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ORIGINAL ARTICLE

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

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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.

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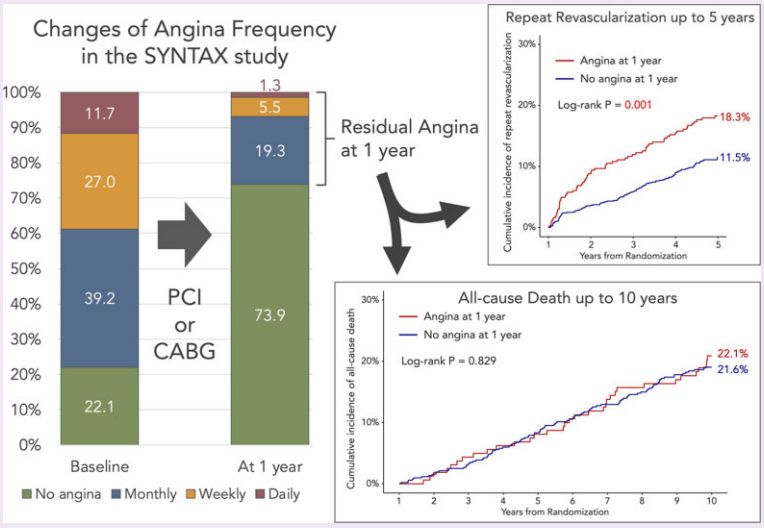
Graphical Abstract

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 revascularization,[6–11] 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

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.[19] Patient-reported anginal status after PCI or CABG has also been reported through 5 years.[9] 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.[22,23] 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'.[22] 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.[7,9]

For the purpose of this study, the presence of angina was defined as a SAQ-AF score $\leq$90.[22,23] 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.[20]

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 χ^2 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/$\leq$40%, intermediate/41–50%, or good/>50%), LMCAD 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.[24]

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 6 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).

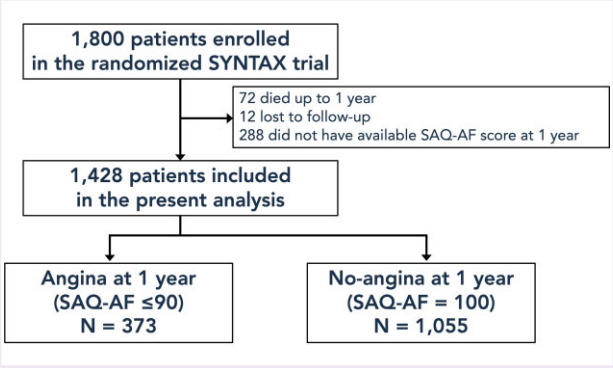


Figure 1 Flowchart of the present study. SYNTAXES, Synergy between PCI with Taxus and Cardiac Surgery Extended Survival; SAQ-AF, Seattle Angina Questionnaire angina frequency scale.

Results

A total of 1800 patients enroled 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 1 Baseline characteristics in patients with or without angina according to SAQ-AF score at 1 year

	Angina at 1 year N = 373	No-angina at 1 year N = 1055	P-value
Randomization			0.047
PCI	56.8 (212/373)	50.8 (536/1055)	
CABG	43.2 (161/373)	49.2 (519/1055)	
Age (year)	63.6 ± 9.9	65.5 ± 9.5	0.001
Sex			0.028
Male	74.3 (277/373)	79.9 (843/1055)	
Female	25.7 (96/373)	20.1 (212/1055)	
BMI (kg/m^2)	28.5 ± 4.5	27.9 ± 4.6	0.016
Diabetes	24.9 (93/373)	23.3 (246/1055)	0.525
On insulin	9.4 (35/373)	9.3 (98/1055)	1.000
Hypertension	70.8 (264/373)	65.0 (686/1055)	0.048
Dyslipidaemia	79.6 (293/368)	77.3 (810/1048)	0.381
Current smoking	20.1 (75/373)	18.1 (190/1052)	0.395
Previous MI	26.4 (97/367)	32.9 (343/1043)	0.022
Previous cerebrovascular disease	15.9 (59/371)	12.7 (133/1049)	0.133
Previous stroke	5.9 (22/371)	3.6 (38/1051)	0.070
Previous TIA	4.6 (17/371)	4.2 (44/1050)	0.766
Previous carotid artery disease	8.3 (31/373)	7.4 (78/1055)	0.571
Peripheral vascular disease	11.0 (41/373)	7.5 (79/1055)	0.039
COPD	11.0 (41/373)	6.9 (73/1055)	0.015
CKD[a]	17.4 (60/345)	18.1 (178/981)	0.807
Creatinine clearance (mL/min)	88.9 ± 29.2	85.5 ± 32.9	0.080
LVEF (%)	59.6 ± 12.8	59.0 ± 12.7	0.410
Congestive heart failure	3.3 (12/364)	2.6 (27/1049)	0.461
Clinical presentation			<0.001
Silent ischaemia	7.5 (28/373)	16.7 (176/1055)	
Stable angina	67.3 (251/373)	53.3 (562/1055)	
Unstable angina	25.2 (94/373)	30.0 (317/1055)	
EuroSCORE	3.4 ± 2.3	3.7 ± 2.6	0.031
Parsonnet SCORE	8.0 ± 6.4	8.3 ± 6.9	0.531
Disease type			0.624
3VD	58.2 (217/373)	59.7 (630/1055)	
LMCAD	41.8 (156/373)	40.3 (425/1055)	
Disease type			0.678
LMCAD only	6.2 (23/373)	5.2 (55/1055)	
LMCAD + 1VD	8.3 (31/373)	7.7 (81/1055)	
LMCAD + 2VD	10.2 (38/373)	12.6 (133/1055)	
LMCAD + 3VD	17.2 (64/373)	14.8 (156/1055)	
2VD (no LMCAD)	1.9 (7/373)	2.2 (23/1055)	
3VD (no LMCAD)	56.3 (210/373)	57.5 (607/1055)	
Number of lesions	4.3 ± 1.8	4.4 ± 1.8	0.414
SYNTAX score	27.7 ± 11.6	28.8 ± 11.5	0.092
SYNTAX score tercile			
Low	36.6 (136/372)	31.8 (334/1051)	0.096
Intermediate	33.1 (123/372)	34.3 (360/1051)	0.703
High	30.4 (113/372)	34.0 (357/1051)	0.223
Predicted 10-year mortality rates by SYNTAX score II 2020 (%)	24.9 ± 17.9	25.9 ± 17.5	0.327
Any total occlusion	20.5 (76/371)	23.4 (246/1050)	0.279
Any bifurcation	69.0 (256/371)	73.5 (772/1050)	0.105
Number of stents	4.7 ± 2.4	4.6 ± 2.2	0.390
Total stent length per patient	88.7 ± 52.3	84.5 ± 47.2	0.291
Off pump CABG	10.7 (17/159)	12.5 (64/514)	0.676

Table 1 Continued

	Angina at 1 year N = 373	No-angina at 1 year N = 1055	P-value
Number of total conduits	2.7 ± 0.7	2.7 ± 0.7	0.770
Number of arterial conduits	1.4 ± 0.7	1.4 ± 0.7	0.782
Number of venous conduits	1.3 ± 0.9	1.3 ± 0.9	0.820
Complete revascularization	63.0 (233/370)	60.1 (633/1054)	0.353
Residual SYNTAX score	4.06 ± 5.58	3.82 ± 5.64	0.612
Residual SYNTAX score ≥ 8	18.4 (39/212)	13.1 (69/527)	0.084
Medication at discharge			
Any antiplatelet therapy			
Aspirin	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).
[a]CKD 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

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

[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*.

had lower EuroSCOREs, and significantly lower SAQ-AF scores at baseline. Of note, the prevalence of diabetes, the mean anatomical SYNTAX score, the rate of complete revascularization, and the mean residual SYNTAX score did not differ significantly between patients with or without RA.

Differences in GDMT with its components and anti-anginal medications up to 5 years between patients with and without RA are shown in Supplementary material online, *Tables S1* and *S2*. There were no statistically significant differences between angina and no-angina groups in terms of any medical therapy, except for nitrates which were more frequently prescribed in patients with RA than in those without.

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

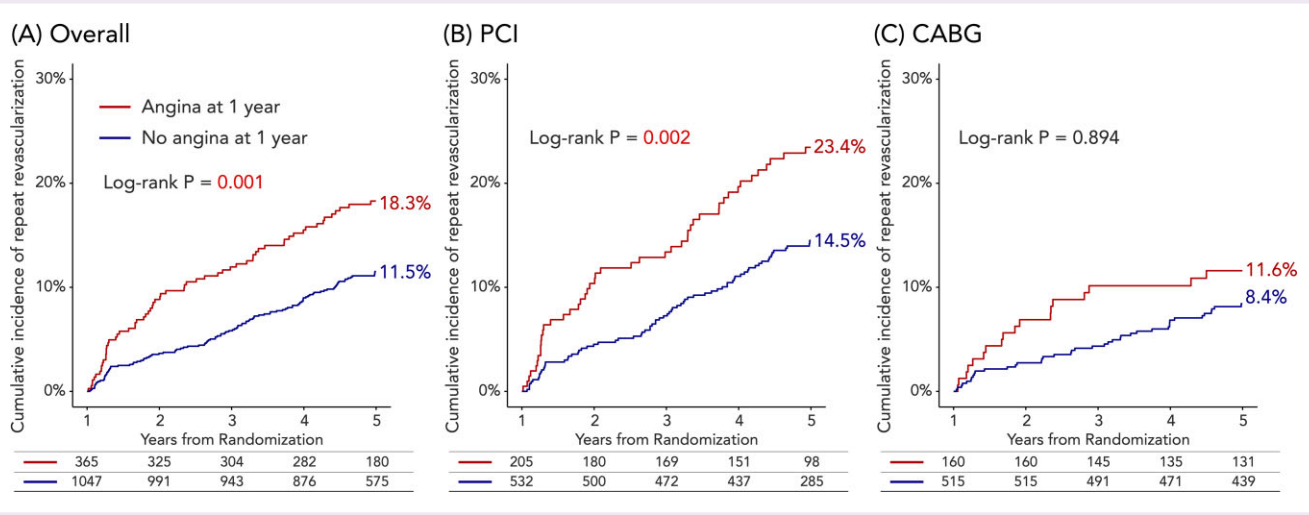


Figure 2 Cumulative incidences of repeat revascularization up to 5 years in patients with or without RA after initial PCI or CABG. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; other abbreviations as in *Figure 1*.

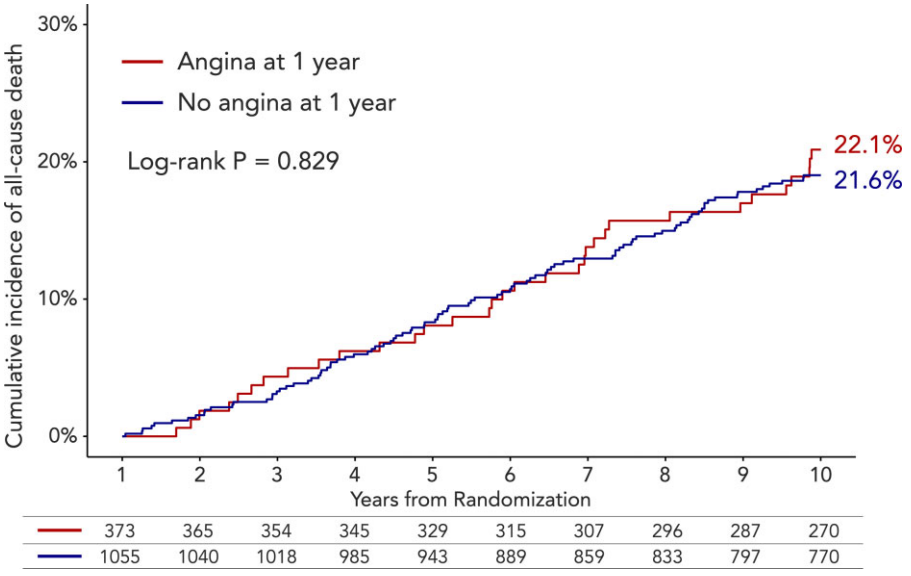


Figure 3 Cumulative incidence of all-cause death at 10 years in patients with or without patient-reported angina at 1-year visit. There was no significant difference in incidence of all-cause death up to 10 years between angina and no-angina at a 1-year visit.

revascularization (HR: 1.54; 95% CI: 1.10–2.15, *Table 2*) remained statistically significant.

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*).

Frequency of angina at the 1-year visit and clinical outcomes

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

Table 3 Unadjusted and adjusted hazard for clinical outcomes stratified by frequency of patient-reported angina at 1 year

Clinical outcomes	*N*	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
All-cause death at 10 years	300				
Frequency of angina (vs. no-angina)					
Monthly angina	58	1.00 (0.75–1.34)	0.997	1.08 (0.79–1.48)	0.613
Daily/weekly angina	22	1.11 (0.72–1.72)	0.639	1.19 (0.71–1.97)	0.511
Continuous SAQ-AF score (per 10 decrease)		1.03 (0.96–1.11)	0.460	1.05 (0.97–1.14)	0.210
Revascularization at 5 years	178				
Frequency of angina (vs. no-angina)					
Monthly angina	45	1.62 (1.15–2.28)	0.006	1.48 (1.02–2.15)	0.037
Daily/weekly angina	19	1.98 (1.22–3.21)	0.006	1.73 (1.00–2.98)	0.049
Continuous SAQ-AF score (per 10 decrease)		1.17 (1.08–1.26)	<0.001	1.16 (1.07–1.26)	<0.001

Adjusted covariates are listed in *Table 2*.
Abbreviations are as in *Tables 1* and *2*.

HR: 1.98; 95% CI: 1.22–3.21, adjusted HR: 1.73; 95% CI: 1.00–2.98) (*Table 3* and Supplementary material online, *Figure S2*). As a continuous variable, a 10-point decrease in SAQ-AF score at 1-year follow-up was associated with a 16% increase (95% CI: 1.07–1.26) 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 ($P_{interaction} = 0.661$).

Sensitivity analysis using 6-month angina status

The results of the sensitivity analysis using 6-month anginal status are shown in Supplementary 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 (Supplementary 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: 0.70–1.20). 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,[7] 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.[22] 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)[8] and the EXCEL trial (21.1% in PCI and 20.5% in CABG),[10] 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

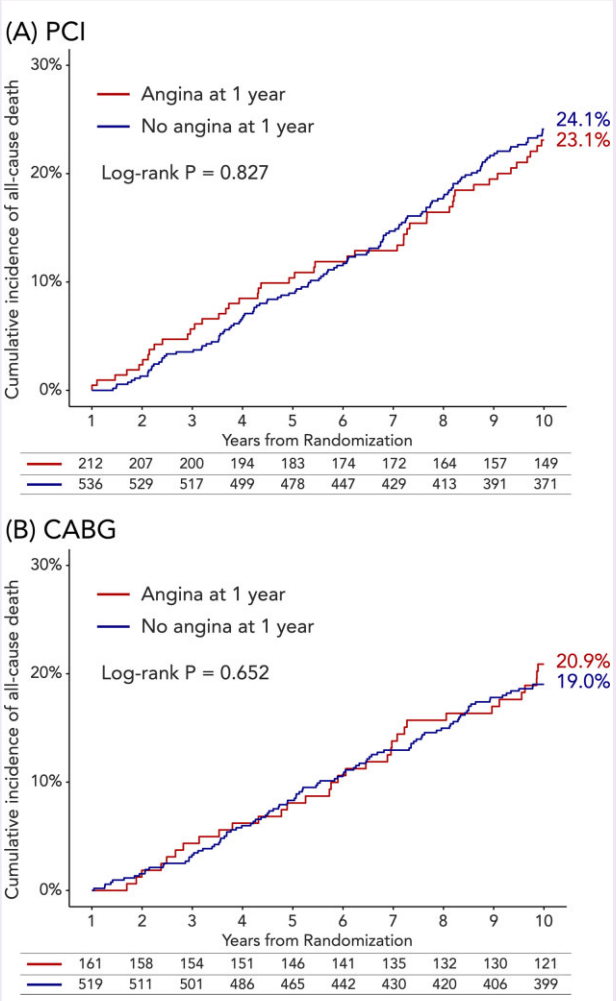


Figure 4 Cumulative Kaplan–Meier estimates of all-cause death up to 10 years according to 1-year anginal status in patients undergoing initial PCI or CABG. There were no significant differences in all-cause mortality at 10 years between angina and no-angina groups irrespective of the revascularization mode (PCI or CABG). Abbreviations as in *Figure 2*.

association is entirely plausible since RA could reflect restenosis or incomplete revascularization during the index procedure, both of which may lead to additional revascularization procedures. Moreover, since a primary treatment goal is to eliminate angina, it makes clinical sense that patients with RA would undergo subsequent revascularization to achieve this goal and improve patients' QoL. Accordingly, the presence of RA is a key factor, as per the Academic Research Consortium (ARC) definition, to consider when adjudicating whether a repeat revascularization is clinically indicated or not when the diameter stenosis is <70%.[25] It should be noted, however, that 63% of patients with RA at 1 year had complete revascularization (*Table 1*), implying that the majority of RA was not attributable to the incompleteness of the index procedure. Also, the occurrence of repeat revascularization was 18.3% at 5 years among those with RA at 1 year, indicating that >80% of patients with RA did not require repeat revascularization up to 5 years (*Figure 2*). There are several potential explanations for what might appear to be an 'underuse' of repeat revascularization during follow-up. One possibility is that some patients did not report their symptoms to their physician; previous studies have suggested that there is considerable underrecognition of angina among such individuals.[26] Alternatively, it is well recognized that epicardial CAD is only one potential explanation for angina. It is possible that many of these cases of RA were attributed to alternative causes such as coronary spasms or microvascular dysfunction.[6,27–29] In fact, patients with RA had significantly lower SAQ-AF scores at baseline than those without RA (*Table 1*), which might reflect the underlying coexistence of functional mechanisms beyond coronary epicardial stenoses in those patients. Noteworthy, a small number of patients with silent ischaemia ($N = 28$) at baseline had angina at 1 year (*Table 1*). Treating silent ischaemia by revascularization may have made the patient more aware and conscious of their ailment, with a more sensitive perception of pain induced by other causes than epicardial vessel stenosis, such as ischaemia with non-obstructive coronary arteries (INOCA).[6,30]

In contrast to repeat revascularization, the occurrence of MI was significantly lower in patients with RA than in those without, especially when PCI was the index mode of revascularization (*Tables 2* and *4*). These findings (which were unexpected) may reflect the play of chance given the small number of events—especially as this trend was not observed in the sensitivity analysis with 6-month RA (Supplementary material online, *Table S4*). There are several biologically plausible alternative explanations, however. For example, it may 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*).

Table 4 Unadjusted and adjusted hazard for clinical outcomes stratified by patient-reported angina at 1 year after initial PCI or CABG

	PCI		CABG		
Clinical outcomes	**Unadjusted HR (95% CI)**	***P*-value**	**Unadjusted HR (95% CI)**	***P*-value**	***P* for interaction**
			Unadjusted model		
All-cause death at 10 years	0.96 (0.69–1.35)	0.827	1.10 (0.74–1.63)	0.652	0.629
All-cause death at maximum follow-up	1.12 (0.84–1.50)	0.424	0.95 (0.67–1.36)	0.798	0.481
Cardiac death at 5 years	0.66 (0.29–1.53)	0.335	1.00 (0.33–3.07)	1.000	0.565
MI at 5 years	0.24 (0.07–0.80)	0.020	—	0.446	0.978
Stroke at 5 years	0.73 (0.15–3.51)	0.694	0.72 (0.16–3.32)	0.672	0.989
Revascularization at 5 years	1.75 (1.21–2.54)	0.003	1.47 (0.85–2.56)	0.170	0.618
			Adjusted model		
All-cause death at 10 years	1.07 (0.74–1.54)	0.720	1.13 (0.72–1.77)	0.599	0.714
All-cause death at maximum follow-up	1.21 (0.89–1.66)	0.229	0.98 (0.66–1.47)	0.930	0.533
Cardiac death at 5 years	0.79 (0.33–1.90)	0.603	0.57 (0.11–3.01)	0.510	0.785
MI at 5 years	0.30 (0.09–1.02)	0.053	—	0.876	0.971
Stroke at 5 years	0.89 (0.13–6.02)	0.909	0.82 (0.15–4.49)	0.818	0.830
Revascularization at 5 years	1.66 (1.11–2.50)	0.014	1.29 (0.71–2.34)	0.412	0.661

In the CABG arm, the hazard ratios in MI could not be assessed due to the too small number of event incidences ($N = 5$).
Adjusted covariates are listed in *Table 2*.
Abbreviations are as in *Tables 1* and *2*.

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] Future 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. Indeed, 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.

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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 critical revision of the manuscript. H.K., M.L., R.W., H.H., and C.G. gathered, cleaned data, and contributed to revision of the article. J. W. and J.J.P. interpreted data and contributed to revision of the article. S.G., N.O'L.,

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Data availability statements

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

References

1. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP *et al.* 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2012;**126**:3097–3137.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al.* 2019 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
3. Arnold SV, Kosiborod M, Li Y, Jones PG, Yue P, Belardinelli L *et al.* Comparison of the Seattle Angina Questionnaire with Daily Angina Diary in the TERISA Clinical Trial. *Circ Cardiovasc Qual Outcomes* 2014;**7**:844–850.
4. Patel KK, Arnold SV, Chan PS, Tang Y, Jones PG, Guo J *et al.* Validation of the Seattle Angina Questionnaire in women with ischemic heart disease. *Am Heart J* 2018;**201**:117–123.
5. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle Angina Questionnaire as an outcome measure in clinical trials and clinical care: a review. *JAMA Cardiology* 2021;**6**:593.
6. Crea F, Bairey Merz CN, Beltrame JF, Berry C, Camici PG, Kaski JC *et al.* Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. *Eur Heart J* 2019;**40**:2455–2462.
7. Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P *et al.* Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 2011;**364**:1016–1026.
8. Abdallah MS, Wang K, Magnuson EA, Spertus JA, Farkouh ME, Fuster V *et al.* Quality of life after PCI vs. CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 2013;**310**:1581–1590.
9. Abdallah MS, Wang K, Magnuson EA, Osnabrugge RL, Kappetein AP, Morice MC *et al.* Quality of life after surgery or DES in patients with 3-vessel or left main disease. *J Am Coll Cardiol* 2017;**69**:2039–2050.
10. Baron SJ, Chinnakondepalli K, Magnuson EA, Kandzari DE, Puskas JD, Ben-Yehuda O *et al.* Quality-of-life after everolimus-eluting stents or bypass surgery for left-main disease: results from the EXCEL trial. *J Am Coll Cardiol* 2017;**70**:3113–3122.
11. Nishi T, Piroth Z, De Bruyne B, Jagic N, Möbius-Winkler S, Kobayashi Y *et al.* Fractional flow reserve and quality-of-life improvement after percutaneous coronary intervention in patients with stable coronary artery disease. *Circulation* 2018;**138**:1797–1804.
12. Navarese EP, Lansky AJ, Kereiakes DJ, Kubica J, Gurbel PA, Gorog DA *et al.* Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. *Eur Heart J* 2021; **42**: 4638–4651.
13. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. *Circulation* 2002;**106**:43–49.

14. Mozaffarian D, Bryson CL, Spertus JA, McDonell MB, Fihn SD. Anginal symptoms consistently predict total mortality among outpatients with coronary artery disease. *Am Heart J* 2003;**146**:1015–1022.
15. Berecki-Gisolf J, Humphreyes-Reid L, Wilson A, Dobson A. Angina symptoms are associated with mortality in older women with ischemic heart disease. *Circulation* 2009;**120**:2330–2336.
16. Beatty AL, Spertus JA, Whooley MA. Frequency of angina pectoris and secondary events in patients with stable coronary heart disease (from the Heart and Soul Study). *Am J Cardiol* 2014;**114**:997–1002.
17. Steg PG, Greenlaw N, Tendera M, Tardif JC, Ferrari R, Al-Zaibag M *et al.* Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med* 2014;**174**:1651–1659.
18. Eisen A, Bhatt DL, Steg PG, Eagle KA, Goto S, Guo J *et al.* Angina and future cardiovascular events in stable patients with coronary artery disease: insights from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *J Am Heart Assoc* 2016;**5**: e004080.
19. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ *et al.* Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet North Am Ed* 2019;**394**: 1325–1334.
20. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
21. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet North Am Ed* 2013;**381**:629–638.
22. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Fihn SD. Monitoring the quality of life in patients with coronary artery disease. *Am J Cardiol* 1994;**74**:1240–1244.
23. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M *et al.* Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995;**25**:333–341.
24. Pocock SJ, McMurray JJV, Collier TJ. Statistical controversies in reporting of clinical trials: part 2 of a 4-part series on statistics for clinical trials. *J Am Coll Cardiol* 2015;**66**:2648–2662.
25. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J *et al.* Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Circulation* 2018;**137**:2635–2650.
26. Qintar M, Spertus JA, Gosch KL, Beltrame J, Kureshi F, Shafiq A *et al.* Effect of angina under-recognition on treatment in outpatients with stable ischaemic heart disease. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:208–214.
27. Jeremias A, Kutscher S, Haude M, Heinen D, Holtmann G, Senf W *et al.* Nonischemic chest pain induced by coronary interventions: a prospective study comparing coronary angioplasty and stent implantation. *Circulation* 1998;**98**:2656–2658.
28. Abbate A, Biondi-Zoccai GG, Agostoni P, Lipinski MJ, Vetrovec GW. Recurrent angina after coronary revascularization: a clinical challenge. *Eur Heart J* 2007;**28**:1057–1065.
29. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S *et al.* Stratified medical therapy using invasive coronary function testing in angina: the CorMicA Trial. *J Am Coll Cardiol* 2018;**72**:2841–2855.
30. Stone GW, Ellis SG, Gori T, Metzger DC, Stein B, Erickson M *et al.* Blinded outcomes and angina assessment of coronary bioresorbable scaffolds: 30-day and 1-year results from the ABSORB IV randomised trial. *Lancet North Am Ed* 2018;**392**:1530–1540.
31. Ottani F, Galvani M, Ferrini D, Sorbello F, Limonetti P, Pantoli D *et al.* Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation* 1995;**91**:291–297.
32. Fujita M, Sasayama S, Ohno A, Nakajima H, Asanoi H. Importance of angina for development of collateral circulation. *Heart* 1987;**57**:139–143.
33. Seiler C, Stoller M, Pitt B, Meier P. The human coronary collateral circulation: development and clinical importance. *Eur Heart J* 2013;**34**:2674–2682.
34. Parasca CA, Head SJ, Milojevic M, Mack MJ, Serruys PW, Morice MC *et al.* Incidence, characteristics, predictors, and outcomes of repeat revascularization after percutaneous coronary intervention and coronary artery bypass grafting: the SYNTAX Trial at 5 years. *JACC: Cardiovasc Interv* 2016;**9**:2493–2507.
35. Giustino G, Serruys PW, Sabik JF, III, Mehran R, Maehara A, Puskas JD *et al.* Mortality after repeat revascularization following PCI or CABG for left main disease: the EXCEL Trial. *JACC: Cardiovasc Interv* 2020;**13**:375–387.