Typical angina during exercise stress testing improves the prediction of future acute coronary syndrome

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Abstract

Introduction: The prognostic value of angina during exercise stress testing is controversial, possibly due to previous studies not differentiating typical from non-typical angina. We aimed to assess the prognostic value of typical angina alone, or in combination with ST depression, during exercise stress testing for predicting cardiovascular events.

Methods: We conducted a prospective observational cohort study including all patients who performed a clinical exercise stress test at the department of Clinical Physiology, Kalmar County Hospital between 2005 and 2012. The association between typical angina/ST depression and incident acute coronary syndrome (ACS) and cardiovascular mortality were analysed using Cox regression for long-term and 1-year follow-up.

Results: Out of 11605 patients (median follow-up 6.7 years), 623 (5.4%) developed ACS and 319 (2.7%) died from cardiovascular causes. Compared to patients with no angina and no ST depression, typical angina and ST depression were associated with increased risk of future ACS; hazard ratio (HR) 3.5 ([95%CI] 2.6–4.7). This association was even stronger for ACS within one year (typical angina with and without concomitant ST depression; HR 20.8 (13.9–31.3) and 9.7 (6.1–15.4), respectively). Concordance statistics for ST depression in predicting ACS during long-term follow-up was 0.58 (0.56–0.60) and 0.69 (0.65–0.73) for ACS within one year, and 0.64 (0.62–0.66) and 0.77 (0.73–0.81), respectively, when typical angina was added to the model.

Conclusions: Typical angina during exercise stress testing is predictive of future ACS, especially in combination with ST depression, and during the first year after the test.

Keywords:
acute myocardial infarction, exercise ECG, risk stratification, unstable angina

Cole et al. found that typical angina during treadmill exercise testing among patients with ST depression was associated with increased risk of developing acute coronary syndrome (ACS) but did not evaluate the predictive value of typical angina in the absence of ST depression (Cole & Ellestad, 1978). More recently, Daugherty et al (2011) found angina to be the strongest predictor for AMI in women, but not in men (Daugherty, et al. 2011). Others have found no additional value of angina for predicting future risk (Forslund, et al. 2000). In two of these prior studies, however, the type of angina was not clearly defined (Daugherty, et al. 2011; Forslund, et al. 2000), which is problematic in clinical implementation.

Clinically, the exercise ECG is always interpreted in the light of other variables, such as the presence of typical angina. Since the landmark study by Cole et al. more than 40 years ago, the prognostic value of typical angina has not been evaluated. As the role of the exercise test is currently being questioned (Knuuti, et al. 2018), evaluation of its diagnostic and prognostic accuracy beyond only ECG changes is important.

The aim of the present study was to assess the prognostic value of typical angina at exercise stress testing, alone or in combination with ST depression, in predicting future ACS and cardiovascular mortality during long-term follow-up and future ACS within 1 year after the test.

We performed a prospective observational cohort study of all patients who performed a clinical bicycle exercise stress test, according to a nationally standardized protocol, at the Department of Clinical Physiology at Kalmar County Hospital between Jan 2005 and Sep 2012 (n = 13587). For patients who performed more than one test, the most recent test was included.

Exclusion criteria were age < 18 years, previous AMI, previous UA or baseline ECG abnormalities known to affect exercise ECG interpretation (e.g. bundle branch block, ventricular pacing, left ventricular hypertrophy with secondary ST abnormalities, pre-excitation, digoxin-induced ST-segment changes (Jorfeldt & Pahlm, 2013)). The presence of baseline ECG abnormalities at rest was noted by the attending physician at the time of the test. Resting ECGs were not re-interpreted for the purpose of this study.

We cross-linked the database to obtain mortality data from the Swedish Causes of Death Register (until 30 Apr 2019). Data on hospital admissions and hospital outpatient clinic data were obtained from the National Patient Register (until 12 Dec 2017). Near-complete coverage of these data was possible since all deaths (including the cause of death) are reported to the Swedish Cause of Death Register, and > 99% of all somatic hospital discharge diagnoses are registered in the National Patient Register.

### 2.1 Exercise stress testing

All exercise tests were performed using an electrically braked, regularly calibrated bicycle (Rodby Inc, Karlskoga, Sweden). A 12-lead ECG was recorded at rest, during exercise and at least 4 min after exercise using digitally processed ECG recordings (CASE 12; Marquette Electronics Inc., Milwaukee, WI, USA and CASE v 6.51, GE Healthcare). Every 2 min during exercise, the patients were queried regarding rating of perceived exercise (RPE), and systolic blood pressure (SBP) was measured. Exercise was commenced at a starting load of 40–100 W (men)/30–50 W (women) with an incremental increase of 10–20 W/min (Jorfeldt & Pahlm, 2013). The test was terminated at the patient's will or if any termination criteria were fulfilled (severe chest pain, ST depression ≥ 0.4 mV, a drop in SBP or malignant dysrhythmias). The achieved exercise capacity (% of predicted $W_{max}$) was determined using reference values derived from the same database as the present study (Brudin, et al. 2014).

### 2.2 ST depression

The amplitude and slope of the ST segment during the exercise stress test were measured 60 ms following the J-point (ST60) at supine rest before and at 4 min after exercise as well as at peak exercise.
Significant ST depression was defined as horizontal or down-sloping ST depression ≥ 0.1 mV in any of the leads V4, V5, or V6, or ≥ 0.05 mV in aVL or I at peak exercise or at 4-min post-exercise. This definition was based on a previous study on the accuracy of ST depression during exercise stress testing (Vilkk et al. 1998). If resting ST depression was present (<0.1 mV), ST depression was measured as the additional ST depression from baseline (all patients with ST depression exceeding 0.1 mV in leads V4–V6 at rest were excluded).

2.3 | Angina

Angina during the test was categorized as typical or atypical by the attending physician and/or an experienced exercise stress test technician. Typical angina was defined as chest pain or chest discomfort of typical quality (pressure, burning, squeezing) during exercise, with typical temporal features, that is intensification with increasing workload and relief after cessation of exercise. The classification of atypical or non-typical angina relied on either a definitively non-typical characteristic, such as dyspnoea, a stinging pain or a pain located in a distinct, small area of the chest or on a non-typical temporal presentation. In this study, atypical or non-typical angina was considered as the same entity, here referred to as non-typical chest pain.

2.4 | Outcomes

The primary outcome was incident ACS, that is the first diagnosis of AMI or UA during follow-up. All definitions of diagnoses are found in Table S1. Secondary outcomes were death with cardiovascular disease as underlying cause of death during follow-up and incident ACS within 1 year.

2.5 | Ethical considerations

The study complies with the Declaration of Helsinki and was approved by the Regional Ethical Review Board (Dnr 2012/379-31 and 2018/141-31). Informed consent was waived by the Ethical Review Board.

2.6 | Statistical analysis

Continuous variables were described using mean and standard deviation (SD) if normally distributed, otherwise as median and interquartile range (IQR). Proportional differences between groups were assessed using the chi-squared test. Time-to-event analysis was performed using Kaplan–Meier with censoring at study end (31 Dec 2017). The association between typical angina/ST depression and incident ACS was analysed using multivariable Cox proportional hazard regression models; unadjusted and adjusted for age, sex, hypertension, heart failure, stable angina, cerebrovascular disease, valvular heart disease, hypercholesterolaemia, diabetes mellitus, body mass index, beta-blocker therapy and exercise capacity (% of predicted). Hazard ratios (HRs) were presented with 95% confidence intervals (CIs). The assumption of proportional hazards was confirmed using Schoenfeld’s residuals. Three sensitivity analyses were performed: (a) excluding patients not reaching a rating of perceived exertion (RPE) ≥17 (since tests may be prematurely terminated for patients experiencing chest pain), (b) using AMI as a sole outcome (since UA may be prone to incorporation bias), and (c) excluding patients with a time to event less than 30 days, in order to both those who performed the test as in-hospital patients, and who were subsequently diagnosed with ACS. This latter sensitivity analysis would also reduce incorporation bias since a diagnosis made early after the test may be at greater risk of such bias (both regarding ST depression and anginal symptoms). The model for cardiovascular mortality was additionally adjusted for atrial fibrillation. ST depression was analysed alone, and typical angina and ST depression in the following combinations: absence of typical angina and absence of ST depression (Ang-/ECG-); typical angina but no ST depression (Ang+/ECG-); ST depression but no typical angina (Ang-/ECG+); and typical angina and ST depression (Ang+/ECG+). Concordance statistics was used for evaluation of predictive accuracy of the models. Statistical analysis was performed using R version 3.5.3, packages: Survival v. 3.1-12, Survminer v. 0.4.6.

3 | RESULTS

In total, 11605 patients were included. The median follow-up was 6.7 years (IQR 3.9–9.7; range 0–12.6). No participants were lost to follow-up. Baseline characteristics are presented in Table 1 (and Table S2). Selected exercise stress test variables stratified by typical angina and significant ST depression are presented in Table 2.

During follow-up, 623 (5.4%) patients developed ACS and 319 patients died from a cardiovascular cause. Typical angina was present in 458 cases (Figure 1b), of which 21.8% were diagnosed with ACS during follow-up, compared to 4.7% of patients without typical angina (p < 0.001) (Table 3). Significant ST depression was present in 1552 patients. Among these patients, 7.9% developed ACS during follow-up compared to 4.2% of patients without ST depression (p < 0.001). The highest incidence of future ACS was found among patients with both typical angina and ST depression (30.3%), compared with only 3.9% in patients with neither typical angina nor ST depression. Concordance statistics for ST depression in predicting incident ACS during long-term follow-up was 0.58 (0.56–0.60) and 0.69 (0.65–0.73) for ACS within one year, respectively, and 0.64 (0.62–0.66) and 0.77 (0.73–0.81) when typical angina was added to the model. Hazard ratios for incident ACS stratified by combinations of typical angina and ST depression are presented in Figure 2 and Table 3. Data on AMI only are presented in Table 4.
Among patients without typical angina and no ST depression, 0.7% suffered ACS within 1 year compared to 4.1% among those with ST depression but no typical angina \( (p < 0.001) \). Among patients with typical angina but no ST depression, 9.2% had an ACS episode within 1 year compared to 22.7% for those with both typical angina and ST depression \( (p < 0.001) \). The risk of ACS within 1 year was 21 times higher in patients with typical angina and ST depression when compared to patients free from both \( (\text{HR} \ 20.8 \ (13.9-31.1)) \). Typical angina was associated with an increased risk of AMI, both in combination with ST depression and without \( (\text{sensitivity analysis, Table 4}) \). Patients with both typical angina and ST depression had a relative risk of suffering from AMI within 1 year at 11.1 \( (6.1–20.4) \) in reference to patients without angina or ST depression.

Non-typical angina \( (n = 590) \) was not associated with increased risk of ACS, neither during long-term follow-up \( (\text{HR}: 0.8 \ (0.5–1.2)) \) nor for ACS within 1 year \( (1.6 \ (0.6 – 3.0)) \) when compared to patients without any chest pain. Typical angina was not associated with increased cardiovascular mortality after adjustment for confounding factors \( (1.08 \ (0.73–1.60)) \), whereas ST depression was \( (1.69 \ (1.34–2.14)) \).

### 3.1 Female subjects

Two hundred females \( (3.7\%) \) were diagnosed with ACS during follow-up, and 134 \( (2.5\%) \) died from a cardiovascular cause. Incident ACS was more than four times as frequent in females with typical angina \( (n = 209) \) than in those without typical angina \( (n = 5257) \), 13.4% vs. 3.3% \( (p < 0.001) \). ACS occurred in 23.3% of patients with both typical angina and ST depression, compared to 2.8% for those with neither typical angina nor ST depression \( (p < 0.001) \). Hazard ratios for incident ACS during complete follow-up for females are presented in Table S3.

After adjusting for confounding factors, the HR for ACS within 1 year was 19.6 \( (8.9–43.1) \) for patients with typical angina and ST depression, 4.2 \( (1.6–11.1) \) for patients with typical angina but no ST depression, and 2.8 \( (1.5–5.3) \) for patients with ST depression but no
TABLE 2
Selected exercise stress test variables stratified by typical angina and significant ST depression

<table>
<thead>
<tr>
<th></th>
<th>All (N = 11 605)</th>
<th>Ang−/ECG− (n = 9780)</th>
<th>Ang+/ECG− (n = 273)</th>
<th>Ang−/ECG+ (n = 1367)</th>
<th>Ang+/ECG+ (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR max, min⁻¹</td>
<td>155 (34)</td>
<td>155 (34)</td>
<td>139 (29)</td>
<td>141 (34)</td>
<td>131 (28)</td>
</tr>
<tr>
<td>% of pred. max HR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95 (15)</td>
<td>95 (14)</td>
<td>81 (21)</td>
<td>84 (23)</td>
<td>87 (18)</td>
</tr>
<tr>
<td>SBP max, mmHg</td>
<td>195 (35)</td>
<td>195 (35)</td>
<td>190 (35)</td>
<td>195 (40)</td>
<td>190 (40)</td>
</tr>
<tr>
<td>W&lt;sub&gt;max&lt;/sub&gt; of pred. in %</td>
<td>89.2 (24.3)</td>
<td>90.4 (24.3)</td>
<td>80.9 (21.0)</td>
<td>83.9 (22.3)</td>
<td>74.6 (18.1)</td>
</tr>
<tr>
<td>RPE ≥ 17, n (%)</td>
<td>10 543 (90.9)</td>
<td>9012 (93.5)</td>
<td>223 (83.2)</td>
<td>1182 (87.7)</td>
<td>126 (68.1)</td>
</tr>
</tbody>
</table>

Abbreviations: Ang−, no typical angina; Ang+, typical angina; ECG−, no significant ST depression during or at 4 min after exercise; ECG+, significant ST depression during or at 4 min after exercise; HR, heart rate; max, maximal; min, minutes; pred, predicted; RPE, rating of perceived exertion; SBP, systolic blood pressure; W<sub>max</sub>, maximal work load (exercise capacity) in Watts.

All variables are presented as median (interquartile range) except for RPE: n (%).
<sup>a</sup>Predicted maximal heart rate: 220 – age.

typical angina, in reference to patients with neither typical angina nor ST depression.

3.2 | Male subjects

Among male patients, 423 (6.9%) were diagnosed with ACS during follow-up, and 185 (3.0%) died from a cardiovascular cause. Incident ACS was more common in male patients with typical angina (n = 249) compared to those without typical angina (n = 5890), 28.9% vs. 6.0% (p < 0.001). ACS occurred in 33.6% of patients with both typical angina and ST depression, compared to 4.9% for those with neither typical angina nor ST depression (p < 0.001). For men, typical angina and ST depression yielded a similar risk of incident ACS as typical angina without ST depression (Table S3).

The adjusted HR for ACS within 1 year was 19.1 (11.8–31.0) for males with typical angina and ST depression, 15.6 (9.1–26.7) for males with typical angina but no ST depression, and 4.3 (2.7–6.8) for males with ST depression but no typical angina, in reference to males with neither typical angina nor ST depression.

4 | DISCUSSION

Our study shows that the prognostic value of exercise stress testing could be improved by considering presence of typical angina during the test. Both typical angina and ST depression during the test were associated with increased risk of future ACS, in both men and women. The greatest risk of future cardiovascular events was found among patients who presented with both entities, and particularly high for ACS within 1 year. Even in the absence of ST depression, typical angina increased the risk of future ACS, particularly in male patients.

On the other hand, most patients who suffered from ACS did not have typical angina during the stress test. This was evident especially among women, among whom less than 15% who suffered from future ACS had typical angina. This is not unexpected, since typical angina is more likely to occur with obstructive coronary heart disease, and while obstructive lesions are more likely to become occluded, the majority of AMI occurs in non-obstructive lesions (Falk, et al. 1995). In emergency care settings, women have been reported to experience atypical anginal symptoms more commonly than men (Patel, et al. 2004). In patients presenting with chest pain in a primary care setting, however, typical angina was not more common in men than in women, among those who eventually diagnosed with coronary heart disease (Bösner, et al. 2009).

Our findings confirm and extend those from Cole et al. who reported that AMI, angina progression and cardiovascular death were twice as frequent during follow-up among patients with angina during treadmill testing compared to those without (Cole & Ellestad, 1978). Importantly, we also show that the risk of incident ACS during the first year after an exercise test is low among patients with no typical angina or ST depression. For example, in patients without typical angina, only 1% was diagnosed with ACS within 1 year, and even less if neither ST depression nor typical angina was present (0.7%). The risk was increased more than twenty times in patients with both typical angina and ST depression during the test. These results are of direct clinical importance for physicians interpreting exercise tests.

Our findings highlight the value of assessing symptoms during exercise, as it has been shown that clinical history of angina cannot predict neither ACS (Fanaroff, et al. 2015) nor inducible ischaemia during stress testing (Hermann, et al. 2010). In a primary care setting, known cardiovascular disease, a history of worsened pain during exercise, and an assumed cardiac origin according to the patient were associated with an increased risk coronary heart disease.
Studies on the accuracy of clinical history in the setting of chronic coronary heart disease are lacking. When symptoms were assessed by experienced personnel during standardized exercise provocation, typical angina was strongly associated with future ACS, both during short-term and long-term follow-up. As opposed to clinical history, standardized testing allows for an excellent possibility to account for also the typical temporal pattern of angina symptoms. It remains to be elucidated, whether this adds incremental information to the clinical history alone. It should be noted that when sensitivity analysis was performed for AMI as a sole outcome, the association was weaker, albeit still very strong for prediction of AMI within 1 year after the test.


![Flow chart of patient inclusion and exclusion](image1)

![Venn diagram showing the number and proportion of patients with typical angina with or without ST depression in relation to total sample. The area of the circles is proportional to the size of each group](image2)
was not associated with future ACS. In another study, chest pain was more common in patients with coronary artery disease compared to those with normal coronary arteries (5% vs. >29%), but only ST depression was included when reporting the accuracy of the test (Hecht, et al. 1993). As shown in our study, relying only on ST depression when determining the clinical value of exercise stress testing is inferior to systematically considering additional clinical information such as the occurrence of typical angina. In addition, the SBP response (Hedman, et al. 2019; Sipila, et al. 2019; Tsuda, et al. 1993), exercise capacity (Forslund, et al. 2000; Myers, et al. 2002; Salokari, et al. 2019; Sipila, et al. 2019) and heart rate recovery (Cole, et al. 1999; Sipila, et al. 2019) have been shown prognostic of future ACS and mortality. In the same cohort, we have previously shown that exercise capacity is strongly associated with both all-cause and cardiovascular mortality, as well as hospitalization for ischaemic heart disease and heart failure (Lindow, et al. 2019). Thus, despite that exercise stress testing has been shown to have poor diagnostic accuracy regarding obstructive coronary heart disease, using anatomical coronary angiography as reference standard (Knuuti, et al. 2018), this study highlights the clinical usefulness of exercise stress testing, especially from a prognostic perspective, but also the importance of not interpreting the test based on the ST response alone. In addition, in an era when interventional treatment of coronary heart disease is being questioned (Al-Lamee, et al. 2018; Maron, et al. 2020; Maron, et al. 2009), prognostic information may be even more important to guide therapeutic decisions. For that purpose, exercise stress testing is a cheap and widely available alternative.

In treadmill exercise stress testing, the Duke Treadmill score is commonly used, and is well validated for risk stratification (Mark, et al. 1987; Mark, et al. 1991). In that score, an "angina index" is incorporated with a value of 0 in the absence of angina during the test, 1 for non-limiting angina and 2 points if the patient stopped the due to anginal symptoms. This is in line with our findings that typical angina was

### TABLE 3  Outcomes, hazard ratios and c statistics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>HR (Crude)</th>
<th>c</th>
<th>HR (Model I)</th>
<th>c</th>
<th>HR (Model II)</th>
<th>c</th>
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<tbody>
<tr>
<td><strong>ACS during complete follow-up</strong></td>
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<td></td>
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<tr>
<td>Ang−/ECG−</td>
<td>9780</td>
<td>383 (3.9)</td>
<td>1.0</td>
<td>0.64 (0.62–0.66)</td>
<td>1.0</td>
<td>0.74 (0.72–0.76)</td>
<td>1.0</td>
<td>0.81 (0.79–0.83)</td>
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<td>Ang+/ECG−</td>
<td>273</td>
<td>44 (16.1)</td>
<td>3.9 (2.9–5.5)</td>
<td>3.1 (2.3–4.3)</td>
<td>2.4 (2.0–3.0)</td>
<td>1.7 (1.4–2.0)</td>
<td>2.7 (2.0–3.7)</td>
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<tr>
<td>Ang−/ECG+</td>
<td>1367</td>
<td>140 (10.2)</td>
<td>2.7 (2.3–3.3)</td>
<td>4.6 (3.9–5.3)</td>
<td>6.6 (4.9–8.7)</td>
<td>3.5 (2.6–4.7)</td>
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<tr>
<td>Ang+/ECG+</td>
<td>185</td>
<td>56 (30.3)</td>
<td>8.8 (6.6–11.7)</td>
<td>6.6 (4.9–8.7)</td>
<td>3.5 (2.6–4.7)</td>
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<td><strong>ACS within 1 year</strong></td>
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<tr>
<td>Ang−/ECG−</td>
<td>9780</td>
<td>65 (0.7)</td>
<td>1.0 (0.77–0.80)</td>
<td>1.0</td>
<td>11.6 (7.3–18.5)</td>
<td>0.85 (0.83–0.88)</td>
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<td>273</td>
<td>25 (9.2)</td>
<td>14.6 (9.1–27.2)</td>
<td>5.4 (3.8–7.7)</td>
<td>3.9 (2.7–5.7)</td>
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<tr>
<td>Ang−/ECG+</td>
<td>1367</td>
<td>56 (4.1)</td>
<td>6.3 (4.4–9.0)</td>
<td>28.9 (19.6–42.8)</td>
<td>20.8 (13.9–31.1)</td>
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<tr>
<td>Ang+/ECG+</td>
<td>185</td>
<td>42 (22.7)</td>
<td>39.9 (27.1–58.8)</td>
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<td><strong>Death from cardiovascular cause</strong></td>
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<tr>
<td>Ang−/ECG−</td>
<td>9780</td>
<td>195 (2.0)</td>
<td>1.0 (0.62–0.65)</td>
<td>1.0</td>
<td>0.78 (0.75–0.80)</td>
<td>1.0</td>
<td>0.87 (0.85–0.89)</td>
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<tr>
<td>Ang+/ECG−</td>
<td>273</td>
<td>10 (3.7)</td>
<td>1.6 (0.8–3.0)</td>
<td>0.9 (0.6–2.1)</td>
<td>0.9 (0.5–1.8)</td>
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<td>Ang−/ECG+</td>
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<td>18 (9.7)</td>
<td>4.4 (2.7–7.2)</td>
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<td>1.5 (0.9–2.5)</td>
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</table>

**Abbreviations:** ACS, acute coronary syndrome; Ang−, no typical angina; Ang+, typical angina; ECG−, no ST depression; ECG+, ST depression; HR, hazard ratio.

c = concordance statistics with 95% confidence interval.

Model I: adjusted for % of predicted exercise capacity.

Model II: adjusted as in I + age, sex, hypertension, heart failure, cerebrovascular disease, valvular heart disease, stable angina, hypercholesterolaemia, diabetes mellitus and BMI.

*At atrial fibrillation is included in the adjustment for cardiovascular mortality.
strongly predictive of future risk but fairly uncommon (~4%), it may be well suited for inclusion in a similar score for bicycle exercise testing. Interestingly, we found ST depression, but not typical angina, to be associated with increased cardiovascular mortality, despite that patients with typical angina had a higher incidence of ACS. This confirms the results by Daugherty et al, who reported that typical angina was associated with increased risk of AMI, but not with cardiovascular mortality (Daugherty, et al. 2011). It is possible that typical angina is mainly associated with obstructive coronary heart disease, but that ST depression can occur not only in those patients but also in patients with other myocardial pathology, for example valvular or hypertensive heart disease (Fitzgerald, et al. 2019), or even microvascular dysfunction (Ong, et al. 2014). This hypothesis is, in part, supported in our data by a larger prevalence of hypertension in the group of patients with positive ECG but no typical angina. Asymptomatic ST depression during exercise has been reported to be associated with increased risk of sudden cardiac death, particularly in patients with hypercholesterolaemia or hypertension (Laakkanen, et al. 2009). Another potential explanation could be that exercise tests among patients with ST depression, but no angina had been falsely interpreted as negative and that patients thereby were not treated to reduce the risk of future ACS. Given the low prevalence of ACS within 1 year after test in those patients, this seems unlikely.

In many studies evaluating the diagnostic accuracy of exercise ECG for the diagnosis of obstructive ischaemic heart disease, the leads included are not specified (Beygui, et al. 2000; Chae, et al. 1993; Daou, et al. 2002; Hecht, et al. 1993; Kajinami, et al. 1995; Koskinen, et al. 1987; Nallamothu, et al. 1995). We used a definition of ST depression based on a previous study evaluating the diagnostic value of different leads (Viik, et al. 1998). In that study, sensitivity increased when aVL and I were included with a separate cut-off value (0.05 mV), without any loss in specificity. Despite this, ST depression had marginal prognostic value in the absence of typical angina. It is, however, possible that the prognostic value of ST depression is different if other criteria are applied.

The major strength of this study is the large number of patients with extensive follow-up through national patient registries with no patients lost to follow-up, except for potential emigration. A limitation of this study is the lack of information on smoking habits, a well-known risk factor for ischaemic heart disease. Importantly, we also lack information on how patients were managed after the test, for example regarding both medical treatment and revascularization procedures, both of which are important determinants of the prognosis of the patients. This information would have been necessary
to understand how differences in patient management may have affected the ACS incidence among the different groups in this study.

This study did not include assessment of chest pain based on the commonly used Category Rating 10 scale (CR-10), since this does not take the type of angina into account, and this may complicate comparisons with other studies on this topic. In addition, it is possible that our main outcome ACS (including a diagnosis of UA) may be prone to incorporation bias, if clinicians included the typical symptoms from the exercise test in the incident diagnosis. However, our sensitivity analyses revealed a strong association when assessing only AMI as outcome, as well as when patients with a time to event within 30 days were excluded. The presence of typical angina during the test was assessed by a large number of observers during the test period, and we acknowledge that although the observers were instructed to emphasize the temporal behaviour of the anginal symptoms, inter-observer variability may have affected the results. However, we consider this to closely resemble a real-life clinical setting, where multiple physicians are involved in test interpretations.

5 | CONCLUSION

Typical angina during exercise stress testing is predictive of future acute coronary syndrome, especially in combination with ST depression, and particularly during the first year after the test. We show that the exercise test is an important prognostic tool, especially when not including ECG changes only in the prediction models. This should be considered in future updates on guidelines for evaluation of ACS.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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