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FULL RESEARCH PAPER
CVD Risk Factors

Ten-year all-cause mortality according to smoking status in patients with severe coronary artery disease undergoing surgical or percutaneous revascularization

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Aims To evaluate the impact of various smoking status on 10-year all-cause mortality and to examine a relative treatment benefit of coronary artery bypass grafting (CABG) vs. percutaneous coronary intervention (PCI) according to smoking habits.

Methods and results The SYNTAX Extended Survival study evaluated vital status up to 10 years in 1800 patients with *de novo* three-vessel disease and/or left main coronary artery disease randomized to CABG or PCI in the SYNTAX trial. In the present analysis, patients were divided into three groups (current, former, or never smokers), and the primary endpoint of 10-year all-cause mortality was assessed according to smoking status. Smoking status was available in 1793 (99.6%) patients at the time of randomization, of whom 363 were current smokers, 798 were former smokers, and 632 were never smokers. The crude rates of 10-year all-cause mortality were 29.7% in current smokers, 25.3% in former smokers, and 25.9% in never smokers (Log-rank $P = 0.343$). After adjustment for imbalances in baseline characteristics, current smokers had a significantly higher risk of 10-year all-cause mortality than never smokers [adjusted hazard ratio (aHR): 2.29; 95% confidence interval (CI): 1.60–3.27; $P < 0.001$], whereas former smokers did not. PCI was associated with a higher risk of all-cause mortality than CABG among current smokers (HR: 1.60; 95% CI: 1.09–2.35; $P = 0.017$), but it failed to show a significant interaction between revascularization strategies and smoking status ($P_{interaction} = 0.910$).

Conclusion Current smokers had a higher adjusted risk of 10-year all-cause mortality, whereas former smokers did not. The treatment effect of CABG vs. PCI did not differ significantly according to smoking status.

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Keywords Coronary artery bypass grafting • Left main coronary artery disease • Percutaneous coronary intervention • Smoking • Three-vessel disease

Introduction

Smoking is a well-established risk factor for the development of coronary artery disease (CAD). In 1968, Weinblatt *et al.*[1] first reported a paradoxical phenomenon that current smokers had a lower rate of all-cause mortality at 1 month compared with non-smokers (27.5% vs. 38.0%) among 881 patients presenting with myocardial infarction (MI). This finding has been dubbed the 'smoker's paradox'. Since then, numerous studies supported this finding, showing that smokers had a significantly lower crude rate of all-cause mortality compared with non-smokers,[2,3] especially in the era of fibrinolytic therapy.[4–7] Smoking is known to cause endothelial dysfunction, increase platelet aggregation, and decrease fibrinolytic factors, which all enhance the risk of arterial thrombosis.[8] Consequently, smokers presenting with MI are more likely to have thrombotic lesions with less underlying atherosclerotic burden, a scenario in which fibrinolytic therapy can be more effective, hence resulting in a lower mortality among smokers.[6,7] In addition, current smokers, when compared with non-smokers, are more likely to be younger and have fewer co-existent comorbidities at the time of presentation, an observation that also helps to explain this paradox.[9]

To date, there are limited data as to whether this smoker's paradox exists in the context of stable patients with complex CAD and whether very long-term outcome of revascularization differs according to smoking status.[10–14] Previously, we assessed the impact of smoking status on clinical outcomes at 5 years in 1800 patients of the SYNTAX trial with *de novo* three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD) randomized to treatment with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) in the SYNTAX trial,[11] showing that current smoking was not an independent predictor or treatment effect modifier for all-cause mortality at 5 years ($P_{interaction}$ = 0.675).[11] Recently, the SYNTAX Extended Survival (SYNTAXES) study has reported 10-year all-cause mortality in patients who were originally enrolled in the SYNTAX trial.[15] The aim of this study was to investigate the association of smoking status with 10-year all-cause mortality in patients with complex CAD undergoing revascularization and to assess a relative treatment benefit of CABG vs. PCI according to smoking status.

Methods

Study design and population

The design of the SYNTAX trial and its primary and final 5-year results have been previously reported.[16] In brief, the SYNTAX trial was a prospective, international, multicentre, randomized controlled trial conducted across 85 centres in Europe and the USA. Based on clinical judgement and the consensus of a Heart Team (consisting of a cardiothoracic surgeon and interventional cardiologist at each site), patients with *de novo* 3VD and/or LMCAD who were anticipated to achieve clinical equipoise between CABG and PCI were enrolled and randomized in a 1:1 fashion either to receive CABG (n = 897) or PCI (n = 903) with TAXUS Express paclitaxel-drug eluting stents (PES) (Boston Scientific Corporation, Marlborough, MA, USA). The SYNTAX trial (NCT00114972) completed patient follow-up at 5 years, and the SYNTAXES study (NCT03417050) has evaluated vital status between 5 and 10 years.[15] These 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.

Study endpoint

The pre-specified primary and secondary endpoint of the SYNTAXES trial was all-cause mortality at 10 years and at a maximum follow-up of 12.9 years, respectively.[15] Vital status was confirmed by contact with medical care personnel or using electronic healthcare record review and national death registries.

Smoking status

Smoking status was assessed by participant self-report. Current smokers were defined per protocol as those who actively smoke or who quit smoking within 1 month before randomization. Former smokers were defined as those who quit smoking more than 1 month before randomization. Never smokers were defined as those who had never smoked before randomization. The SYNTAX trial did not collect information on smoking pack-years or on time since cessation for former smokers.

Statistical analyses

Continuous variables were reported as mean ± standard deviations or median and interquartile range and were compared using Student's t tests or Mann–Whitney U test, respectively. Categorical variables were reported as percentages and numbers, and were compared using χ^2 or Fisher's exact test, as appropriate.

The cumulative incidence of clinical adverse events up to 10 years was assessed using the Kaplan–Meier method and compared using the log-rank test. Hazard ratio (HR) with 95% confidence intervals (CIs) was determined by a Cox proportional regression model. To assess the association of smoking status with 10-year all-cause mortality, a multivariable analysis was performed to account for the following variables; randomization to PCI vs. CABG, age, sex, body mass index (kg/m^2), medically treated diabetes, hypertension, chronic kidney disease (defined as creatinine clearance < 60 mL/min), previous history of MI, peripheral vascular disease (PVD), left ventricular ejection fraction (LVEF), and anatomical SYNTAX score, the sum of the individual scores of coronary lesions with ≥ 50% diameter stenosis in vessel ≥ 1.5 mm, weighted for their physiological impact.[17] Treatment effect of PCI vs. CABG according to smoking status was assessed using the unadjusted Cox regression model due to the nature of randomization. All the analyses were performed according to the intention-to-treat principle. Patients with missing vital status were included in the analysis and censored at the time of lost to follow-up or at 5 years if recruiting centres did not participate in the SYNTAXES study for 10-year extended follow-up.[15] All tests were two-sided and a P-value

of <0.05 was considered to be statistically significant. All analyses were performed using SPSS Statistics, version 25 (IBM Corp., N.Y., USA) and R version 3.5.3 (R Foundation, Vienna, Austria).

Results

Study population

The SYNTAX trial randomized a total of 1800 patients to either treatment with CABG ($n = 897$) or PCI with PES ($n = 903$) at 85 European and US sites between March 2005 and April 2007. Among them, there were two sites which enrolled five patients and elected not to participate in the SYNTAXES study. Information on smoking status at baseline was available in 1,793 (99.6%) patients, of whom 363 (20.2%) were current smokers, 798 (44.5%) were former smokers, and 632 (35.2%) were never smokers.

Baseline characteristics according to smoking status (current smokers vs. former smokers vs. never smokers) are presented in *Table 1*. Current smokers were less frequently randomized to PCI than never smokers. Current smokers were nearly 10 years younger and less likely to have diabetes, while they had a higher prevalence of PVD, chronic obstructive pulmonary disease (COPD), and lower LVEF. The mean anatomical SYNTAX score was lower in current smokers compared with other two groups. Although the number of lesions treated was slightly lower in current smokers, the number of stents implanted and number of bypass grafts were similar among the three groups.

Outcomes according to smoking status

In the overall cohort, the crude rates of the primary endpoint, all-cause mortality at 10 years, was 29.7% in current smokers, 25.9% in former smokers, and 25.3% in never smokers (Log-rank $P = 0.343$) (*Figure 1A*). Following adjustment for differences in baseline characteristics, however, the adjusted risk of 10-year all-cause mortality was significantly higher in current smokers vs. never smokers, whereas former smokers had a similar adjusted risk of 10-year mortality compared to never smokers (*Table 2*).

In the PCI arm, the crude rate of 10-year all-cause mortality was numerically higher in current smokers compared with the other two groups (36.2% for current smokers vs. 25.9% for former smokers vs. 27.4% for never smokers, Log-rank $P = 0.059$) (*Figure 1B*) with a significantly increased adjusted risk of 10-year all-cause mortality in current smokers compared with never smokers (*Table 2*). In the CABG arm, the crude rates of all-cause mortality were similar according to smoking status (24.1% for current smokers vs. 24.7% for former smokers vs. 23.9% for never smokers; Log-rank $P = 0.906$) (*Figure 1C*). After adjustment for baseline differences, the risk of all-cause mortality was significantly higher in current smokers compared with never smokers, whereas the adjusted risk was comparable between former and never smokers (*Table 2*).

Relative treatment benefit of coronary artery bypass grafting vs. percutaneous coronary intervention according to smoking status

Baseline characteristics in patients randomized to PCI vs. CABG according to smoking status are presented in *Table 3*. By randomization, clinical and procedural variables at baseline were generally well balanced between the PCI and CABG arm according to smoking status. Treatment effect between revascularization strategies and smoking status for all-cause mortality at 10 years is presented in the upper panel of *Figures 2 and 3*. Among current smokers, an unadjusted risk of 10-year all-cause mortality was significantly higher in patients with PCI compared with CABG (HR: 1.60; 95% CI: 1.09–2.35; $P = 0.017$), whereas the risk was similar between the two revascularization strategies among former smokers (HR: 1.02; 95% CI: 0.77–1.35; $P = 0.878$) or never smokers (HR: 1.22; 95% CI: 0.89–1.68; $P = 0.222$). There was no significant heterogeneity of treatment effect of PCI vs. CABG across smoking status ($P_{interaction} = 0.910$). Results at a maximum follow-up of 12.9 years are consistent with the ones at 10 years (lower panel of Figures 2 and 3).

Discussion

The main findings of this study can be summarized as follows: (i) compared with former smokers or never smokers, current smokers were on average nearly 10 years younger and had a lower prevalence of medically treated diabetes and lower SYNTAX score, but a higher rate of PVD, COPD, and low LVEF; (ii) the crude rates of all-cause mortality at 10 years were comparable according to smoking status. Following adjustment for imbalances in baseline characteristics, however, the adjusted risk of 10-year all-cause mortality was significantly higher in current smokers vs. never smokers, indicating that the 'smoker's paradox' did not exist in stable patients with complex CAD; (iii) of note, former smokers had a similar adjusted risk of all-cause mortality at 10 years compared with never smokers, which underlies an important role of smoking cessation in lowering risk of mortality irrespective of revascularization strategy; (iv) among current smokers, the risk of 10-year all-cause mortality was significantly higher in patients randomized to PCI relative to CABG, whereas the risk was similar between PCI and CABG among former smokers or never smokers (however, there was no statistical heterogeneity of treatment benefit from CABG vs. PCI according to the three smoking categories).

Outcomes according to smoking status

Previous studies have reported the so-called 'smoker's paradox' in patients with MI, demonstrating that current smokers had a lower crude rate of all-cause mortality compared with non-smokers.[2–7] Similar findings with respect to the role of smoking status on clinical outcomes have been reported in the setting of stable CAD.[18,19] More recently, a patient-level pooled analysis from 18 randomized controlled trials ($n = 24\,354$), of which 13 trials enrolled patients with stable CAD or unstable angina, has reported that there was no significant difference in the crude risk of all-cause mortality in smokers vs. non-smokers at 5 years after contemporary PCI procedures (8.6% vs. 9.0%; $P = 0.59$). However, following adjustment for baseline differences, smoking was shown to be associated with a significantly higher risk of all-cause mortality at 5 years (adjusted HR: 1.86; 95% CI: 1.63–2.12; $P < 0.0001$).[20] By demonstrating that current smokers were at increased risk of 10-year all-cause mortality in complex CAD patients

Table 1 Baseline characteristics according to smoking status at randomization

	Current smoker ($n = 363$)	Former smoker ($n = 798$)	Never smoker ($n = 632$)	*P*-value
Randomization				0.001
PCI	46.0 (167)	47.5 (379)	56.5 (357)	
CABG	54.0 (196)	52.5 (419)	43.5 (275)	
Age (years)	58.3 ± 9.4	65.9 ± 8.8	67.9 ± 9.2	<0.001
Sex				<0.001
Male	82.6 (300)	88.2 (704)	61.6 (389)	
Female	17.4 (63)	11.8 (94)	38.4 (243)	
Body mass index (kg/m^2)	27.6 ± 4.9	28.2 ± 4.3	28.0 ± 5.0	0.081
Diabetes	19.6 (71)	26.1 (208)	27.1 (171)	0.022
On insulin	10.2 (37)	9.9 (79)	10.4 (66)	0.944
Metabolic syndrome	47.5 (141)	44.1 (271)	46.9 (242)	0.514
Hypertension	62.5 (227)	66.4 (530)	68.7 (434)	0.143
Dyslipidaemia	76.9 (273)	80.0 (636)	76.3 (479)	0.202
Previous MI	36.0 (128)	31.8 (252)	32.3 (202)	0.365
Previous cerebrovascular disease	11.6 (42)	16.0 (127)	12.9 (81)	0.084
Previous stroke	2.5 (9)	5.9 (47)	3.2 (20)	0.007
Previous transient ischaemic attach	4.1 (15)	4.9 (39)	4.6 (29)	0.844
Previous carotid artery disease	6.9 (25)	8.6 (69)	8.1 (51)	0.595
Peripheral vascular disease	12.1 (44)	11.3 (90)	6.6 (42)	0.004
Chronic obstructive pulmonary disease	11.8 (43)	7.9 (63)	7.6 (48)	0.045
Chronic kidney disease	10.8 (36)	17.9 (129)	25.8 (149)	<0.001
Creatinine clearance (mL/min)	101.2 ± 36.4	84.4 ± 31.4	79.7 ± 29.3	<0.001
LVEF (%)	56.3 ± 13.9	59.2 ± 13.1	59.4 ± 12.3	0.007
Congestive heart failure	4.7 (17)	5.5 (43)	3.7 (23)	0.280
Clinical presentation				0.003
Silent ischaemia	17.4 (63)	14.9 (119)	12.0 (76)	
Stable angina	52.6 (191)	60.5 (483)	55.7 (352)	
Unstable angina	30.0 (109)	24.6 (196)	32.3 (204)	
EuroSCORE	2.9 ± 2.3	3.6 ± 2.5	4.4 ± 2.8	<0.001
Parsonnet SCORE	5.5 ± 4.5	8.4 ± 6.7	10.2 ± 7.6	<0.001
Disease extent				0.489
LMCAD only	6.9 (25)	4.4 (35)	4.6 (29)	
LMCAD + 1VD	7.5 (27)	8.1 (65)	6.8 (43)	
LMCAD + 2VD	12.4 (45)	12.3 (98)	11.9 (75)	
LMCAD + 3VD	13.5 (49)	14.4 (115)	14.7 (93)	
2VD	2.8 (10)	2.4 (19)	1.1 (7)	
3VD	56.9 (206)	58.4 (466)	60.9 (385)	
Number of lesions	4.1 ± 1.9	4.4 ± 1.8	4.4 ± 1.8	0.016
SYNTAX score	26.9 ± 10.9	29.0 ± 11.6	29.6 ± 11.2	0.002
SYNTAX score tercile				0.007
Low (0–22)	38.5 (139)	32.5 (258)	27.7 (174)	
Intermediate (23–32)	31.9 (115)	32.5 (258)	37.6 (236)	
High (≥33)	29.6 (107)	35.0 (278)	34.7 (218)	
Any total occlusion	22.8 (82)	25.6 (203)	20.6 (129)	0.084
Any bifurcation	70.3 (253)	71.9 (571)	75.3 (472)	0.181
Number of stents	4.4 ± 2.4	4.6 ± 2.2	4.8 ± 2.2	0.205
Total stent length per patient	80.9 ± 46.9	85.6 ± 48.5	88.0 ± 47.9	0.296
Number of total conduits	2.8 ± 0.7	2.8 ± 0.7	2.7 ± 0.7	0.363
Number of arterial conduits	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.6	0.435
Number of venous conduits	1.4 ± 0.9	1.4 ± 0.9	1.4 ± 0.9	0.955
Use of LIMA	84.4 (162)	86.7 (351)	86.3 (227)	0.744
Off pump CABG	18.3 (35)	15.1 (61)	12.5 (33)	0.235
Complete revascularization	63.6 (227)	59.9 (471)	57.8 (357)	0.203

Data are presented as mean ± standard deviation or percentage (number).
CABG, coronary artery bypass grafting; CAD, coronary artery disease; LIMA, left internal mammary artery; LMCAD, left main coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; 3VD, three-vessel disease; TIA, transient ischaemic attack.

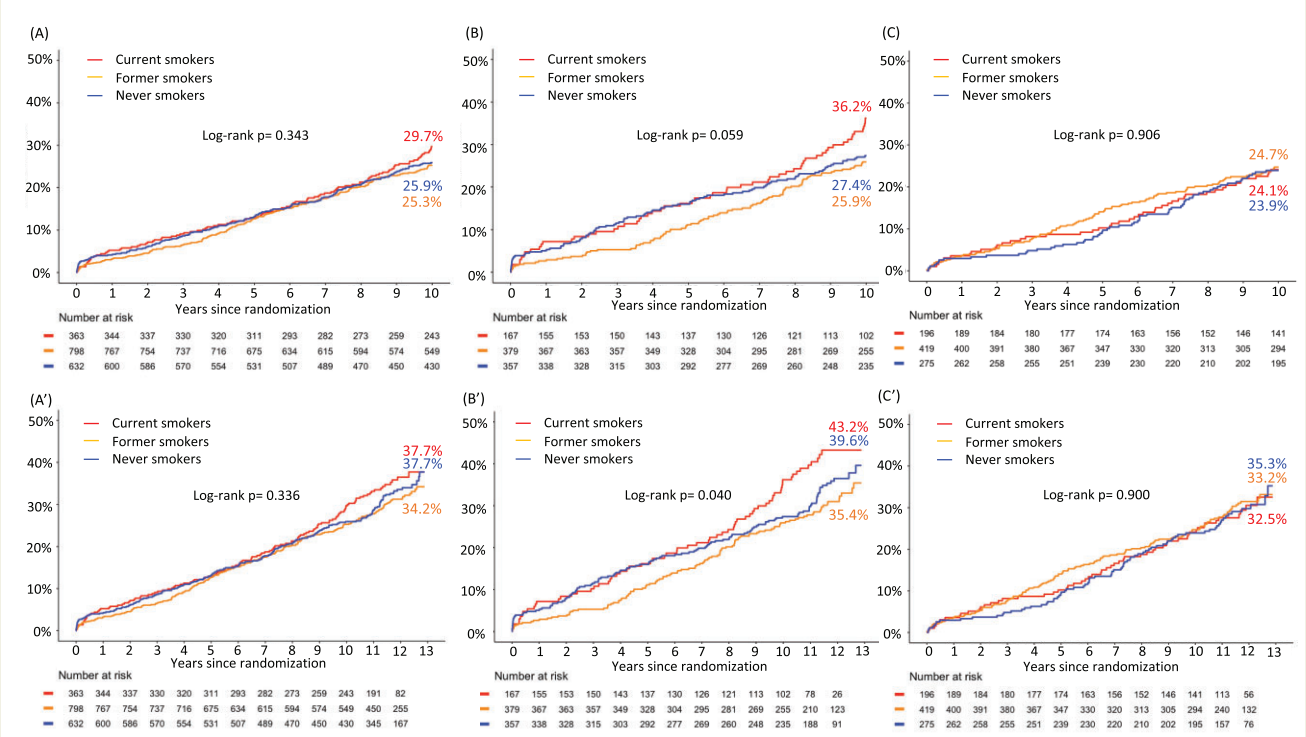

Figure 1 Kaplan–Meier curves for all-cause mortality at 10 years (upper panel) and at maximum follow-up of 12.9 years (lower panel) in current smokers (red), former smokers (orange), and never smokers (blue) among the overall cohort (*A* and *A'*), PCI arm (*B* and *B'*), and CABG arm (*C* and *C'*). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

undergoing PCI (*Table 2*), the present study supports previous findings and further extends this timeframe up to 10 years.

In contrast to observations in the setting of PCI, conflicting results have been reported during the past three decades with respect to the impact of smoking status in patients who underwent CABG. Early studies reported that CABG was not a preferred revascularization strategy in current smokers because of an increased risk of postoperative morbidity and mortality and early vein graft failure with subsequent early reoperation.[21,22] However, recent studies have suggested that smoking status did not impact early outcomes after surgical revascularization, but did influence late outcomes.[23] A recent large-scale observational study ($n = 21\,534$) confirmed these findings, showing that current smoking had a similar risk of 30-day all-cause mortality [adjusted odds ratio (OR): 1.05; 95% CI: 0.76–1.44; $P = 0.772$], whereas it was associated with a significantly increased risk of all-cause mortality at 5 years (adjusted OR: 1.73; 95% CI: 1.47–2.05; $P < 0.001$).[24] In the present analysis, we found that current smokers had a poorer long-term prognosis irrespective of whether revascularization was by PCI or CABG (*Table 2*), and these findings underscore the importance of risk factor modification at the time of revascularization, since smoking cessation has been shown to be associated with a lower risk of mortality than in persistent smokers after revascularization.[18] Nevertheless, only 60% of patients stopped smoking after revascularization with a relatively high relapse of smoking in the SYNTAX trial,[11] suggesting difficulty in quitting smoking permanently and a need for a dedicated smoking cessation interventions.[25]

Relative treatment benefit of coronary artery bypass grafting vs. percutaneous coronary intervention according to smoking status

To date, there have been limited data in terms of a treatment benefit of PCI vs. CABG according to smoking status,[10–13] in part because non-randomized data are inherently unsuitable for assessment of the benefit of one treatment over the other in an unbiased fashion. Previously, we assessed the impact of smoking status on clinical outcomes at 5 years in 1800 patients with complex CAD in the SYNTAX trial,[11] showing current smoking was not an independent predictor or treatment effect modifier for all-cause mortality at 5 years ($P_{interaction} = 0.675$).[11] Conversely, the present study with 10-year patient follow-up found that PCI was associated with a significantly higher risk of all-cause mortality at 10 years compared with CABG among current smokers, although this did not show a significant heterogeneity of treatment benefit of CABG vs. PCI at 10 years according to smoking status ($P_{interaction} = 0.910$) (*Figure 3*). Nevertheless, it would be plausible that PCI might be inferior to CABG among smokers, since smokers are at increased risk of MI, and PCI treats only stenotic lesions, whereas CABG bypasses obstructive and non-obstructive stenoses that can prevent MI, which may result

Table 2 Unadjusted and adjusted risk of all-cause mortality at 10 years and at maximum follow-up in current smokers vs. never smokers and in former smokers vs. never smokers

	Current smoker (*n* = 363)	Former smoker (*n* = 798)	Never smoker (*n* = 632)	Log-rank *P*-value	Current smokers vs. Never smokers			Former smokers vs. Never smokers		
					Unadjusted HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value	Unadjusted HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
At 10 years												
Overall	29.7 (105)	25.9 (194)	25.3 (158)	0.343	1.15 (0.90–1.47)	0.273	2.29 (1.60–3.27)	<0.001	0.96 (0.78–1.19)	0.733	1.12 (0.82–1.51)	0.481
PCI arm	36.2 (59)	25.9 (94)	27.4 (95)	0.059	1.33 (0.96–1.84)	0.086	2.30 (1.43–3.69)	0.001	0.90 (0.68–1.19)	0.462	0.97 (0.63–1.48)	0.888
CABG arm	24.1 (46)	24.7 (100)	23.9 (63)	0.906	1.02 (0.70–1.49)	0.919	2.37 (1.37–4.11)	0.002	1.07 (0.78–1.47)	0.671	1.29 (0.82–2.04)	0.270
At maximum follow-up												
Overall	37.7 (124)	34.2 (237)	37.7 (197)	0.336	1.10 (0.88–1.38)	0.409	2.38 (1.72–3.29)	<0.001	0.93 (0.77–1.13)	0.478	1.11 (0.84–1.46)	0.480
PCI arm	43.2 (68)	35.4 (113)	40.0 (119)	0.040	1.26 (0.93–1.70)	0.130	2.30 (1.49–3.56)	<0.001	0.85 (0.66–1.10)	0.226	0.88 (0.59–1.31)	0.524
CABG arm	32.5 (56)	33.2 (124)	35.3 (78)	0.900	1.00 (0.71–1.41)	0.995	2.58 (1.58–4.23)	<0.001	1.06 (0.80–1.41)	0.690	1.40 (0.92–2.13)	0.113

Data are presented as percentage (number of deaths).
CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Adjusted for age, sex, medically treated diabetes mellitus, body mass index, hypertension, chronic kidney disease (defined as creatinine clearance < 60 mL/min), previous MI, peripheral vascular disease, left ventricular ejection fraction, baseline anatomical SYNTAX score, and randomized treatment (PCI vs. CABG).

in a reduction in mortality.[26] Indeed, the FREEDOM trial, which enrolled patients with diabetes and multivessel disease (MVD), has recently shown a significant interaction between smokers and revascularization strategies in terms of 5-year MACE (composite of all-cause mortality, nonfatal stroke, or non-fatal MI) ($P_{interaction}$ = 0.04),[12] such that PCI was inferior to CABG especially in smokers with diabetes and MVD. Furthermore, a recent extended follow-up of the FREEDOM trial has found a significant smoking-by-treatment interaction ($P_{interaction}$ = 0.01) in terms of all-cause mortality, showing a survival benefit in favour of CABG especially among smokers with diabetes and MVD.[13] These findings suggest that patient's smoking status may be taken into account when deciding on the optimal revascularization strategy in this specific cohort of patients with diabetes and MVD.[13]

Limitations

Our findings should be interpreted in light of the following limitations. First, in contrast to our previous report,[11] the present analysis did not take into account smoking status as a time-varying variable, because we did not assess smoking status beyond 5 years, precluding assessment of smoking crossover and its impact on clinical outcomes over time. Indeed, smoking is a behavioural coronary risk factor that can be modified after revascularization, and as previously described,[11] not all current smokers remained smokers after the index procedure. Second, as in other major randomized trials,[12,13] the SYNTAX trial did not capture the number of cigarettes smoked by current or former smokers (e.g. pack-years). Third, although the SYNTAX trial collected baseline information that are related to mortality and the present analysis accounted for imbalances in multivariable models, the role of unmeasured confounders cannot be excluded. Fourth, the SYNTAX trial was conducted between 2005 and 2007 with a predominant use of the first-generation PES for treatment with PCI, which may limit generalizability of our findings to current practice. Of note, however, it is 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. Fifth, the SYNTAXES study collected data on all-cause mortality and did not have information on the causes of death. Nevertheless, the study is the first randomized data that was meticulously conducted and achieved a high follow-up rate of 93.8% for 10-year vital status (1689 out of 1800 enrolled patients).[15]

Conclusion

Among 1793 (99.6%) patients in whom data were available for smoking status, and who were randomized to treatment with CABG or PCI, current smokers had a more than two-fold higher adjusted risk of all-cause mortality at 10 years compared with never smokers. Conversely, former smokers had a similar adjusted risk of all-cause mortality compared to never smokers. The relative efficacy of PCI vs. CABG did not differ significantly according to smoking status.

Table 3 Baseline characteristics stratified according to revascularization strategies and smoking status

	Current smokers (*n* = 363)			Former smokers (*n* = 798)			Never smokers (*n* = 632)		
	PCI (*n* = 167)	CABG (*n* = 196)	*P*-value	PCI (*n* = 379)	CABG (*n* = 419)	*P*-value	PCI (*n* = 357)	CABG (*n* = 275)	*P*-value
Age (years)	59.2 ± 9.5	57.5 ± 9.2	0.085	65.5 ± 9.0	66.3 ± 8.6	0.202	67.8 ± 9.2	68.1 ± 9.2	0.677
Sex			0.996			0.718			0.538
Male	82.6 (138)	82.7 (162)		88.7 (336)	87.8 (368)		60.5 (216)	62.9 (173)	
Female	17.4 (29)	17.3 (34)		11.3 (43)	12.2 (51)		39.5 (141)	37.1 (102)	
Body mass index (kg/m^2)	27.6 ± 5.2	27.6 ± 4.6	0.991	28.4 ± 4.6	28.1 ± 4.1	0.302	28.0 ± 4.8	27.9 ± 5.2	0.663
Diabetes	21.0 (35)	18.4 (36)	0.535	26.9 (102)	25.3 (106)	0.604	26.3 (94)	28.0 (77)	0.640
On insulin	9.6 (16)	10.7 (21)	0.722	10.0 (38)	9.8 (41)	0.909	9.8 (35)	11.3 (31)	0.549
Metabolic syndrome	45.7 (64)	49.0 (77)	0.566	43.1 (128)	45.0 (143)	0.640	49.0 (147)	44.0 (95)	0.260
Hypertension	67.7 (113)	58.2 (114)	0.062	66.2 (251)	66.6 (279)	0.914	72.3 (258)	64.0 (176)	0.026
Dyslipidaemia	76.1 (124)	77.6 (149)	0.733	81.7 (308)	78.5 (328)	0.256	76.7 (273)	75.7 (206)	0.782
Previous MI	33.7 (56)	37.9 (72)	0.415	31.7 (119)	31.9 (133)	0.961	31.3 (110)	33.7 (92)	0.516
Prior cerebrovascular disease	11.4 (19)	11.8 (23)	0.918	14.2 (54)	17.6 (73)	0.199	12.9 (46)	12.8 (35)	0.970
Previous stroke	3.6 (6)	1.5 (3)	0.207	4.2 (16)	7.5 (31)	0.055	3.7 (13)	2.6 (7)	0.441
Previous TIA	1.8 (3)	6.2 (12)	0.038	5.3 (20)	4.6 (19)	0.643	4.5 (16)	4.8 (13)	0.866
Previous carotid artery disease	7.8 (13)	6.1 (12)	0.533	7.7 (29)	9.5 (40)	0.342	8.7 (31)	7.3 (20)	0.519
Peripheral vascular disease	12.6 (21)	11.7 (23)	0.807	9.5 (36)	12.9 (54)	0.131	7.0 (25)	6.2 (17)	0.681
Chronic obstructive pulmonary disease	10.8 (18)	12.8 (25)	0.561	7.4 (28)	8.4 (35)	0.614	7.0 (25)	8.4 (23)	0.522
Impaired renal function	11.5 (18)	10.2 (18)	0.703	16.4 (58)	19.3 (71)	0.300	26.7 (91)	24.5 (58)	0.550
Creatinine clearance (mL/min)	102.5 ± 40.5	100 ± 32.5	0.530	86.2 ± 35.3	82.7 ± 27.0	0.140	79.9 ± 30.9	79.5 ± 26.9	0.891
LVEF (%)	58.1 ± 13.3	54.8 ± 14.2	0.065	59.0 ± 13.5	59.4 ± 12.7	0.760	59.5 ± 12.0	59.2 ± 12.8	0.812
Congestive heart failure	2.4 (4)	6.8 (13)	0.052	4.5 (17)	6.3 (26)	0.266	4.2 (15)	2.9 (8)	0.392
Clinical presentation			0.979			0.599			0.850
Silent ischaemia	17.4 (29)	17.3 (34)		14.2 (54)	15.5 (65)		12.3 (44)	11.6 (32)	
Stable angina	52.1 (87)	53.1 (104)		59.6 (226)	61.3 (257)		56.3 (201)	54.9 (151)	
Unstable angina	30.5 (51)	29.6 (58)		26.1 (99)	23.2 (97)		31.4 (112)	33.5 (92)	
EuroSCORE	2.8 ± 2.3	2.9 ± 2.4	0.745	3.6 ± 2.5	3.7 ± 2.6	0.361	4.4 ± 2.7	4.4 ± 2.8	0.901
Parsonnet SCORE	5.7 ± 4.4	5.4 ± 4.5	0.460	8.2 ± 6.5	8.5 ± 6.8	0.446	10.2 ± 7.9	10.2 ± 7.3	0.951
Disease extent			0.754			0.514			0.648
LMCAD only	7.8 (13)	6.2 (12)		3.7 (14)	5.0 (21)		4.2 (15)	5.1 (14)	
LMCAD + 1VD	5.4 (9)	9.2 (18)		9.0 (34)	7.4 (31)		6.7 (24)	6.9 (19)	
LMCAD + 2VD	11.4 (19)	13.3 (26)		12.4 (47)	12.2 (51)		12.9 (46)	10.5 (29)	
LMCAD + 3VD	13.8 (23)	13.3 (26)		16.4 (62)	12.6 (53)		14.3 (51)	15.3 (42)	
2VD	3.0 (5)	2.6 (5)		2.6 (10)	2.1 (9)		0.6 (2)	1.8 (5)	
3VD	58.7 (98)	55.4 (108)		55.9 (212)	60.6 (254)		61.3 (219)	60.4 (166)	
Number of lesions	4.3 ± 2.0	4.0 ± 1.8	0.170	4.4 ± 1.7	4.4 ± 1.8	0.961	4.3 ± 1.8	4.6 ± 1.7	0.011
SYNTAX score	26.8 ± 11.0	26.8 ± 10.9	0.994	29.4 ± 11.7	28.6 ± 11.6	0.300	28.0 ± 11.4	31.5 ± 10.8	<0.001
SYNTAX score tercile			0.797			0.692			0.002
Low (0–22)	40.4 (67)	36.9 (72)		31.0 (117)	33.8 (141)		32.3 (115)	21.7 (59)	
Intermediate (23–32)	30.7 (51)	32.8 (64)		32.9 (124)	32.1 (134)		37.9 (135)	37.1 (101)	
High (≥ 33)	28.9 (48)	30.3 (59)		36.1 (136)	34.1 (142)		29.8 (106)	41.2 (112)	
Any total occlusion	24.2 (40)	21.5 (42)	0.542	27.3 (103)	24.0 (100)	0.281	20.8 (74)	20.2 (55)	0.848
Any bifurcation	69.1 (114)	71.3 (139)	0.650	73.7 (278)	70.3 (293)	0.276	72.4 (257)	79.0 (215)	0.056
Number of stents	4.4 ± 2.4			4.6 ± 2.2			4.8 ± 2.2		
Total stent length per patient	81.5 ± 46.7			86.3 ± 48.6			88.7 ± 47.7		
Number of total conduits		2.8 ± 0.7			2.8 ± 0.7			2.7 ± 0.7	
Number of arterial conduits		1.4 ± 0.7			1.4 ± 0.7			1.4 ± 0.6	
Number of venous conduits		1.4 ± 0.9			1.4 ± 0.9			1.4 ± 0.9	
Use of LIMA		84.1 (159)			86.8 (347)			86.2 (224)	
Off pump CABG		18.6 (35)			15.0 (60)			12.3 (32)	
Complete revascularization	58.4 (97)	68.1 (130)	0.059	54.1 (204)	65.3 (267)	0.001	58.6 (207)	56.6 (150)	0.612

Data are presented as mean ± standard deviation or percentage (number).
3VD, three-vessel disease; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LIMA, left internal mammary artery; LMCAD, left main coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

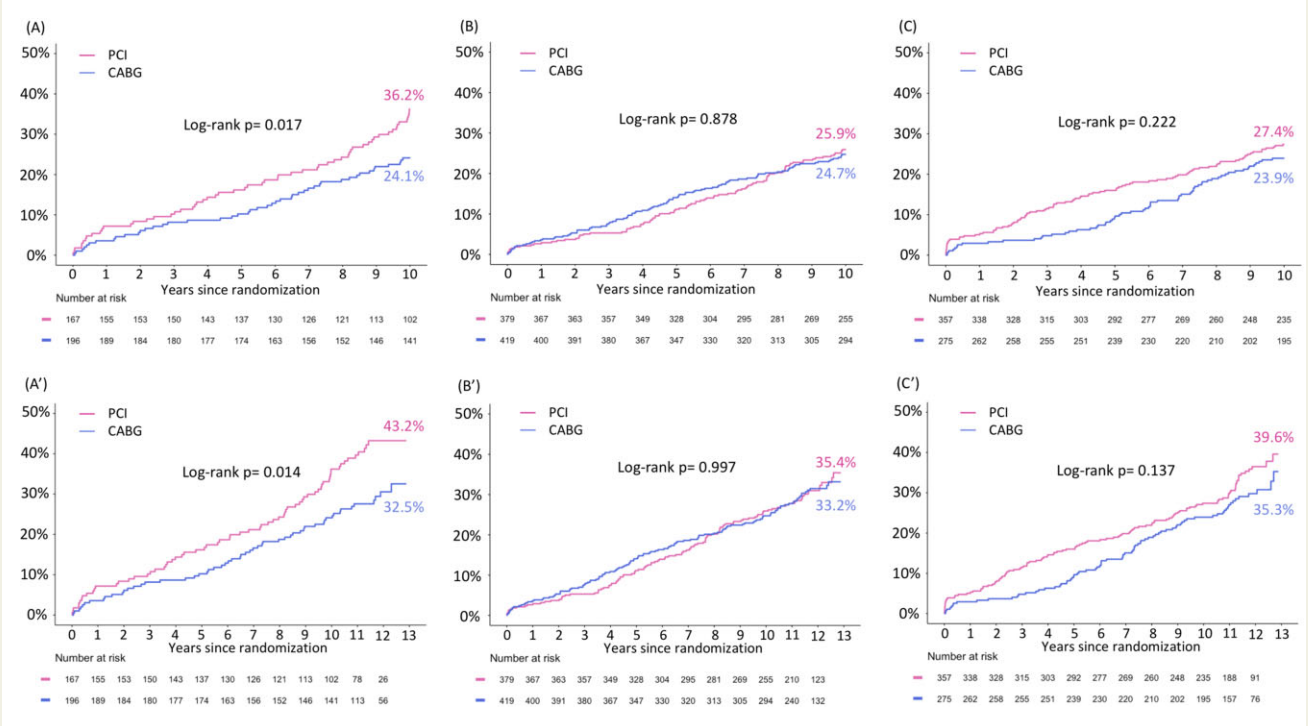

Figure 2 Kaplan–Meier curves for all-cause mortality at 10 years (upper panel) and at maximum follow-up of 12.9 years (lower panel) in patients randomized to PCI (pink) vs. CABG (blue) among current smokers (*A* and *A'*), former smokers (*B* and *B'*), or never smokers (*C* and *C'*). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PCI, percutaneous coronary intervention.

	Randomized to PCI (n= 903)	Randomized to CABG (n= 890)	HR (95% CI)	P-value for interaction
At 10 years				0.910
Current smokers	36.2% (59)	24.1% (46)	1.60 (1.09-2.35)	
Former smokers	25.9% (94)	24.7% (100)	1.02 (0.77-1.35)	
Never smokers	27.4% (95)	23.9% (63)	1.22 (0.89-1.68)	
At maximum follow-up				0.905
Current smokers	43.2% (68)	32.5% (56)	1.56 (1.09-2.22)	
Former smokers	35.4% (113)	33.2% (124)	1.00 (0.77-1.29)	
Never smokers	39.6% (124)	35.3% (78)	1.24 (0.93-1.65)	

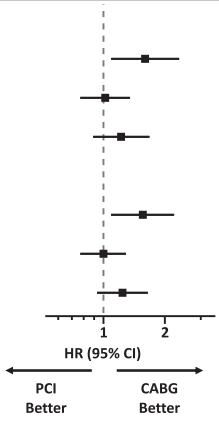

Figure 3 The relative efficacy of PCI vs. CABG for all-cause mortality at 10 years (upper part) and at maximum follow-up of 12.9 years (lower part) according to smoking status. Data are presented as percentage (number of events). CI: confidence interval; CABG, coronary artery bypass grafting; HR: hazard ratio.

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References

1. Weinblatt E, Shapiro S, Frank CW, Sager RV. Prognosis of men after first myocardial infarction: mortality and first recurrence in relation to selected parameters. *Am J Public Health Nations Health* 1968;**58**:1329–1347.
2. Kitchin AH, Pocock SJ. Prognosis of patients with acute myocardial infarction admitted to a coronary care unit. I: survival in hospital. *Br Heart J* 1977;**39**:1163–1166.
3. Molstad P. First myocardial infarction in smokers. *Eur Heart J* 1991;**12**:753–759.
4. Mueller HS, Cohen LS, Braunwald E, Forman S, Feit F, Ross A, Schweiger M, Cabin H, Davison R, Miller D. Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction. Analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation* 1992;**85**:1254–1264.
5. Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkila J, Kristinsson A, Moulopoulos S, Paolasso EA, Van der Werf T. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. *Circulation* 1993;**87**:53–58.
6. Grines CL, Topol EJ, O'Neill WW, George BS, Kereiakes D, Phillips HR, Leimberger JD, Woodlief LH, Califf RM. Effect of cigarette smoking on outcome after thrombolytic therapy for myocardial infarction. *Circulation* 1995;**91**:298–303.
7. Zahger D, Cercek B, Cannon CP, Jordan M, Davis V, Braunwald E, Shah PK. How do smokers differ from nonsmokers in their response to thrombolysis? (the TIMI-4 trial). *Am J Cardiol* 1995;**75**:232–236.
8. McEvoy JW, Blaha MJ, DeFilippis AP, Lima JA, Bluemke DA, Hundley WG, Min JK, Shaw LJ, Lloyd-Jones DM, Barr RG, Budoff MJ, Blumenthal RS, Nasir K. Cigarette smoking and cardiovascular events: role of inflammation and subclinical atherosclerosis from the MultiEthnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2015;**35**:700–709.
9. Robertson JO, Ebrahimi R, Lansky AJ, Mehran R, Stone GW, Lincoff AM. Impact of cigarette smoking on extent of coronary artery disease and prognosis of patients with non-ST-segment elevation acute coronary syndromes: an analysis from the ACUITY Trial (Acute Catheterization and Urgent Intervention Triage Strategy). *JACC Cardiovasc Interv* 2014;**7**:372–379.
10. BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000;**35**:1122–1129.
11. Zhang YJ, Iqbal J, van Klaveren D, Campos CM, Holmes DR, Kappetein AP, Morice MC, Banning AP, Grech ED, Bourantas CV, Onuma Y, Garcia-Garcia HM, Mack MJ, Colombo A, Mohr FW, Steyerberg EW, Serruys PW. Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: the SYNTAX trial at 5-year follow-up. *J Am Coll Cardiol* 2015;**65**:1107–1115.
12. Qintar M, Humphries KH, Park JE, Arnold SV, Tang Y, Jones P, Salisbury AC, Kureshi F, Farkouh ME, Fuster V, Cohen DJ, Spertus JA. Individualizing revascularization strategy for diabetic patients with multivessel coronary disease. *J Am Coll Cardiol* 2019;**74**:2074–2084.
13. Farkouh ME, Domanski M, Dangas GD, Godoy LC, Mack MJ, Siami FS, Hamza TH, Shah B, Stefanini GG, Sidhu MS, Tanguay J-F, Ramanathan K, Sharma SK, French J, Hueb W, Cohen DJ, Fuster V, Sharma SK, Zazif TN, Thai H, Shah B, Ramanathan K, Tanguay J-F, Ramanathan K, Burton JR, Schampaert E, Escobedo J, Dubois-Rande J-L, Macaya C, Carrie D, Richardt G, Roguin A, Lotan C, Kornowski R, Presbitero P, Hueb W, Sousa JE, Velásquez JG, Rodriguez A, Devlin G, French JK, Kaul U. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM follow-on study. *J Am Coll Cardiol* 2019;**73**:629–638.
14. Shahim B, Redfors B, Chen S, Morice MC, Gersh BJ, Puskas JD, Kandzari DE, Merkely B, Horkay F, Crowley A, Serruys PW, Kappetein AP, Sabik JF 3rd, Ben-Yehuda O, Stone GW. Outcomes after left main coronary artery revascularization by percutaneous coronary intervention or coronary artery bypass grafting according to smoking status. Am J Cardiol 2020;127:16-24.
15. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, Holmes DR Jr, Curzen N, Davierwala P, Noack T, Milojevic M, Dawkins KD, da Costa BR, Juni P, Head SJ; Investigators SES. 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 2019;394(10206):1325–1334.
16. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, Investigators S. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
17. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *Eurointervention* 2009;**5**:50–56.
18. Hasdai D, Garratt KN, Grill DE, Lerman A, Holmes DR Jr. Effect of smoking status on the long-term outcome after successful percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:755–761.
19. Cohen DJ, Doucet M, Cutlip DE, Ho KK, Popma JJ, Kuntz RE. Impact of smoking on clinical and angiographic restenosis after percutaneous coronary intervention: another smoker's paradox? *Circulation* 2001;**104**:773–778.
20. Yadav M, Mintz GS, Genereux P, Liu M, McAndrew T, Redfors B, Madhavan MV, Leon MB, Stone GW. The smoker's paradox revisited: a patient-level pooled analysis of 18 randomized controlled trials. *JACC Cardiovasc Interv* 2019;**12**:1941–1950.
21. Underwood MJ, Bailey JS. Coronary bypass surgery should not be offered to smokers. *BMJ* 1993;**306**:1047–1048.
22. Voors AA, van Brussel BL, Plokker HW, Ernst SM, Ernst NM, Koomen EM, Tijssen JG, Vermeulen FE. Smoking and cardiac events after venous coronary bypass surgery. A 15-year follow-up study. *Circulation* 1996;**93**:42–47.
23. Ashraf MN, Mortasawi A, Grayson AD, Oo AY. Effect of smoking status on mortality and morbidity following coronary artery bypass surgery. *Thorac Cardiovasc Surg* 2004;**52**:268–273.
24. Saxena A, Shan L, Reid C, Dinh DT, Smith JA, Shardey GC, Newcomb AE. Impact of smoking status on early and late outcomes after isolated coronary artery bypass graft surgery. *J Cardiol* 2013;**61**:336–341.
25. Piepoli MF, Abreu A, Albus C, Ambrosetti M, Brotons C, Catapano AL, Corra U, Cosyns B, Deaton C, Graham I, Hoes A, Lochen ML, Matrone B, Redon J, Sattar N, Smulders Y, Tiberi M. Update on cardiovascular prevention in clinical practice: a position paper of the European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Prev Cardiol* 2020;**27**:181–205.
26. Doenst T, Haverich A, Serruys P, Bonow RO, Kappetein P, Falk V, Velazquez E, Diegeler A, Sigusch H. PCI and CABG for treating stable coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:964–976.