)	129 (62.6)	13 (65)	59 (67.1)	216 (63.7)	25 (80.6)
Diabetes Mellitus	3 (2.9)	3 (10.7)	0 (0)	5 (2.7)	22 (10.7)	7 (35)	5 (5.7)	40 (11.8)	9 (29)
Body-mass index, mean (SD), kg/m^2	26.9 (5.9)	30.3 (5.1)	26.3 (3.26)	26.2 (5.0)	27.8 (5.8)	31.5 (7.4)	27.1 (5.8)	27.1 (4.5)	30.7 (6.6)
Total burden of CV risk factors, no. (%)									
No. of CV risk factors per patient, mean (SD)	1.2 (0.9)	1.7 (0.9)	1(0.82)	1.20 (0.9)	2.03 (1.2)	2.4 (1.3)	1.22 (0.9)	1.94 (1.1)	2.3 (1.5)
Absence of any CV risk factors	27 (26.2)	3 (10.7)	1 (25)	44 (24.0)	16 (7.8)	0 (0)	19 (21.6)	29 (8.6)	2 (6.5)
Comorbidity									
Peripheral artery or cerebrovascular disease	2 (1.9)	1 (3.6)	0 (0)	6 (3.2)	20 (9.8)	1 (5)	6 (6.8)	31 (9.2)	1 (3.2)
Chronic kidney disease	1 (1.0)	1 (3.6)	0 (0)	1 (0.5)	4 (1.9)	1 (5)	0 (0.0)	9 (2.7)	0 (0)
Type of angina									
Typical angina (cardiac)	4 (3.9)	0 (0.0)	0 (0)	30 (16.4)	15 (7.3)	2 (10)	43 (48.9)	144 (42.5)	14 (45.2)
Atypical angina (possible cardiac)	12 (11.7)	1 (3.6)	0 (0)	81 (44.3)	49 (23.8)	5 (25)	33 (37.5)	110 (32.4)	10 (32.3)
Non-anginal chest pain (non-cardiac)	82 (79.6)	27 (96.4)	4 (100)	56 (30.6)	103 (50.0)	10 (50)	3 (3.4)	61 (18.0)	4 (12.9)
Dyspnoea on exertion	5 (4.9)	0 (0.0)	0 (0)	16 (8.7)	39 (18.9)	3 (15)	9 (10.2)	24 (7.1)	3 (9.7)
Risk scores									
PTP, median (range)	3 (1 to 4)	3 (1 to 4)	3.75 (2.22)	10 (6.8)	112 (7.5)	11.7 (10.8)	24 (6.5)	29 (11.3)	30.03 (10.5)

CAD = coronary artery disease. CV = cardiovascular. PTP = pre-test probability.

Table 2: Type and result of diagnostic tests

Patient characteristic	PTP ≤ 5%			PTP > 5-15%			PTP > 15%		
	CADs ≤20 (n = 103)	CADs >20 (n = 28)	CADs NA (n=4)	CADs ≤20 (n=183)	CADs >20 (n=206)	CADs NA (n=20)	CADs ≤20 (n=88)	CADs >20 (n=339)	CADs NA (n=31)
Any diagnostic test (NIT or ICA) performed, no of patients	36	21	2	108	180	14	65	315	27
Non-invasive diagnostic tests (NIT)									
Cumulative number of NIT	38	25	2	124	217	15	74	376	27
NIT per patient, no.									
0	67	7	2	76	26	6	25	39	7
1	34	17	2	92	143	13	52	229	21
2	2	4	0	13	37	1	11	66	3
≥3	0	0	0	2	0	0	0	5	0
Results of NIT, n (%)									
Positive	0 (0.0)	1 (4.0)	0 (0)	5 (4.0)	21 (9.7)	4 (26.7)	6 (8.1)	66 (17.6)	3 (11.1)
Negative	37 (97.4)	20 (80.0)	1 (50)	107 (86.3)	169 (77.9)	9 (60)	60 (81.1)	226 (60.1)	18 (66.7)
Inconclusive	1 (2.6)	4 (16.0)	1 (50)	12 (9.7)	27 (12.4)	2 (13.3)	8 (10.8)	84 (22.3)	6 (22.2)
Type of non-invasive test									
Exercise ECG	2/38	2/25	1/2	12 (9.7)	27 (12.4)	0 (0)	2 (2.7)	43 (11.4)	1 (3.7)
Stress echocardiography	2/38	2/25	0	2 (1.6)	2 (0.9)	0 (0)	0 (0)	6 (1.6)	0 (0)
CCTA	29/38	12/25	1/2	86 (69.4)	106 (48.8)	7/20	56 (75.7)	192 (51.1)	16 (59.3)
Stress nuclear perfusion test	3/38	8/25	0	24 (19.4)	79 (36.4)	8/20	15 (20.3)	133 (35.4)	10 (37.0)
Cardiac MRI	2/38	1/25	0	0 (0)	3 (1.4)	0 (0)	1 (1.4)	2 (0.5)	0 (0)
Invasive coronary angiography (ICA)									
Patient undergoing ICA, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)	15 (7.3)	3 (15.0)	8 (9.1)	96 (28.3)	8 (25.8)
Cumulative number of ICA	0	0	0	4	15	3	8	107	8
ICA per patient, no.									
0	103	28	4	179	191	17	80	243	23
1	0	0	0	4	15	3	8	86	8
2	0	0	0	0	0	0	0	9	0
≥3	0	0	0	0	0	0	0	1	0
Results of ICA, n (%)									
Positive	-	-	-	3 (75)	12 (80)	1 (33.3)	8 (100)	92 (86)	2 (25)
Negative	-	-	-	1 (25)	3 (20)	2 (66.6)	0 (0)	15 (14)	8 (75)
Inconclusive	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Revascularization									
Patients undergoing revascularization, no (%)	0	0	0	2 (1.1)	9 (4.4)	0 (0.0)	5 (5.7)	58 (17.1)	3 (9.7)
Cumulative number of revascularizations, no.	0	0	0	2	9	0	5	60	3
PCI	-	-	-	1 (50.0)	8 (88.9)	-	4 (80.0)	38 (63.3)	2 (66.7)
CABG	-	-	-	1 (50.0)	1 (11.1)	-	1 (20.0)	22 (36.7)	1 (33.3)

Diseased vessels, no									
3VD or LM disease	-	-	-	1	3	0	0	44	1
2VD	-	-	-	1	3	0	2	15	3
1VD	-	-	-	1	6	2	6	21	2
Obstructive CAD									
Obstructive CAD during follow-up, no.*	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	10 (4.9)	1 (5.0)	6 (6.8)	71 (20.9)	4 (12.9)
Major adverse cardiac events, no. (rate per 100 PY?) **	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.4)	1 (5.0)	2 (2.3)	12 (3.5)	2 (6.5)
Death, no	-	-	-	-	1 (0.5)	1 (5.0)	0 (0.0)	1 (0.3)	1 (3.2)
MI, no	-	-	-	-	0 (0.0)	0 (0.0)	1 (1.1)	4 (1.2)	1 (3.2)
Hospitalisation for UAP	-	-	-	-	2 (1.0)	0 (0.0)	1 (1.1)	5 (1.5)	0 (0.0)
Hospitalisation for HF	-	-	-	-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalisation for ischemic stroke	-	-	-	-	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Major complications from CV procedures	-	-	-	-	2 (1.0)	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)
Follow-up time (months since randomisation)	1235	336	48	2194	2470	240	1055	4065	372

*Significant stenosis or revascularisation. **First event only.

CABG = coronary artery bypass graft. CAD = coronary artery disease. CCTA = cardiac computed tomography angiography. CV = cardiovascular. HF = Heart failure. ICA = invasive coronary angiography. LM = left main. MI = myocardial infarction. MRI = magnetic resonance imaging. NIT = non-invasive test. PCI = percutaneous coronary intervention. PY = person years. UAP = Unstable angina pectoris. VD = vessel disease.

1

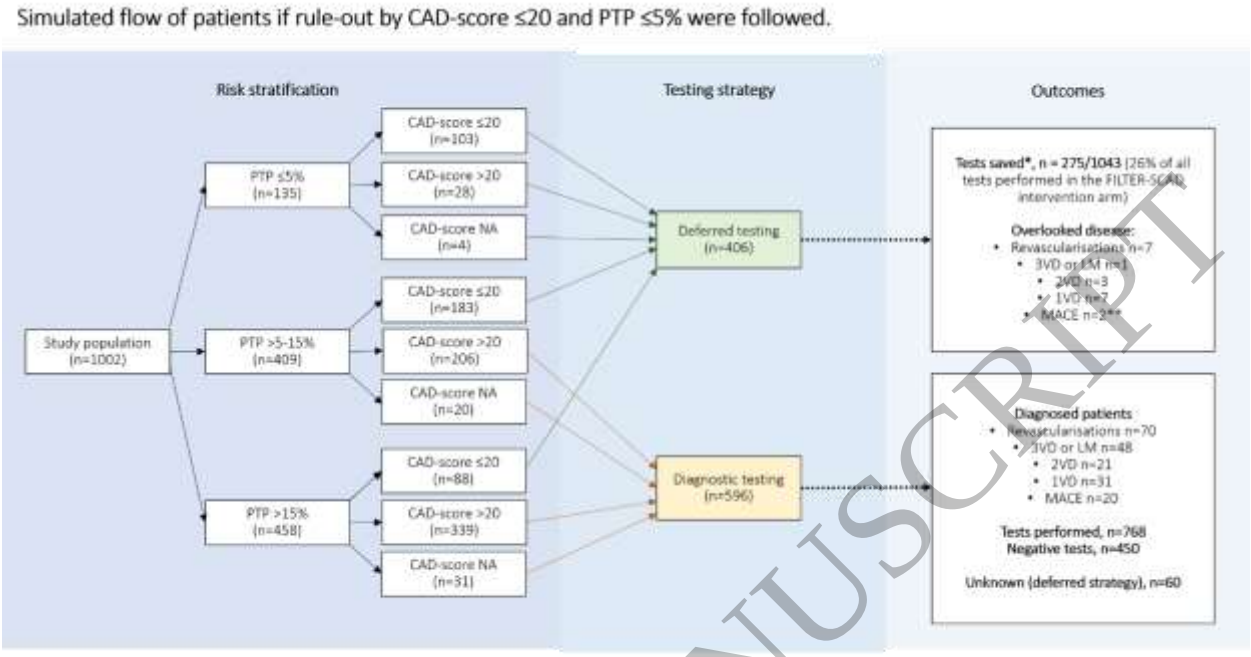

Figure 1
165x92 mm (x DPI)

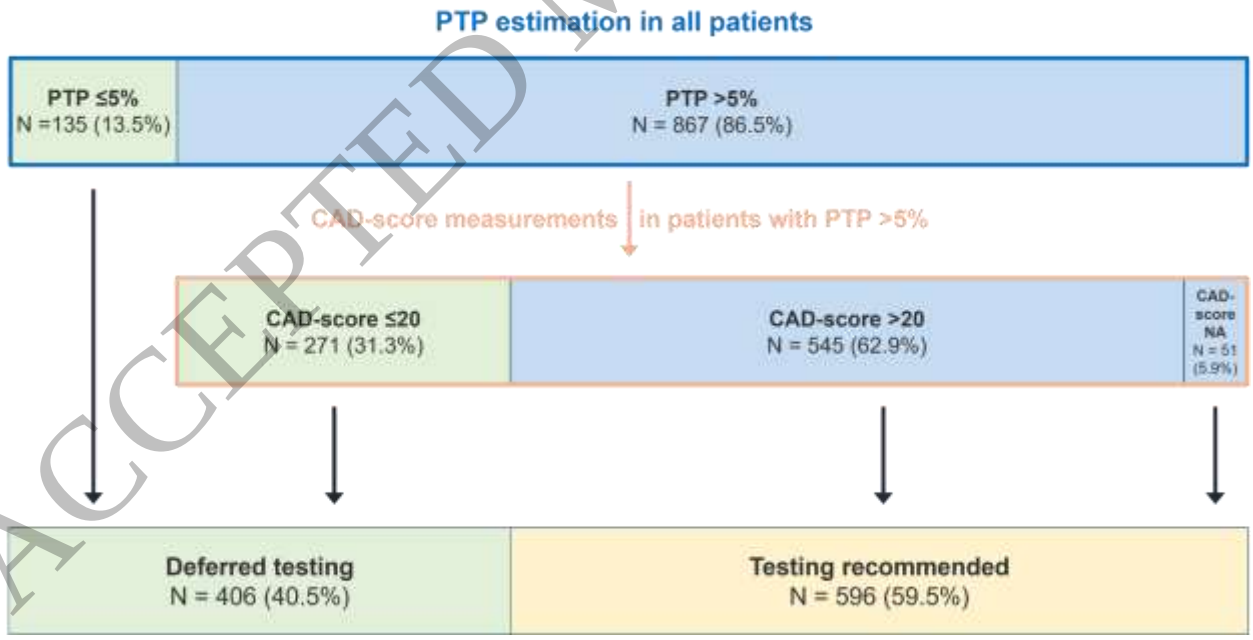

Figure 2
165x84 mm (x DPI)

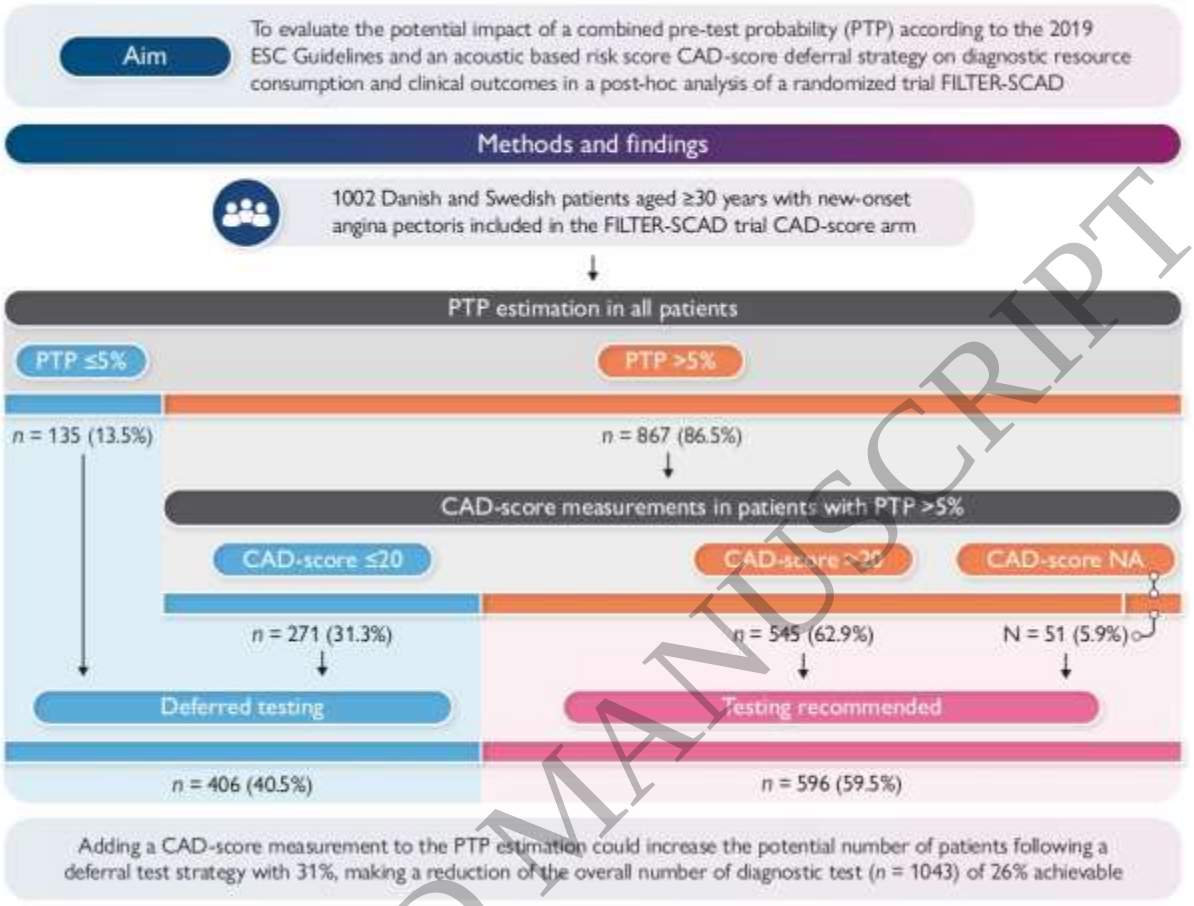

Figure 3
165x124 mm (x DPI)