Impact of residual angina on long-term clinical outcomes after percutaneous coronary intervention or coronary artery bypass graft for complex coronary artery disease


Aims
The aim of this study was to investigate the impact on 10-year survival of patient-reported anginal status at 1 year following percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in patients with left main coronary artery disease (LMCAD) and/or three-vessel CAD (3VD).

Methods and results
In this post hoc analysis of the randomized SYNTAX Extended Survival study, patients were classified as having residual angina (RA) if their self-reported Seattle Angina Questionnaire angina frequency (SAQ-AF) scale was ≤ 90 at the 1-year follow-up post-revascularization with PCI or CABG. The primary endpoint of all-cause death at 10 years was compared between the RA and no-RA groups. A sensitivity analysis was performed using a 6-month SAQ-AF. At 1 year, 373 (26.1%) out of 1428 patients reported RA. Whilst RA at 1 year was an independent correlate of repeat revascularization at 5 years [18.3 vs. 11.5%; adjusted hazard ratio (HR): 1.54; 95% confidence interval (CI): 1.10–2.15], it was not associated with all-cause death at 10 years (22.1 vs. 21.6%; adjusted HR: 1.11; 95% CI: 0.83–1.47). These results were consistent when stratified by the modality of revascularization (PCI or CABG) or by anginal frequency. The sensitivity analysis replicating the analyses based on 6-month angina status resulted in similar findings.

Conclusion
Among patients with LMCAD and/or 3VD, patient-reported RA at 1 year post-revascularization was independently associated with repeat revascularization at 5 years; however, it did not significantly increase 10-year mortality, irrespective of the primary modality of revascularization or severity of RA.

* Corresponding author. Tel: +353 91 524411, Email: patrick.serruys@nuigalway.ie

Trial Registration: SYNTAXES ClinicalTrials.gov reference: NCT03417050.
SYNTAX ClinicalTrials.gov reference: NCT00114972.

© The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Graphical Abstract

Residual angina, which was common (26.1%) at 1 year after coronary revascularization, was associated with repeat revascularization events up to 5 years, but not with all-cause death up to 10 years.

Keywords

Quality of life • CABG • PCI • Revascularization • SYNTAX • Angina • Left-main coronary artery disease • Three-vessel disease • 10-year Survival

Abbreviations

CABG, coronary artery bypass graft
CAD, coronary artery disease
GDMT, guideline-directed medical therapy
LMCAD, left main coronary artery disease
MI, myocardial infarction
PCI, percutaneous coronary intervention
SAQ, Seattle Angina Questionnaire
SYNTAXES, Synergy between PCI with Taxus and Cardiac Surgery Extended Survival
QOL, quality of life
RA, recurrent angina
3VD, three-vessel disease

Introduction

Improving angina is one of the main objectives of coronary revascularization in patients with obstructive coronary artery disease (CAD)1,2. Patient-reported outcome measures, such as the Seattle Angina Questionnaire (SAQ), have been validated and used in clinical trials as the gold standard objective assessment of patients’ symptoms and quality of life (QoL) from their perspective.3–5 Recently, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial demonstrated that an invasive strategy with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) yielded a significant improvement in the SAQ anginal frequency (SAQ-AF) scale compared with conservative treatment with guideline-directed medical therapy (GDMT) alone out to 4 years among patients with stable CAD and moderate to severe myocardial ischaemia. Despite the substantial benefits of revascularization in improving patients’ health status, it is well documented that considerable numbers of patients experience residual angina (RA) after revascularization6–11 and currently, the impact of this on long-term clinical outcomes and vital status has not been fully investigated.

Although the aforementioned ISCHEMIA trial did not show any survival benefit with invasive treatment compared with conservative treatment, a recent meta-analysis suggested that revascularization (by either PCI or CABG) could reduce the incidence of spontaneous myocardial infarction (MI) and cardiac death, particularly over longer follow-up.12 Furthermore, several studies have suggested that patient-reported anginal status, including the SAQ-AF scale, could be associated with future adverse cardiovascular events, potentially identifying the risk for long-term mortality in patients with CAD.13–18 Thus, it is hypothesized that RA, identified using the SAQ-AF scale, in the early phase following PCI or CABG—which may reflect early stent thrombosis/restenosis, graft occlusion/stenosis, incomplete revascularization, and/or progression of CAD—could be associated with increased long-term serious adverse events, especially in high-risk patients with complex CAD. Nevertheless, thus far, no study has reported the relationship between RA after coronary revascularization and very long-term clinical outcomes—particularly among patients with complex CAD. To address this gap in knowledge, we investigated the association of patient-reported RA post coronary revascularization on 10-year all-cause death among patients who underwent PCI or CABG for three-vessel disease (3VD) and/or left main CAD (LMCAD).

Methods

SYNTAXES study

This study is a post hoc analysis of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) Extended Survival (SYNTAXES) study (NCT03417050),19 which was an investigator-driven extended 10-year follow-up of the SYNTAX trial (NCT00114972) beyond its original final follow-up of 5 years.20,21 In brief, the SYNTAX trial was a multicentre, randomized controlled trial done in 85 hospitals across 18 North American and European countries. A total of 1800 patients with de novo three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD), who were deemed eligible for both PCI and CABG based on clinical
Residual angina and 10-year follow-up post revascularization

judgement and the consensus of a Heart Team, were enroled between March 2005 and April 2007 and randomized in a 1:1 fashion either to receive PCI (n = 903) with uniform use of TAXUS Express paclitaxel-drug eluting stents (Boston Scientific Corporation, Marlborough, MA, USA) or CABG (n = 897).

The main 10-year mortality of the SYNTAXES study has been reported previously. Patient-reported anginal status after PCI or CABG has also been reported through 5 years. The SYNTAX (NCT00114972) and SYNTAXES (NCT03417050) trials were approved by the ethics committees at each investigating centre, and all patients provided their written informed consent prior to participation in the SYNTAX trial. Follow-up was performed in accordance with local law and regulations of each participating institution and complied with the Declaration of Helsinki.

**Anginal status**

Anginal status was assessed directly from patients using the self-reported Seattle Angina Questionnaire (SAQ), a valid and reliable measure of angina severity. The SAQ is a 19-item questionnaire that measures five domains of health status related to CAD: angina frequency (AF), physical limitations (PLs), disease perception/QOL, angina stability (AS), and treatment satisfaction (TS). The SAQ-AF scale is comprised of two questions that quantify the frequency of angina: (i) ‘over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina’; and (ii) ‘over the past 4 weeks, on average, how many times have you had to take nitros (nitroglycerin tablets) for your chest pain, chest tightness, or angina’. The score ranges from 0 to 100 (with intervals of 10 points), with higher scores indicating fewer anginal symptoms and a score of 100 indicating no angina over the past 4 weeks. Questionnaires were completed in person or by mail at baseline and at the time of scheduled follow-up visits at 1 and 6 months, and at 1, 3, and 5 years.

For the purpose of this study, the presence of angina was defined as a SAQ-AF score ≤ 90. In addition, the frequency of angina was categorized according to the SAQ-AF score as previously described; monthly angina (SAQ-AF: 70–90), weekly angina (SAQ-AF: 40–60), or daily angina (SAQ-AF: 0–30). Patients were classified as having RA according to their SAQ-AF score at the 1-year follow-up visit after randomization. Patients who died or were lost to follow-up prior to the scheduled 1-year follow-up and those who had no available SAQ-AF score at the 1-year visit were excluded.

**Study endpoints**

The primary endpoint of this study was all-cause death between 1 and 10 years. Vital status was confirmed by using an electronic healthcare record review and national death registries. Patients with missing vital status were included in the analysis and censored at the time of loss to follow-up or at 5 years if recruiting centres did not participate in the SYNTAXES study for 10-year extended follow-up (a total of five patients at two centres). We also assessed the incidence of cardiac death, MI, stroke, and repeat revascularization between 1 and 5 years (as part of the original SYNTAX trial). These events were adjudicated by an independent clinical events committee according to the definitions reported in the protocol and the design publication.

**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation (SD) and were compared using independent t-tests. Categorical variables are presented as counts and percentages and were compared using the χ² test or Fisher’s exact test, as appropriate. The event rates were calculated using the Kaplan–Meier method.

The incidences of all-cause death at 10 years or other clinical endpoints at 5 years were compared between patients with and without RA, both overall and by randomization treatment (PCI or CABG), using unadjusted and adjusted Cox proportional hazard models, with an evaluation of the treatment-by-subgroup interaction. Covariates in the adjusted model included age, sex, medically treated diabetes, hypertension, dyslipidaemia, current smoking, previous MI, cerebrovascular disease, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), creatinine clearance, left ventricular ejection fraction (poor/≤ 40%, intermediate/41–50%, or good/> 50%), LMCA involvement, anatomical SYNTAX score, and achievement of complete revascularization. These covariates were selected based on prior knowledge of the association of these covariables with the outcomes.

In an exploratory analysis, we assessed the incidence of all-cause death at 10 years and repeat revascularization at 5 years according to categorical AF (daily, weekly, or monthly) at the 1-year visit. Finally, as a sensitivity analysis, we evaluated clinical outcomes in patients with or without RA based on the SAQ-AF scale at 5 months post revascularization. For the sensitivity analysis, analyses were identical to those using 1-year RA except that all the clinical endpoints were assessed from 6 months up to 10 years (all-cause death) or 5 years (cardiac death, MI, stroke, repeat revascularization).

A two-sided P value of < 0.05 was considered to indicate statistical significance. All analyses were performed in SPSS Statistics, version 26 (IBM Corp., Armonk, 281 NY, USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

A total of 1800 patients enrolled in the SYNTAX study between March 2005 and April 2007; of those, 72 who died within the first year after randomization, 12 patients who were lost to follow-up, and 288 patients who did not have available anginal status documented at the 1-year visit were excluded from our analysis. The final analytic cohort consisted of 1428 patients (748 in the PCI arm and 680 in the CABG arm) (Figure 1).

The mean value ± SD of the SAQ-AF score at 1 year was 93.1 ± 15.1. A total of 373 (26.1%) patients reported angina [212 (28.3%) in the PCI arm and 161 (23.7%) in the CABG arm], with 19 (5.1%), 78 (20.9%), and 276 (74.0%) patients experiencing daily, weekly, and monthly angina, respectively.

**Patient and lesion characteristics**

Table 1 presents baseline patient and lesion characteristics according to patient-reported angina at 1 year. Compared with those without RA, the patients with RA were younger, more frequently female, had higher BMIs, more frequently had hypertension, previous MI, PVD, and COPD, less frequently presented with silent ischaemia,
<table>
<thead>
<tr>
<th>Baseline characteristics in patients with or without angina according to SAQ-AF score at 1 year</th>
<th>Angina at 1 year</th>
<th>No-angina at 1 year</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomization</strong></td>
<td>56.8 (212/373)</td>
<td>50.8 (536/1055)</td>
<td>0.047</td>
</tr>
<tr>
<td>PCI</td>
<td>43.2 (161/373)</td>
<td>49.2 (519/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td>63.6 ± 9.9</td>
<td>65.5 ± 9.5</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>74.3 (277/373)</td>
<td>79.9 (843/1055)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25.7 (96/373)</td>
<td>20.1 (212/1055)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28.5 ± 4.5</td>
<td>27.9 ± 4.6</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>70.8 (26/373)</td>
<td>65.0 (686/1055)</td>
<td>0.048</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24.9 (93/373)</td>
<td>23.3 (246/1055)</td>
<td>0.525</td>
</tr>
<tr>
<td>On insulin</td>
<td>9.4 (35/373)</td>
<td>9.3 (98/1055)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79.6 (293/368)</td>
<td>77.3 (810/1048)</td>
<td>0.381</td>
</tr>
<tr>
<td>Current smoking</td>
<td>20.1 (75/373)</td>
<td>18.1 (190/1052)</td>
<td>0.395</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>26.4 (97/367)</td>
<td>32.9 (343/1043)</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Previous cerebrovascular disease</strong></td>
<td>15.9 (59/371)</td>
<td>12.7 (133/1049)</td>
<td>0.133</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>5.9 (22/371)</td>
<td>3.6 (38/1051)</td>
<td>0.070</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>4.6 (17/371)</td>
<td>4.2 (44/1050)</td>
<td>0.766</td>
</tr>
<tr>
<td>Previous carotid artery disease</td>
<td>8.3 (31/373)</td>
<td>7.4 (78/1055)</td>
<td>0.571</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11.0 (41/373)</td>
<td>7.5 (79/1055)</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>11.0 (41/373)</td>
<td>6.9 (73/1055)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td>17.4 (60/345)</td>
<td>18.1 (178/981)</td>
<td>0.807</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>88.9 ± 29.2</td>
<td>85.5 ± 32.9</td>
<td>0.080</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>59.6 ± 12.8</td>
<td>59.0 ± 12.7</td>
<td>0.410</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>3.3 (12/364)</td>
<td>2.6 (27/1049)</td>
<td>0.461</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Silent ischaemia</td>
<td>7.5 (28/373)</td>
<td>16.7 (176/1055)</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>67.3 (251/373)</td>
<td>53.3 (562/1055)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>25.2 (94/373)</td>
<td>30.0 (317/1055)</td>
<td></td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>3.4 ± 2.3</td>
<td>3.7 ± 2.6</td>
<td>0.031</td>
</tr>
<tr>
<td>Parsonnet SCORE</td>
<td>8.0 ± 6.4</td>
<td>8.3 ± 6.9</td>
<td>0.531</td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
<td>0.624</td>
</tr>
<tr>
<td><strong>3VD</strong></td>
<td>58.2 (217/373)</td>
<td>59.7 (630/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>LMCAD</strong></td>
<td>41.8 (156/373)</td>
<td>40.3 (425/1055)</td>
<td></td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
<td>0.678</td>
</tr>
<tr>
<td><strong>LMCAD only</strong></td>
<td>6.2 (23/373)</td>
<td>5.2 (55/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>LMCAD + 1VD</strong></td>
<td>8.3 (31/373)</td>
<td>7.7 (81/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>LMCAD + 2VD</strong></td>
<td>10.2 (38/373)</td>
<td>12.6 (133/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>LMCAD + 3VD</strong></td>
<td>17.2 (64/373)</td>
<td>14.8 (156/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>2VD (no LMCAD)</strong></td>
<td>1.9 (7/373)</td>
<td>2.2 (23/1055)</td>
<td></td>
</tr>
<tr>
<td><strong>3VD (no LMCAD)</strong></td>
<td>56.3 (210/373)</td>
<td>57.5 (607/1055)</td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>4.3 ± 1.8</td>
<td>4.4 ± 1.8</td>
<td>0.414</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>27.7 ± 11.6</td>
<td>28.8 ± 11.5</td>
<td>0.092</td>
</tr>
<tr>
<td>SYNTAX score tercile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>36.6 (136/372)</td>
<td>31.8 (334/1051)</td>
<td>0.096</td>
</tr>
<tr>
<td>Intermediate</td>
<td>33.1 (123/372)</td>
<td>34.3 (360/1051)</td>
<td>0.703</td>
</tr>
<tr>
<td>High</td>
<td>30.4 (113/372)</td>
<td>34.0 (357/1051)</td>
<td>0.223</td>
</tr>
<tr>
<td>Predicted 10-year mortality rates by SYNTAX score II 2020 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any total occlusion</td>
<td>24.9 ± 17.9</td>
<td>25.9 ± 17.5</td>
<td>0.327</td>
</tr>
<tr>
<td>Any bifurcation</td>
<td>20.5 (76/371)</td>
<td>23.4 (246/1050)</td>
<td>0.279</td>
</tr>
<tr>
<td>Number of stents</td>
<td>69.0 (256/371)</td>
<td>73.5 (772/1050)</td>
<td>0.105</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>4.7 ± 2.4</td>
<td>4.6 ± 2.2</td>
<td>0.390</td>
</tr>
<tr>
<td>Total stent length per patient</td>
<td>88.7 ± 52.3</td>
<td>84.5 ± 47.2</td>
<td>0.291</td>
</tr>
<tr>
<td>Off pump CABG</td>
<td>10.7 (17/159)</td>
<td>12.5 (64/514)</td>
<td>0.676</td>
</tr>
</tbody>
</table>
Table 1 | Continued

<table>
<thead>
<tr>
<th></th>
<th>Angina at 1 year</th>
<th>No-angina at 1 year</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N = 373 )</td>
<td>( N = 1055 )</td>
<td></td>
</tr>
<tr>
<td>Number of total conduits</td>
<td>2.7 ± 0.7</td>
<td>2.7 ± 0.7</td>
<td>0.770</td>
</tr>
<tr>
<td>Number of arterial conduits</td>
<td>1.4 ± 0.7</td>
<td>1.4 ± 0.7</td>
<td>0.782</td>
</tr>
<tr>
<td>Number of venous conduits</td>
<td>1.3 ± 0.9</td>
<td>1.3 ± 0.9</td>
<td>0.820</td>
</tr>
<tr>
<td>Complete revascularization</td>
<td>63.0 (233/370)</td>
<td>60.1 (633/1054)</td>
<td>0.353</td>
</tr>
<tr>
<td>Residual SYNTAX score</td>
<td>4.06 ± 5.58</td>
<td>3.82 ± 5.64</td>
<td>0.612</td>
</tr>
<tr>
<td>Residual SYNTAX score ≥ 8</td>
<td>18.4 (39/212)</td>
<td>13.1 (69/527)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Medication at discharge

| Any antiplatelet therapy | 93.5 (346/370) | 94.1 (992/1054) | 0.704   |
| Thienopyridine           | 61.6 (228/370) | 59.4 (626/1054) | 0.460   |
| Statin                   | 83.2 (308/370) | 82.5 (870/1054) | 0.811   |
| Beta blocker             | 79.7 (295/370) | 81.0 (854/1054) | 0.593   |
| ACE-I                    | 51.1 (189/370) | 48.8 (514/1054) | 0.468   |
| ARB                      | 10.3 (38/370)  | 9.8 (103/1054)    | 0.762   |

SAQ angina score at baseline 60.1 ± 26.0 72.7 ± 25.2 <0.001

Data are presented as mean ± standard deviation or percentage (number).

aCKD was defined as creatinine clearance < 60 mL/min.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BMI, body mass index; MI, myocardial infarction; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; SS II 2020; SYNTAX score II 2020; LMCAD, left main coronary artery disease; 3VD, three-vessel disease; 1VD, single-vessel disease; 2VD, two-vessel disease; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; ACE-I, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blocker.

Table 2 | Unadjusted and adjusted hazard ratios for clinical outcomes in patients with angina vs. no angina at 1 year

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>( N )</th>
<th>Unadjusted HR (95% CI)</th>
<th>P-value</th>
<th>Adjusted HR(^{a}) (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death at 10 years</td>
<td>300</td>
<td>1.03 (0.80–1.33)</td>
<td>0.829</td>
<td>1.11 (0.83–1.47)</td>
<td>0.481</td>
</tr>
<tr>
<td>All-cause death at maximum follow-up</td>
<td>391</td>
<td>1.06 (0.85–1.33)</td>
<td>0.587</td>
<td>1.12 (0.88–1.43)</td>
<td>0.356</td>
</tr>
<tr>
<td>Cardiac death at 5 years</td>
<td>51</td>
<td>0.79 (0.40–1.53)</td>
<td>0.481</td>
<td>0.92 (0.45–1.91)</td>
<td>0.827</td>
</tr>
<tr>
<td>MI at 5 years</td>
<td>38</td>
<td>0.24 (0.07–0.77)</td>
<td>0.016</td>
<td>0.28 (0.08–0.92)</td>
<td>0.036</td>
</tr>
<tr>
<td>Stroke at 5 years</td>
<td>19</td>
<td>0.71 (0.24–2.13)</td>
<td>0.543</td>
<td>1.03 (0.32–3.29)</td>
<td>0.957</td>
</tr>
<tr>
<td>Revascularization at 5 years</td>
<td>178</td>
<td>1.71 (1.26–2.32)</td>
<td>0.001</td>
<td>1.54 (1.10–2.15)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

\(^{a}\) Adjusted covariates includes age, sex, body mass index, medically treated diabetes, hypertension, dyslipidaemia, current smokers, previous MI, previous cerebrovascular disease, peripheral vascular disease, COPD, creatinine clearance, LVEF, LMCAD involvement, anatomical SYNTAX score, and achievement of complete revascularization at discharge.

HR, hazard ratio; CI, confidence interval; \( N \), number of patients. Other abbreviations are as in Table 1.

Clinical outcomes according to the presence or absence of SAQ angina at the 1 year visit

At 5 years, there was no evidence of an association between the presence of patient-reported angina at 1 year and the crude risk of cardiac death (HR: 0.79; 95% CI: 0.40–1.53) or stroke (HR: 0.71; 95% CI: 0.24–2.13, Table 2). Patients with angina at 1 year had a significantly lower crude risk of MI (HR: 0.24; 95% CI: 0.07–0.77) but a higher crude risk of repeat revascularization (HR: 1.71; 95% CI: 1.26–2.32, Figure 2 and Table 2). After adjusting for potential confounders, these risk differences for MI (HR: 0.28; 95% CI: 0.08–0.92) and repeat...
Figure 2 Cumulative incidences of repeat revascularization up to 5 years in patients with or without RA after initial PCI or CABG. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; other abbreviations as in Figure 1.

Figure 3 Cumulative incidence of all-cause death at 10 years in patients with or without patient-reported angina at 1-year visit. There was no significant difference in incidence of all-cause death up to 10 years between angina and no-angina at a 1-year visit.

Figure 3 Cumulative incidence of all-cause death at 10 years in patients with or without patient-reported angina at 1-year visit. There was no significant difference in incidence of all-cause death up to 10 years between angina and no-angina at a 1-year visit.

The cumulative incidence of all-cause death at 10 years (22.1 vs. 21.6%; HR: 1.03; 95% CI: 0.80–1.33; log-rank P = 0.829, Figure 3 and Table 2), and at the maximum follow-up period (HR: 1.06; 95% CI: 0.85–1.33) was similar between patients with vs. without RA at 1 year. These findings were similar when the analysis was adjusted for confounding variables (adjusted HR: 1.11; 95% CI: 0.83–1.47) or when the analysis was extended to include all available follow-ups—with or without risk adjustment (Table 2).

Clinical outcomes according to AF at the 1-year visit are presented in Table 3. All-cause death at 10 years did not differ significantly according to AF, irrespective of whether it was defined categorically (monthly or daily/weekly) or continuously, with or without risk adjustment (Table 3 and Supplementary material online, Figure S1). In contrast, when compared with those without RA at 1 year, repeat revascularization at 5 years was more frequent in patients with monthly angina (crude HR: 1.62; 95% CI: 1.15–2.28, adjusted HR: 1.48; 95% CI: 1.02–2.15) or daily/weekly angina (crude
There were no significant differences between 6-month RA and no-RA at 5 years (crude HR: 1.88; 95% CI: 1.44–2.46; adjusted HR: 1.94; 95% CI: 1.46–2.58, Supplementary material online, Table S4). The relationship between RA and an increased risk of repeat revascularization at 5 years was driven mainly by PCI (adjusted HR: 1.66; 95% CI: 1.11–2.48) in the adjusted risk of repeat revascularization at 5 years (Table 3).

Revascularization mode of PCI or CABG

When stratified by the randomized treatment arm (PCI or CABG), the risks of cardiac death and stroke at 5 years, as well as all-cause death at 10 years and at maximum follow-up, did not differ significantly between patients with or without SAQ angina at 1 year, regardless of adjustment (Figure 4 and Table 4). Interestingly, among patients assigned to initial PCI, the risk of MI between 1 and 5 years was numerically lower in the RA group compared with the no-RA group (adjusted HR: 0.30; 95% CI: 0.09–1.02). We were unable to assess this relationship among patients assigned to initial CABG because of insufficient events (N = 5). The relationship between RA and an increased risk of repeat revascularization at 5 years was driven mainly by PCI (adjusted HR: 1.66; 95% CI: 1.11–2.50) rather than CABG (adjusted HR: 1.29; 95% CI: 0.71–2.34), although there was no significant treatment-by-subgroup interaction (Pinteraction = 0.661).

Sensitivity analysis using 6-month angina status

The results of the sensitivity analysis using 6-month anginal status are shown in Supplemental material online, Tables S3–S4. Amongst the 1455 patients with an available SAQ-AF scale at 6 months, 434 patients (29.8%) reported RA at 6 months (Supplemental material online, Table S3).

At 10 years, 6-month RA was not associated with all-cause death (crude HR: 0.82; 95% CI: 0.63–1.05; adjusted HR: 0.91; 95% CI: 0.70–1.19). However, similar to the 1-year analysis, RA at 6 months was associated with more frequent repeat revascularization at 5 years (crude HR: 1.88; 95% CI: 1.44–2.46; adjusted HR: 1.94; 95% CI: 1.46–2.58, Supplementary material online, Table S4). There were no significant differences between 6-month RA and no-RA groups in terms of other clinical endpoints, including all-cause death at maximum follow-up and cardiac death, MI, or stroke at 5 years.

Discussion

Identifying residual risk after revascularization can be an important tool in clinical management for identifying patients warranting more aggressive follow-up and treatment. In this study, we examined whether RA 1 year after revascularization was associated with subsequent mortality and other clinical events. The main findings of this study can be summarized as follows: (i) Residual angina was common among patients undergoing PCI or CABG for complex CAD at 1-year follow-up, more than a quarter (26.1%) of patients had RA, defined according to their SAQ-AF score; (ii) Patient-reported RA at 1 year was independently associated with repeat revascularization at 5 years—a difference that was driven mainly by the PCI arm. In addition, a lower SAQ-AF score (higher frequency of angina) at 1 year was associated with a higher risk of repeat revascularization at 5 years; (iii) In contrast to the finding for repeat revascularization, 1-year anginal status was not significantly associated with all-cause death at 10 years, irrespective of the mode of revascularization (PCI or CABG) or the frequency of angina (monthly or daily/weekly angina); (iv) The sensitivity analysis using 6-month self-reported anginal status showed consistent results with RA associated with significantly higher repeat revascularization at 5 years, but not all-cause death at 10 years.

Prevalence of patient-reported RA at 1 year

In the SYNTAX trial, 26.1% of patients (28.3% in PCI and 23.7% in CABG) continued to report angina at 1 year after revascularization. As previously reported, the incidence of RA at 1 year was significantly higher with PCI than with CABG, although the 4.7% absolute difference was not regarded as clinically important. This rate of RA is relatively higher than the 1-year results of the FREEDOM trial (20.5% in PCI and 16.5% in CABG) and the EXCEL trial (21.1% in PCI and 20.5% in CABG), and may be attributable to the presence of more extensive CAD in the SYNTAX trial. Given that a primary treatment goal for CAD is to eliminate angina, identifying these patients for more aggressive treatment underscores the importance of serial health status assessments in patients with CAD.

Clinical outcomes after RA at 1 year

In this study, patient-reported RA either at 6 months or 1 year was independently associated with repeat revascularization at 5 years. This...
was 18.3% at 5 years among those with RA at 1 year, indicating that the index procedure. Also, the occurrence of repeat revascularization that the majority of RA was not attributable to the incompleteness of with RA at 1 year had complete revascularization (stenosis is revascularization is clinically indicated or not when the diameter (ARC) definition, to consider when adjudicating whether a repeat of RA is a key factor, as per the Academic Research Consortium that patients with RA would undergo subsequent revascularization to occur from mechanisms other than reduced epicardial blood flow, be left without treatment. Given that RA post-revascularization could as dismissing the impact of RA post revascularization or that it can be possible that preconditioning or the development of a collateral circulation triggered by recurrent ischaemia played a role in reducing the risk of MI.31–33 One might also speculate that repeat intervention addressing the incomplete revascularization played a role in preventing the occurrence of MI. However, in previous analyses, repeat revascularization was associated with a significantly higher incidence of MI in the SYNTAX trial.34 Similarly, in the EXCEL trial, repeat revascularization was associated with both increased mortality and cardiovascular mortality at 3 years.35 Hence, the preventive effects of repeat revascularization on the occurrence of further MIs are unlikely.

Despite the increased frequency of repeat revascularization, all-cause death up to 10 years did not differ significantly between patients with and without self-reported RA at 1 year or at 6 months (Figure 3, Table 2, and Supplementary material online, Table S4). Although the numbers of patients and events in the current study might be insufficient to determine the actual risk of RA, especially amongst those with the most severe (i.e. daily/weekly angina) category, our study suggests that post-procedural RA may not have a substantial impact on long-term mortality up to 10 years after revascularization. These findings are similar to those reported by Spertus and colleagues in a large cohort of outpatients with chronic CAD.13

Notwithstanding the lack of correlation with long-term mortality, patient-reported outcome measures are still of paramount importance to evaluate the effects of coronary revascularization procedures on patients’ QoL—a key goal of therapy for patients with chronic coronary disease. In particular, our findings should not be interpreted as dismissing the impact of RA post revascularization or that it can be left without treatment. Given that RA post-revascularization could occur from mechanisms other than reduced epicardial blood flow, dedicated physiological assessment of the microcirculation or tests for coronary artery spasm may be needed to appropriately evaluate the clinical significance and necessity of repeating epicardial revascularization on top of GDMT.29 As a matter of fact, the prescription rates of anti-anginal medications were higher in patients with RA than in those without. However, overall these specific antianginal medications seem to have been underprescribed (Supplementary material online, Tables S1 and S2).
some (conscious or unconscious) denial of their symptoms. Finally, of a response to the SAQ questionnaire by these patients may reflect decreased revascularization rates, is intriguing. Putatively, the absence of paradoxical divergence, between increased long-term mortality and significance (Supplementary material online, revascularization, whilst numerically lower did not reach statistical in the RA group up to 10 years, whereas the incidences of repeat patients had a significantly higher all-cause mortality rate than those at 1 year, which could introduce a selection bias. Indeed, the excluded from the current study due to the unavailability of SAQ-AF scores reflected in the SAQ-PL scale, as observed in outpatients with CAD.13 Therefore, analyses should also examine the association of other patient-centered health status domains with clinical events. Third, there were a substantial number of patients (N = 288), who were excluded from the current study due to the unavailability of SAQ-AF scores at 1 year, which could introduce a selection bias. Instead, the excluded patients had a significantly higher all-cause mortality rate than those in the RA group up to 10 years, whereas the incidences of repeat revascularization, whilst numerically lower did not reach statistical significance (Supplementary material online, Figures S3 and S4). This paradoxical divergence, between increased long-term mortality and decreased revascularization rates, is intriguing. Putatively, the absence of a response to the SAQ questionnaire by these patients may reflect some (conscious or unconscious) denial of their symptoms. Finally, the endpoint in the SYNTAXES study was all-cause death only, and data of other adjudicated clinical endpoints including MI, stroke, and repeat revascularization were limited to the 5-year assessment from the original SYNTAX trial.

**Limitations**

There are some limitations of this study that warrant discussion. First, the SYNTAX trial was conducted between 2005 and 2007 with the universal use of first-generation paclitaxel–drug eluting stents for the initial PCI. Technological advances in both PCI devices as well as medical treatment strategies may limit the generalizability of our findings to current practice. It is, however, unavoidable that the findings from long-term follow-up data are based on outdated technology while the evidence for contemporary technology can be derived only from short-term follow-up studies. Second, we assessed RA specifically at 6- and 12-month follow-ups. However, anginal status could change depending on the time of assessment, medical treatments, and repeat revascularization procedures. We selected 1-year (and 6-month) follow-up as the most appropriate timing to assess RA to avoid misinterpretation of surgical chest pain as angina during the very early phase (1-month), as well as to minimize the impact of additional medications/procedures on long-term follow-up. In addition, we focused on the SAQ-AF scale to explicitly examine the association of residual symptoms with mortality. Some patients, however, may limit their activity to minimize their angina, and this would be reflected in the SAQ-PL scale, as observed in outpatients with CAD.13 Therefore, analyses should also examine the association of other patient-centered health status domains with clinical events. Third, there were a substantial number of patients (N = 288), who were excluded from the current study due to the unavailability of SAQ-AF scores at 1 year, which could introduce a selection bias. Instead, the excluded patients had a significantly higher all-cause mortality rate than those in the RA group up to 10 years, whereas the incidences of repeat revascularization, whilst numerically lower did not reach statistical significance (Supplementary material online, Figures S3 and S4). This paradoxical divergence, between increased long-term mortality and decreased revascularization rates, is intriguing. Putatively, the absence of a response to the SAQ questionnaire by these patients may reflect some (conscious or unconscious) denial of their symptoms. Finally, the endpoint in the SYNTAXES study was all-cause death only, and data of other adjudicated clinical endpoints including MI, stroke, and repeat revascularization were limited to the 5-year assessment from the original SYNTAX trial.

**Conclusions**

Among patients with LMCAD and/or 3VD, patient-reported RA, according to the SAQ-AF scale, at 1-year post-revascularization was independently associated with repeat revascularization at 5 years; however, it did not significantly increase 10-year mortality, irrespective of the primary modality of revascularization or severity of RA.

**Supplementary material**

Supplementary material is available at European Heart Journal—Quality of Care and Clinical Outcomes online.

**Funding**

The SYNTAX Extended Survival study, during extension of follow-up up to 10 years, was supported by the German Foundation of Heart Research (Frankfurt am Main, Germany). The SYNTAX trial, during 0–5 year follow-up, was funded by Boston Scientific Corporation (Marlborough, MA, USA).

**Authors contribution**

M.O. gathered, analysed, and interpreted data, wrote the first draft of the article, and contributed to all revisions. P.W.S. and Y.O. designed the study, gathered and interpreted data, and contributed to all revisions. D.R.H., M.-C.M., A.P.K., T.N., and P.M.D. designed the study, gathered and interpreted data, and contributed to all revisions. J. W. and J.J.P. interpreted data and contributed to revision of the article. S.G., N.O’L.,
Role of the Funder/Sponsor
The study funders had no role in the study design, data collection, data analyses, and interpretation of the study data, nor were involved in the decision to publish the final manuscript. The principal investigators and authors had complete scientific freedom.

Collaborators/Appendix
SYNTAX Extended Survival Principal Investigators:
dr. Stuart J. Head, MD PhD, Erasmus MC, Rotterdam, The Netherlands
dr. Piroze M. Davierwala, MD, German Heart Center, Leipzig, Germany
Prof. dr. Friedrich-Wilhelm Mohr, MD PhD, German Heart Center, Leipzig, Germany
Prof. dr. Patrick W.J.C. Serruys, MD PhD, Imperial College London, United Kingdom
Dr. Michael J. Mack, MD, Baylor Scott & White Health, Plano, TX, United States
Dr. David R. Holmes Jr, MD, Mayo Clinic, Rochester, MN, United States
Dr. Marie-Claude Morice, MD, ICPS Ramsay-Générale de Santé, Massy, France
Prof. dr. A. Pieter Kappetein, MD PhD, Erasmus MC, Rotterdam, The Netherlands

Chief Investigators:
SYNTAX Extended Survival Chief Investigator/Study Director:
Daniel J.F.M. Thuijs, MD, Erasmus MC, Rotterdam, The Netherlands

SYNTAX Extended Survival Participating Sites with Local Principal Investigators:
1. Aalst, Onze Lieve Vrouwziekenhuis (OLVZ), Belgium: Filip Cas-selman, Bernard de Bruyne, MD
2. Aarhus, Aarhus Universitetshospital, Denmark: Evald Hej Christiansen, MD PhD
3. Alicante, Hospital General de Alicante, Spain: Juan M. Ruiz-Nodar, MD PhD
4. Antwerp, ZNA Middelheim, Belgium: Paul Vermeersch, MD PhD
5. Bad Oeynhausen, Universitätsklinikum der Ruhr-Universität Bochum, Germany: Werner Schultz, MD PhD
6. Barcelona, Hospital Clinic de Barcelona, Spain: Manel Sabaté, MD PhD
7. Bergamo, Ospedale Papa Giovanni di Bergamo, Italy: Giulio Guagliumi, MD
8. Berlin, Charité Universitätsmedizin Berlin, Germany: Herko Gubitzschi, MD PhD, Karl Stangl, MD PhD
9. Bordeaux, Clinique ST Augustin, France: Olivier Darremont, MD PhD
10. Breda, Amphia Ziekenhuis, The Netherlands: M. Bentala, MD PhD
11. Budapest, Cardiovascular Center of the Semmelweis University, Hungary: Istvan Preda, MD PhD
12. Dallas, Baylor University Medical Centre, TX, USA: Robert Stoler, MD
13. Dallas, Medical City Dallas Hospital, TX, USA: Michael J. Mack, MD
14. Debrecen, University of Debrecen, Hungary: Tamás Szerafin, MD PhD
15. Denver, UCH Denver Colorado, USA: John K. Buckner, MD, and Myles S. Guber, MD
16. Eindhoven, Catharina Ziekenhuis, The Netherlands: Niels Verberkmoes, MD, Ferdi Akca, MD PhD
17. Evanston, Northshore University HealthSystem, IL, USA: Ted Feldman, MD
18. Freiburg, Heart Center, University of Freiburg, Germany: Friedhelm Beyersdorf, MD PhD
19. Gent, Universitair Ziekenhuis Gent, Belgium: Benny Drieghe, MD
20. Glasgow, Golden Jubilee National Hospital, Clydebank, UK: Keith Oldroyd, MD, Geoff Berg, MD
21. Gothenborg, Sahlgrenska University Hospital, Sweden: Anders Jeppsson, MD PhD
22. Grand Blanc, Genesys Regional Medical Center, Grand Blanc, MI, USA: Kimberly Barber, MD PhD
23. Grand Rapids, Spectrum Health Hospitals Cook Research Department, MI, USA: Kevin Wolschleger, MD, John Heiser, MD
24. Groningen, Universitair Medisch Centrum Groningen, The Netherlands: Pim van der Harst, MD PhD, Massimo A. Mariani, MD PhD
25. Hamburg, University Heart Center Hamburg, Germany: Hermann Reichenspurner, MD PhD
26. Helsinki, University of Helsinki Meilahti Hospital, Finland: Christoffer Stark, MD, Mika Laine, MD PhD
27. Honolulu, Kaiser Permanente, HI, USA: Paul C. Ho, MD and John C. Chen, MD
28. Hyannis, Cape Cod Hospital, MA, USA: Richard Zelman, MD, Myles S. Guber, MD
29. Iowa, University of Iowa Hospitals & Clinics, IA, USA: Phillip A. Horwitz, MD
30. Katowice, Centrum Badawczo-Rozwojowe, American Heart of Poland, Poland: Agata Krauze PhD, Andrzej Bochenek, MD PhD
31. Kiel, Universitätsklinikum Campus Kiel, Germany: Christina Grothusen, MD
32. Krakow, John Paul II Hospital, Poland: Dariusz Dudek, MD PhD
33. Langhorne, St. Mary Medical Center, PA, USA: George Heyrich, MD
34. Leipzig, Heart Center, University of Leipzig, Germany: Piroze Davierwala, MD, Thilo Noack, MD
35. Liege, University Hospital of Liege, Belgium: Victor LeGrand, MD PhD, Philippe Kohli, MD PhD
36. Lisbon, Hospital de Santa Marta, Portugal: Pedro Coelho, MD PhD
37. Lubeck, University Medical Center Schleswig-Holstein, Campus Lübeck, Germany: Stephan Ensminger, MD, Boris Nasser, MD
38. Lund, Skånes Universitetssjukvård, Sweden: Richard Ingemanson, MD PhD, Goran Olivecrona, MD PhD
39. Madrid, Hospital Clinico San Carlos, Spain: Javier Escaned, MD PhD, Reddy Guera, MD
40. Massa, Fondazione CNR/Regione Toscana per la Ricerca Medica e di Santità Pubblica-Ospedale del Cuore G.Pasquinucci, Italy: Sergio Berti, MD
41. Massy, Cardiovascular Institute Paris-Sud (ICPS), Hospital privé Jacques Cartier, Ramsey, Générale de Santé Massy, France: Marie-Claude Morice, MD
42. Milan, San Raffaele Hospital, Milan, Italy: Aliaide Chieffo, MD
43. Minneapolis, Minneapolis Heart Institute Foundation, MN, USA: Nicholas Burke, MD, Michael Mooney, MD
44. Mirano, Ospedale di Mirano, Italy: Alvise Spolaor, MD
45. Munich, Klinikum der Universität München, Campus Großhadern, Germany: Christian Oldroyd, MD, Mike Flüeler, MD
46. Nieuwegein, Sint Antonius Hospital, The Netherlands: Marleen Jan Suttorp, MD PhD
47. Norfolk, Sentara Cardiovascular Research Institute, Norfolk, VA, USA: Ronald A. Stine, MD
48. Oklahoma, Oklahoma Cardiovascular Research Group, OK, USA: Thomas McGarry, MD PhD, Scott Lucas, MD PhD
49. Olso, Oslo universitetssykehus HF, Norway: Knut Endresen, MD PhD
50. Orlando, Florida Hospital Cardiovascular Research, Florida, USA: Andrew Taussig, MD, Kevin Accola, MD
51. Pavia, IRCCS Policlinico San Matteo, Italy: Umberto Canosi, BS
Conflict of interest: P.W.S. reports personal fees from Biosensors, Micel Technologies, Sinomedical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. H.H. reports a grant for studying overseas from the Japanese Circulation Society and a grant from the Fukuda Foundation for Medical Technology, outside the submitted work. J.J.P. reports personal fees and non-financial support from Philips/Volcano, outside the submitted work. M.C.M. is the chief executive officer and shareholder of the European Center for Cardiovascular Research, outside the submitted work. A.P.K. reports work as an employee of Medtronic, outside the submitted work. J.A.S. reports grants from Abbott Vascular, outside the submitted work; in addition, J.A.S. has a patent copyright to the Seattle Angina Questionnaire with royalties paid. D.J.C. reports grants from Boston Scientific to Saint Luke’s Mid America Heart Institute during the conduct of the study; grants and personal fees from Boston Scientific; grants and personal fees from Abbott; and grants and personal fees from Medtronic, outside the submitted work. All other authors have no conflict of interest to declare.

Data availability statements

The anonymized data that support the findings of this study are available from the corresponding author for reasonable requests.

References


