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CLINICAL RESEARCH
Diabetes and metabolic disorders

Ten-year all-cause death after percutaneous or surgical revascularization in diabetic patients with complex coronary artery disease

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Aims The aim of this article was to compare rates of all-cause death at 10 years following coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) in patients with or without diabetes.

Methods and results The SYNTAXES study evaluated up to 10-year survival of 1800 patients with three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD) randomized to receive either PCI or CABG in the SYNTAX trial. Ten-year all-cause death according to diabetic status and revascularization strategy was examined. In diabetics ($n = 452$), the risk of mortality was numerically higher with PCI compared with CABG at 5 years [19.6% vs. 13.3%, hazard ratio (HR): 1.53, 95% confidence interval (CI): 0.96, 2.43, $P = 0.075$], with the opposite seen between 5 and 10 years (PCI vs. CABG: 20.8% vs. 24.4%, HR: 0.82, 95% CI: 0.52, 1.27, $P = 0.366$). Irrespective of diabetic status, there was no significant difference in all-cause death at 10 years between patients receiving PCI or CABG, the absolute treatment difference was 1.9% in diabetics (PCI vs. CABG: 36.4% vs. 34.5%, difference: 1.9%, 95% CI: -7.6%, 11.1%, $P = 0.551$). Among insulin-treated patients ($n = 182$), all-cause death at 10 years was numerically higher with PCI (47.9% vs. 39.6%, difference: 8.2%, 95% CI: -6.5%, 22.5%, $P = 0.227$).

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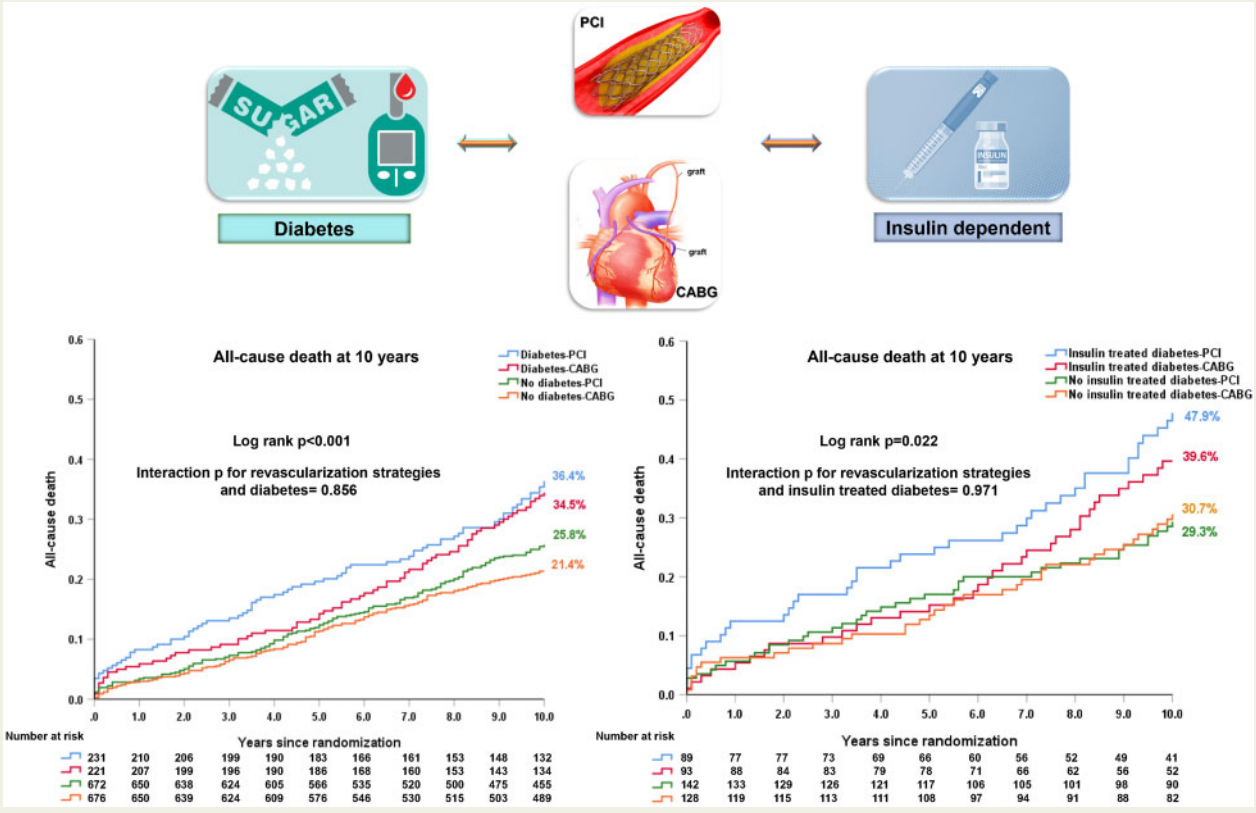
Conclusions The treatment effects of PCI vs. CABG on all-cause death at 10 years in patients with 3VD and/or LMCAD were similar irrespective of the presence of diabetes. There may, however, be a survival benefit with CABG in patients with insulin-treated diabetes. The association between revascularization strategy and very long-term ischaemic and safety outcomes for patients with diabetes needs further investigation in dedicated trials.

Trial registration SYNTAX: ClinicalTrials.gov reference: NCT00114972 and SYNTAX Extended Survival: ClinicalTrials.gov reference: NCT03417050.

Graphical Abstract



The treatment effects of PCI versus CABG on all-cause death at 10 years in 3VD/LMCAD patients with pharmacologically treated diabetes and insulin-treated diabetes.

Keywords All-cause death • Coronary artery bypass grafting • Diabetes • Percutaneous coronary intervention • SYNTAX

Introduction

Cardiovascular disease (CVD) is a major comorbidity and affects nearly a third of diabetics.[1] Diabetes is associated with worse outcomes after coronary revascularization and has been identified as an independent predictor of adverse events in patients with CVD.[2]

The first randomized trial dedicated to diabetics (CARDia) demonstrated that percutaneous coronary intervention (PCI) had an increased rate of the composite primary endpoint of all-cause death, myocardial infarction (MI) and stroke at 12 months compared with coronary artery bypass grafting (CABG) surgery.[3] Subsequently, the FREEDOM trial showed that CABG was superior to drug-eluting stents (DES) for the composite primary endpoint of death, stroke, and MI at 5 years.[4] Similarly, the diabetes subgroup analysis of the SYNTAX study reported that PCI resulted in higher rates of 5-year MACCE (major adverse cardiovascular and cerebrovascular event: a composite endpoint of all-cause death, cerebrovascular accident, MI, or repeat revascularization), compared with CABG, which was driven by a higher rate of repeat revascularization.[5] Moreover, a recent pooled analysis of individual patient data demonstrated that diabetes had a significant treatment interaction between PCI and CABG for 5-year all-cause mortality.[6] Based on these findings in this specific

subgroup, current guidelines recommend CABG as the preferred revascularization procedure in patients with diabetes, especially for those with multivessel coronary artery diseases (CAD).[7] Most available studies have limited follow-up of only 5 years; however, the BARI trial, which reported outcomes at 10 years, demonstrated that CABG conferred a survival benefit over PCI with balloon angioplasty in patients with diabetes and multivessel disease [59%: two-vessel disease and 41%: three-vessel disease (3VD)].[8] Whether this benefit remains in these patients when CABG is compared with PCI with DES remains to be established.

A suitable population to address this outstanding question comes from the SYNTAXES study, which established 10-year survival status in 94% of the 1800 patients with *de novo* 3VD and/or left main coronary artery disease (LMCAD) who were originally randomized to CABG or PCI in the SYNTAX trial.[9] The aims of the present study were therefore (i) to evaluate the association between diabetes and all-cause death at 10 years; (ii) to examine the specific impact of diabetes with insulin dependence on all-cause death at 10 years; (iii) to investigate the 10-year treatment effect on survival of PCI vs. CABG, according to diabetes, in patients with complex CAD.

Methods

Study design

The design and the primary results of the SYNTAX study have been reported previously.[10–12] Briefly, all-comer patients with *de novo* 3VD and/or LMCAD deemed to be eligible for both PCI and CABG were enrolled and randomized to either CABG ($n = 897$) or PCI ($n = 903$) with TAXUS DES (Boston Scientific, Marlborough, MA, USA). The SYNTAX trial completed patient follow-up at 5 years.[12] The SYNTAXES study was an investigator-driven initiative that extended follow-up and aimed to evaluate vital status at up to 10 years.[9] The German Heart Research Foundation (GHF, Frankfurt am Main, Germany) funded the extended follow-up, which was performed in accordance with local regulations of each participating centre and complied with the declaration of Helsinki.

Study endpoints

The present analysis is a pre-specified sub-study of the SYNTAXES study.[9] The primary endpoint was all-cause death at 10 years. The secondary endpoint was all-cause death at maximum available follow-up. Vital status was confirmed by contact with medical care personnel or by electronic healthcare record review and national death registry. The aim of the study was to examine the impact of pharmacologically (non-insulin or insulin) treated diabetes (categorized at the time of randomization), on subsequent all-cause death at 10 years. The impact of all diabetes (pharmacological and diet-controlled) on all-cause death at 10 years was performed as a sensitivity analysis.

The following exploratory analyses were performed: elderly (>70 years old), anatomical SYNTAX score tertiles (≤22, 23–32, or ≥33), disease type (3VD or LMCAD), impact of haemoglobin A1c (HbA1c); C-reactive protein (<2, or ≥2), residual SYNTAX score (rSS = 0, >0–4, >4–8, and >8), type of revascularization (single or multiple arterial bypass graft) and optimal medical therapy. Finally, we applied SYNTAX score II 2020 to the diabetic and non-diabetic population.[13]

Statistical analysis

Continuous variables are shown as mean ± standard deviations and are compared using Student's *t*-tests or Mann–Whitney *U* test. Categorical variables are reported as percentages and numbers and are compared using χ^2 tests, or Fisher's exact test when appropriate.

Time-to-event Kaplan–Meier estimates with the log-rank test were used to compare PCI and CABG in patients with and without diabetes, and to compare diabetes vs. no diabetes in PCI and CABG groups. Hazard ratio (HR) with 95% confidence interval (CI) was assessed on the basis of the Cox proportional regression. The mean restricted life expectancy was estimated by the area under the survival curve between 0 and 10 years.[8] The adjusted cubic spline was used to show the association between HbA1c and the risk of all-cause death at 10 years. Multivariable analyses were performed in the Cox proportional hazards regression model to evaluate whether pharmacologically treated or insulin-treated diabetes was an independent predictor of all-cause death at 10 years. The following covariates were included: age, gender, body mass index (BMI), current smoking, hypertension, peripheral vascular disease (PVD), chronic obstructive pulmonary disease, creatinine clearance (mL/min), left ventricular ejection fraction (as categorical: good ≥50%, moderate: 30–49%, and poor: <30%), anatomical SYNTAX score, prior MI, and stroke. All these variables were selected based on the previous knowledge of their association with clinical outcomes.[14] All analyses were performed using SPSS Statistics, version 25 (IBM Corp., Armonk, 281 NY, USA), and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics

Out of 1800 patients, 511 had diabetes, of which 59 were treated by diet alone, and of the remaining 452 treated pharmacologically, 182 were on insulin. The median maximum follow-up was 11.2 (interquartile range: 7.7, 12.1) years. Baseline characteristics according to diabetes are shown in Supplementary material online, *Table S1*. Compared with patients without diabetes, patients with diabetes were more frequently female, had more comorbidities (dyslipidaemia, PVD, previous stroke, carotid artery disease, and congestive heart failure), had a higher BMI, EuroSCORE, Parsonnet SCORE, more frequently had 3VD, with more lesions treated, whereas they were less likely to be current smokers. By randomization, baseline characteristics according to revascularization strategy were generally well balanced in diabetic and non-diabetic patients (*Table 1*).

All-cause death according to diabetes

Overall compared with patients without diabetes, those with pharmacologically treated diabetes had a higher risk of all-cause death at 10 years (35.4% vs. 23.6%, adjusted HR: 1.58, 95% CI: 1.27, 1.95, $P < 0.001$, *Figure 1A*, *Table 2*). Similar results were observed for all-cause death at maximum follow-up (*Table 2*, Supplementary material online, *Figure S1*). Results were similar when including the 59 patients with diet-controlled diabetes (Supplementary material online, *Figures S2* and *S3*).

After adjustment for baseline confounders, pharmacologically treated diabetes was an independent predictor of all-cause death at 10 years in the overall cohort (HR: 1.58, 95% CI: 1.27, 1.95, $P < 0.001$), the PCI arm (HR: 1.54, 95% CI: 1.15, 2.06, $P = 0.003$), and the CABG arm (HR: 1.65, 95% CI: 1.19, 2.28, $P = 0.003$, Supplementary material online, *Table S2*), with poorer outcomes in those receiving insulin (Supplementary material online, *Table S3*).

Table 1 Baseline characteristics according to diabetes and revascularization strategies

	No diabetes		*P*-value	Diabetes		*P*-value
	PCI (*n* = 672)	CABG (*n* = 676)		PCI (*n* = 231)	CABG (*n* = 221)	
Age (years)	65.2 ± 9.9	64.7 ± 9.9	0.356	65.2 ± 9.1	65.6 ± 9.3	0.637
Male sex	78.1 (525/672)	81.7 (552/676)	0.106	71.4 (165/231)	70.6 (156/221)	0.844
Body mass index (kg/m^2)	27.6 ± 4.5	27.4 ± 4.3	0.445	29.5 ± 5.4	29.4 ± 5.1	0.736
Glycated haemoglobin (%)	5.8 ± 0.5	5.8 ± 0.6	0.830	7.4 ± 1.3	7.3 ± 1.1	0.598
Metabolic syndrome	30.2 (203/672)	28.8 (195/676)	0.193	58.9 (136/231)	55.2 (122/221)	0.546
Hypertension	67.0 (450/672)	63.6 (430/676)	0.196	74.5 (172/231)	65.2 (144/221)	0.031
Dyslipidaemia	77.6 (520/670)	75.9 (509/671)	0.447	81.9 (185/226)	81.2 (177/218)	0.857
Current smoker	19.6 (132/672)	23.8 (160/671)	0.062	15.2 (35/231)	16.4 (36/219)	0.708
Previous MI	31.4 (209/665)	34.9 (233/668)	0.181	33.3 (76/228)	30.6 (67/219)	0.535
Previous stroke	3.4 (23/670)	4.2 (28/671)	0.479	5.2 (12/229)	6.8 (15/219)	0.474
Previous TIA	3.6 (24/671)	5.1 (34/670)	0.178	6.5 (15/230)	5.0 (11/218)	0.504
Previous CAD	7.7 (52/672)	7.0 (47/676)	0.580	9.1 (21/231)	12.7 (28/221)	0.221
PVD	6.8 (46/672)	9.6 (65/676)	0.064	15.6 (36/231)	13.6 (30/221)	0.545
COPD	7.0 (47/672)	9.2 (62/676)	0.143	10.4 (24/231)	9.5 (21/221)	0.753
Impaired renal function	18.6 (125/672)	15.7 (106/676)	< 0.001	18.2 (42/231)	19.5 (43/221)	0.003
Creatinine clearance (mL/min)	86.4 ± 34.2	85.6 ± 28.2	0.648	87.5 ± 39.3	85.5 ± 33	0.586
LVEF (%)	59.6 ± 12.6	58.3 ± 13.2	0.163	57.5 ± 13.7	58.0 ± 13.1	0.736
Congestive heart failure	3.3 (22/669)	4.2 (28/665)	0.375	6.1 (14/229)	8.8 (19/215)	0.274
Clinical presentation			0.877			0.164
Silent ischemia	14.7 (99/672)	13.8 (93/676)		12.1 (28/231)	18.1 (40/221)	
Stable angina	57.3 (385/672)	58.0 (392/676)		55.8 (129/231)	54.8 (121/221)	
Unstable angina	28.0 (188/672)	28.3 (191/676)		32.0 (74/231)	27.1 (60/221)	
EuroSCORE	3.7 ± 2.6	3.7 ± 2.7	0.755	4.0 ± 2.7	4.0 ± 2.7	0.971
Parsonnet score	7.6 ± 6.9	7.4 ± 6.7	0.596	11.1 ± 6.5	11.5 ± 6.4	0.584
Disease extent			0.556			0.733
3VD	58.5 (393/672)	60.1 (406/676)		66.2 (153/231)	64.7 (143/221)	
LMCAD	41.5 (279/672)	39.9 (270/676)		33.8 (78/231)	35.3 (78/221)	
Disease location			0.658			0.883
LMCAD only	5.1 (34/672)	6.2 (42/675)		3.5 (8/231)	3.2 (7/221)	
LMCAD +1VD	8.0 (54/672)	8.6 (58/675)		5.6 (13/231)	5.9 (13/221)	
LMCAD +2VD	12.8 (86/672)	12.6 (85/675)		11.3 (26/231)	9.5 (21/221)	
LMCAD +3VD	15.6 (105/672)	12.6 (85/675)		13.4 (31/231)	16.7 (37/221)	
2VD	1.8 (12/672)	1.8 (12/675)		2.2 (5/231)	3.2 (7/221)	
3VD	56.7 (381/672)	58.2 (393/675)		64.1 (148/231)	61.5 (136/221)	
Anatomical SYNTAX score	28.3 ± 11.5	28.9 ± 11.5	0.326	28.6 ± 11.5	29.5 ± 10.9	0.396
No. of lesions	4.3 ± 1.8	4.3 ± 1.8	0.720	4.5 ± 1.8	4.6 ± 1.7	0.492
Any total occlusion	0.2 ± 0.4	0.2 ± 0.4	0.283	0.2 ± 0.4	0.2 ± 0.4	0.933
Any bifurcation	0.7 ± 0.5	0.7 ± 0.4	0.443	0.7 ± 0.4	0.7 ± 0.4	0.566
No. of stents	4.6 ± 2.2	—		4.7 ± 2.3	—	
TSL per patient	85.5 ± 47.5	—		89.0 ± 49.3	—	
Off—pump CABG	—	14.2 (96/676)		—	14.5 (32/221)	
LIMA use	—	83.0 (561/676)		—	78.3 (173/221)	
No. of total conduits	—	2.8 ± 0.7		—	2.8 ± 0.7	
No. of arterial conduits	—	1.4 ± 0.6		—	1.4 ± 0.7	
No. of venous conduits	—	1.4 ± 0.9		—	1.4 ± 0.9	
Complete revascularization	59.3 (395/666)	64.0 (425/664)	0.078	49.1 (113/230)	60.7 (125/206)	0.016

Metabolic syndrome defined as at least three of the following: (i) waist circumference >102 cm in males, >88 cm in females; (ii) triglycerides ≥150 mg/dL; (iii) high-density lipoprotein <40 mg/dL in males, <50 mg/dL in females; (iv) blood pressure ≥130/85 mmHg; and (v) fasting glucose ≥110 mg/dL. Impaired renal function defined as a calculated creatinine clearance <60 mL/min. Glycated haemoglobin was core laboratory reported.

3VD, three-vessel disease; CABG, coronary artery bypass grafting; CAD, carotid artery disease; COPD, chronic obstructive pulmonary disease; LMCAD, left main coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischaemic attack; TSL, total stent length.

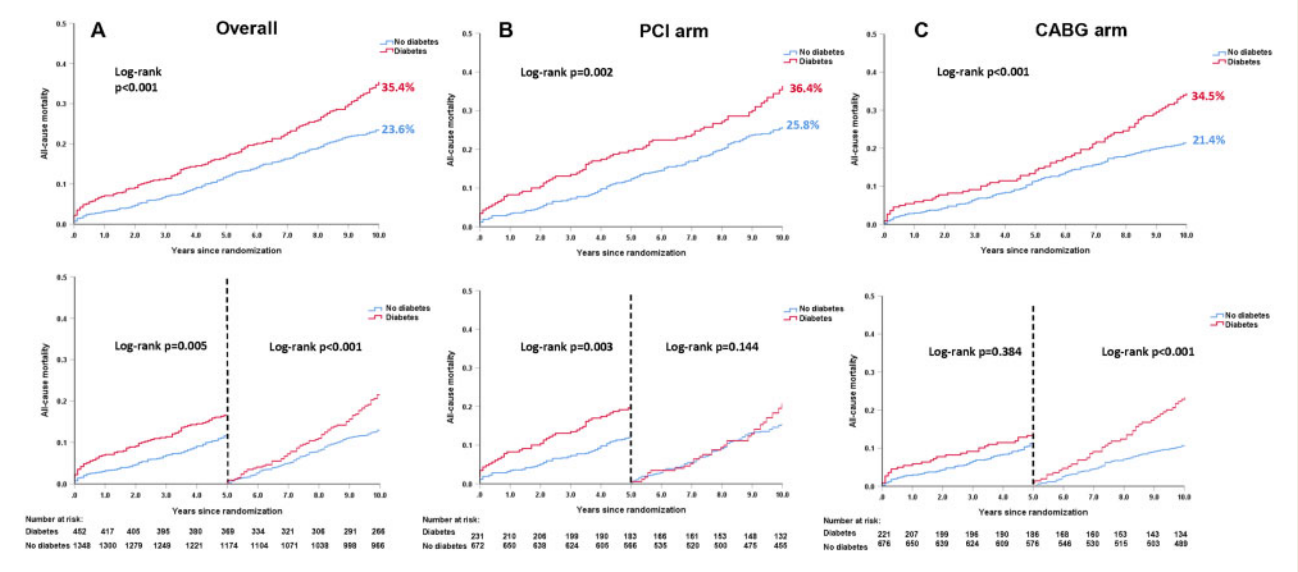


Figure 1 Kaplan–Meier curves for all-cause death at 10 years according to diabetes. (*A*) All-cause death at 10 years according to diabetes in the overall cohort. (*B*) All-cause death at 10 years according to diabetes in the percutaneous coronary intervention arm. (*C*) All-cause death at 10 years according to diabetes in the coronary artery bypass grafting arm. Event rates represent Kaplan–Meier estimates. Note: As Kaplan–Meier estimates, the rate is not the same as the ratio of the numerator and denominator.

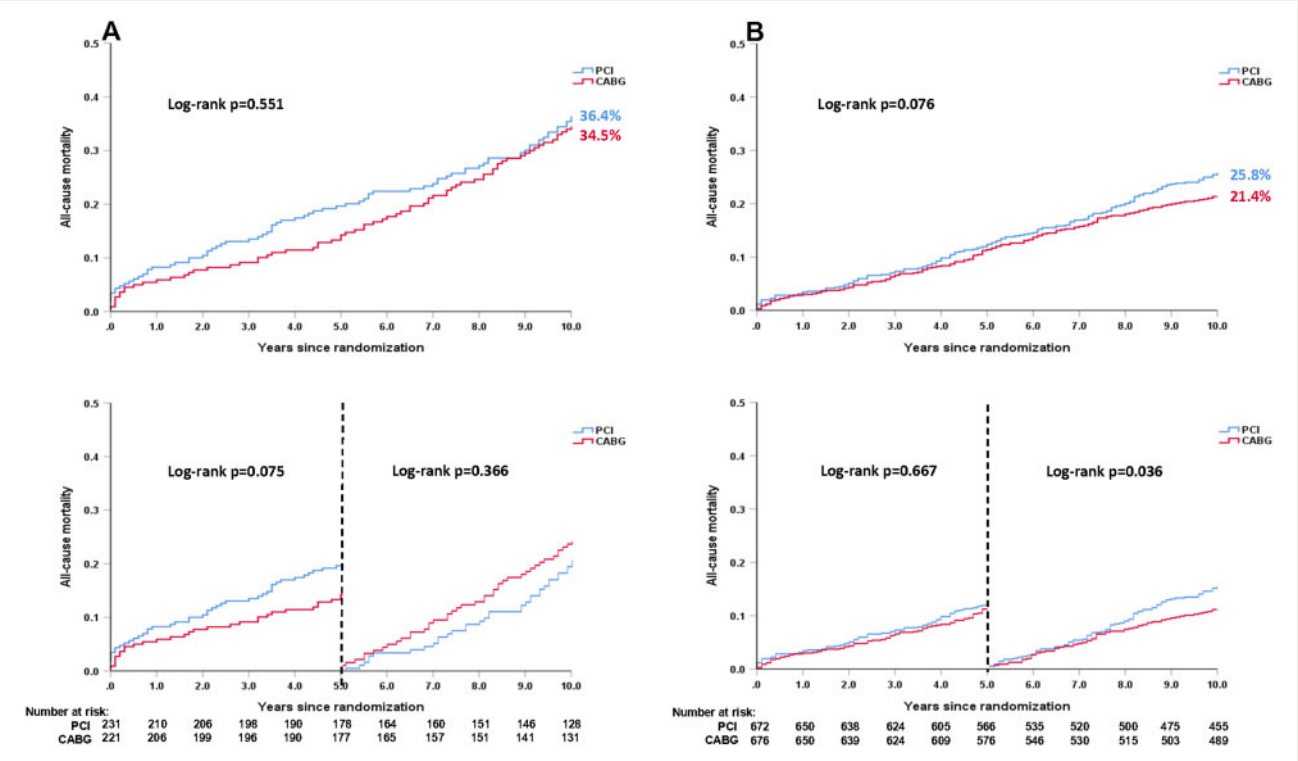


Figure 2 Kaplan–Meier curves for all-cause death at 10 years according to treatment strategies in patients with (*A*) and without (*B*) diabetes. (*A*) All-cause death at 10 years according to treatment strategies in patients with diabetes. (*B*) All-cause death at 10 years according to treatment strategies in patients without diabetes. Event rates represent Kaplan–Meier estimates. Note: As Kaplan–Meier estimates, the rate is not the same as the ratio of the numerator and denominator.

Table 2 Impact of diabetes on all-cause death according to treatment strategies

	Diabetes (*n* = 452)	No diabetes (*n* = 1348)	*P*-value	Unadjusted HR (95% CI)	Unadjusted *P*-value	Adjusted HR (95% CI)	Adjusted *P*-value
10 years							
Overall	35.4% (152)	23.6% (308)	<0.001	1.61(1.32–1.95)	<0.001	1.58(1.27–1.95)	<0.001
PCI	36.4% (80)	25.8% (168)	0.002	1.53(1.17–2.00)	0.002	1.54(1.15–2.06)	0.003
CABG	34.5% (72)	21.4% (140)	<0.001	1.70(1.28–2.26)	<0.001	1.65(1.19–2.28)	0.003
Maximum follow-up							
Overall	60.7% (187)	35.4% (381)	<0.001	1.66(1.40–1.98)	<0.001	1.67(1.38–2.02)	<0.001
PCI	51.2% (94)	37.5% (209)	0.001	1.49(1.16–1.89)	0.001	1.55(1.19–2.01)	0.001
CABG	67.0% (93)	32.2% (172)	<0.001	1.88(1.46–2.42)	<0.001	1.85(1.38–2.47)	<0.001

Percentage of deaths at a given time point, based on Kaplan–Meier estimates (number of deaths). The number of patients entered into the multivariable Cox model was 87.2% (1570/1800) patients in the overall population, 90.0% (813/903) patients in the PCI arm, and 84.4% (757/897) patients in the CABG arm.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

All-cause death according to diabetes and revascularization strategy

In non-diabetics, there was no significant absolute treatment difference in the risk of death at 10 years (PCI 25.8% vs. CABG 21.4%, difference: 4.4%, 95% CI: -0.2%, 9.0%, $P = 0.076$, *Figure 2B*, Supplementary material online, *Table S4*). The mean restricted life expectancy in non-diabetics was 8.89 and 8.74 years in patient receiving CABG and PCI, respectively ($P = 0.076$).

In diabetics, all-cause death at 10 years occurred in 80 (36.4%) patients in the PCI arm and 72 (34.5%) patients in the CABG arm (difference: 1.9%, 95% CI: -7.6%, 11.1%, $P = 0.551$, *Figure 2A*, *Table 3* and Supplementary material online, *Table S4*). Landmark analyses showed that the risk of mortality was numerically higher with PCI compared with CABG at 5 years (19.6% vs. 13.3%, HR: 1.53, 95% CI: 0.96, 2.43, $P = 0.075$), with the opposite seen between 5 and 10 years (PCI vs. CABG: 20.8% vs. 24.4%, HR: 0.82, 95% CI: 0.52, 1.27, $P = 0.366$, *Figure 2A*). The mean restricted life expectancy for diabetic patients treated with CABG and PCI was, respectively, 8.41 and 8.08 years ($P = 0.551$). The treatment effect of PCI vs. CABG on mortality at 10 years was not statistically different according to the presence of diabetes ($P_{\text{-interaction}} = 0.856$, *Table 3*), with similar findings at maximum follow-up (*Table 3* and Supplementary material online, *Table S4* and *Figure S4*) and when including diet-controlled diabetics (Supplementary material online, *Figures S5* and *S6*).

Impact of insulin treatment on all-cause death

At 10 years, all-cause death occurred in 75 (43.6%) insulin-treated and 77 (30.0%) non-insulin-treated patients (adjusted HR: 1.59, 95% CI: 1.10%, 2.29%, $P = 0.014$, Supplementary material online, *Table S5*).

Patients receiving insulin had a non-significant numerically higher all-cause death at 10 years with PCI vs. CABG (47.9% vs. 39.6%, difference: 8.2%, 95% CI: -6.5%, 22.5%, $P = 0.227$, *Table 4* and Supplementary material online, *Table S4*), with no significant heterogeneity of treatment effect ($P_{\text{-interaction}} = 0.971$, *Table 4*). The mean restricted life expectancy in these patients was possibly longer with CABG than PCI; however, the differences were not statistically significant (8.24 vs. 7.55 years, $P = 0.230$) due to the limited sample size ($n = 182$) and restricted power.

Impact of age

No significant interaction between revascularization mode and age on mortality at 10 years was observed amongst diabetics ($P_{\text{-interaction}} = 0.358$) and non-diabetics ($P_{\text{-interaction}} = 0.365$, *Figure 3*).

Impact of haemoglobin A1c on all-cause death

The spline curve in the overall population showed that an HbA1c of 6.0% had the lowest HR for all-cause death at 10 years, so this was used as the reference value (Supplementary material online, *Figure S7*). The adjusted cubic spline model showed a U-shaped relationship between HbA1c and all-cause death at 10 years in the overall population (Supplementary material online, *Figure S7A*) and the PCI arm (Supplementary material online, *Figure S7B*), whilst the relationship in the CABG arm was linear (Supplementary material online, *Figure S7C*).

Anatomical SYNTAX score subgroups

In diabetic patients, there were no significant differences in all-cause death at 10 years and at maximum follow-up between PCI and CABG groups in any anatomical SYNTAX score tertile (Supplementary material online, *Figure S8*). In non-diabetic patients with SYNTAX scores ≥33, all-cause death was significantly higher with PCI at 10 years (32.8% vs. 23.6%, adjusted HR: 1.56, 95% CI: 1.04, 2.33) and at maximum follow-up (38.1% vs. 29.0%, adjusted HR: 1.59, 95% CI: 1.09, 2.32, Supplementary material online, *Figure S9*).

Three-vessel disease and left main coronary artery disease subgroups

In diabetic patients with 3VD, PCI and CABG had comparable mortality at 10 years (37.3% vs. 33.5%, adjusted HR: 1.29, 95% CI: 0.81, 2.06, $P = 0.289$, Supplementary material online, *Figure S10A* and *Table S6*). Landmark analysis showed that mortality was significantly higher with PCI at 5 years (19.8% vs. 11.3%, adjusted HR: 2.27, 95% CI: 1.14, 4.52, $P = 0.020$), whereas it was numerically higher with CABG

Table 3 Treatment effect (percutaneous coronary intervention vs. coronary artery bypass grafting) on all-cause death in diabetic and non-diabetic patients

	PCI (*n* = 903)	CABG (*n* = 897)	Unadjusted HR (95% CI)	Unadjusted *P*-value	Adjusted HR (95% CI)	Adjusted *P*-value	$P_{\text{-interaction}}$
10 years							
Diabetes	36.4% (80)	34.5% (72)	1.10 (0.80–1.52)	0.551	1.15 (0.80–1.65)	0.440	0.856
No diabetes	25.8% (168)	21.4% (140)	1.23 (0.98–1.53)	0.076	1.30 (1.01–1.66)	0.041	
Maximum follow-up							
Diabetes	51.7% (94)	67.3% (93)	1.00 (0.75–1.33)	0.991	1.06 (0.77–1.47)	0.712	0.394
No diabetes	37.9% (209)	33.3% (172)	1.26 (1.03–1.55)	0.024	1.34 (1.07–1.68)	0.010	

Percentage of deaths at a given time point, based on Kaplan–Meier estimates (number of deaths). The number of patients entered into the multivariable Cox model was 87.3% (1177/1348) patients in non-diabetic group and 86.9% (393/452) patients in diabetic group, respectively. Test of interaction is on adjusted Cox proportional hazards model.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 4 Treatment effect (percutaneous coronary intervention vs. coronary artery bypass grafting) on all-cause death in insulin-treated and non-insulin agent-treated diabetic patients

	PCI (*n* = 231)	CABG (*n* = 221)	Unadjusted HR (95% CI)	Unadjusted *P*-value	Adjusted HR (95% CI)	Adjusted *P*-value	$P_{\text{-interaction}}$
10 years							
Insulin	47.9% (40)	39.6% (35)	1.32 (0.84–2.08)	0.227	1.40 (0.81–2.42)	0.229	0.971
Non-insulin agents	29.3% (40)	30.7% (37)	0.98 (0.63–1.53)	0.920	1.17 (0.70–1.95)	0.547	
Maximum follow-up							
Insulin	57.8% (44)	71.9% (39)	1.31 (0.85–2.01)	0.224	1.27 (0.76–2.13)	0.359	0.757
Non-insulin agents	48.7% (50)	69.3% (54)	0.83 (0.57–1.22)	0.351	1.06 (0.68–1.65)	0.798	

Percentage of deaths at a given time point, based on Kaplan–Meier estimates (number of deaths). The number of patients entered into the multivariable Cox model was 85.6% (231/270) patients in the non-insulin agent-treated diabetes group and 89.0% (162/182) patients in the insulin-treated diabetes group. Test of interaction is on adjusted Cox proportional hazards model.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

between 5 and 10 years (21.7% vs. 24.3%, adjusted HR: 0.70, 95% CI: 0.36, 1.37, $P = 0.295$). In non-diabetic patients with 3VD, the risk of mortality was significantly higher with PCI at 5 years (12.8% vs. 9.3%, HR: 2.04, 95% CI: 1.22, 3.41, $P = 0.007$) and 10 years (25.9% vs. 17.3%, adjusted HR: 1.82, 95% CI: 1.28, 2.60, $P = 0.001$, Supplementary material online, *Table S7*).

In patients with LMCAD, there was no significant difference in mortality at 10 years between PCI and CABG among patients with diabetes (34.7% vs. 36.1%, adjusted HR: 0.91, 95% CI: 0.48, 1.74, $P = 0.781$, Supplementary material online, *Table S6*, *Figure S10B*) or without (25.5% vs. 27.3%, adjusted HR: 0.87, 95% CI: 0.60, 1.25, $P = 0.455$, Supplementary material online, *Table S7*). Results at maximum follow-up are shown in Supplementary material online, *Figure S11* and *Tables S6* and S7. Ten-year mortality according to SYNTAX score tertiles and revascularization strategies in diabetic and non-diabetic patients with 3VD/LMCAD are shown in Supplementary material online, *Figures S12* and *S13*.

Impact of residual SYNTAX score

The rSS was available in 890 (98.6%) patients in the PCI cohort and was significantly higher in diabetic compared with non-diabetic patients (5.92 ± 8.27 vs. 3.97 ± 6.22, $P < 0.001$). The percentages of diabetic patients in the sub-categories of rSS = 0, >0 to 4, >4 to 8, and >8 group were 20.5%, 26.6%, 26.3%, and 37.3%, respectively ($P < 0.001$). The risk of mortality at 10 years was significantly higher with an rSS > 8 compared with an rSS ≤ 8, for both diabetic (61.2% vs. 28.7%, $P < 0.001$) and non-diabetic patients (43.8% vs. 22.8%, $P < 0.001$, Supplementary material online, *Figure S14*).

Impact of type of revascularization (single or multiple arterial bypass grafts)

In patients with diabetes, there was no significant difference in all-cause death at 10 years between patients receiving a single (SAG) or multiple arterial bypass graft (MAG) or PCI ($P = 0.432$, Supplementary material online, *Figure S15*).

Among patients with diabetes, there were no significant treatment-by-subgroup interactions for C-reactive protein or optimal medical therapy for mortality at 10 years (*Figure 3*).

SYNTAX score II 2020 for predicting death at 10 years in patients with and without diabetes

The ability of the SYNTAX score II 2020 to predict rates of all-cause death at 10 years after PCI or CABG was equally valuable in diabetic

	PCI	CABG	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	Adjusted p	p value for interaction
Diabetes							
Elderly	51.6%(33/67)	56.2%(40/75)	0.99(0.62-1.57)	0.964	1.27(0.73-2.22)	0.392	0.358
Non-elderly	30.2%(47/164)	23.2%(32/146)	1.35(0.86-2.12)	0.190	1.20(0.71-2.02)	0.494	
3VD	37.3%(54/153)	33.5%(46/143)	1.17(0.79-1.74)	0.429	1.29(0.81-2.06)	0.289	0.332
LMCAD	34.7%(26/78)	36.1%(26/78)	0.99(0.57-1.70)	0.960	0.91(0.48-1.74)	0.781	
0-22	27.2%(20/75)	27.8%(16/61)	0.99(0.51-1.91)	0.976	0.76(0.35-1.65)	0.487	0.608
23-32	36.3%(27/79)	36.5%(27/77)	0.99(0.58-1.70)	0.985	1.26(0.67-2.37)	0.473	
≥33	44.8%(32/75)	37.2%(28/82)	1.44(0.86-2.38)	0.163	1.15(0.63-2.12)	0.643	
OMT	35.9%(44/132)	29.4%(19/171)	1.13(0.73-1.74)	0.591	1.23(0.67-2.25)	0.498	0.605
Non-OMT	37.1%(36/99)	34.6%(46/139)	1.34(0.78-2.30)	0.281	1.28(0.76-2.17)	0.351	
CRP<2	26.4%(20/78)	28.3%(17/163)	0.95(0.50-1.81)	0.867	1.25(0.59-2.62)	0.564	0.719
CRP≥2	41.5(54/139)	37.8(45/126)	1.16(0.78-1.73)	0.454	1.18(0.76-1.83)	0.451	
Non-diabetes							
Elderly	41.7%(90/233)	36.4%(74/210)	1.15(0.85-1.57)	0.372	1.19(0.85-1.68)	0.318	0.365
Non-elderly	17.9%(78/449)	14.6%(66/466)	1.24(0.90-1.73)	0.192	1.43(0.99-2.08)	0.058	
3VD	25.9%(99/393)	17.3%(68/406)	1.57(1.15-2.13)	0.004	1.82(1.28-2.60)	0.001	0.003
LMCAD	25.5%(69/279)	27.3%(72/270)	0.90(0.65-1.25)	0.532	0.87(0.60-1.25)	0.455	
0-22	21.1%(45/224)	18.0%(37/214)	1.15(0.74-1.77)	0.532	1.05(0.66-1.67)	0.836	0.726
23-32	23.5%(53/231)	21.0%(45/223)	1.12(0.75-1.67)	0.570	1.19(0.75-1.88)	0.460	
≥33	32.8%(69/215)	23.6%(54/233)	1.49(1.04-2.13)	0.028	1.56(1.04-2.33)	0.031	
OMT	27.0%(84/321)	22.4%(46/209)	1.19(0.87-1.61)	0.244	1.25(0.84-1.85)	0.275	0.747
Non-OMT	24.3%(82/347)	20.5%(91/456)	1.23(0.86-1.77)	0.250	1.25(0.90-1.75)	0.189	
CRP<2	20.6%(45/225)	15.2%(33/220)	1.40(0.89-2.19)	0.143	1.66(1.01-2.72)	0.046	0.503
CRP≥2	28.5%(114/413)	24.3%(90/384)	1.19(0.90-1.57)	0.222	1.19(0.89-1.60)	0.234	

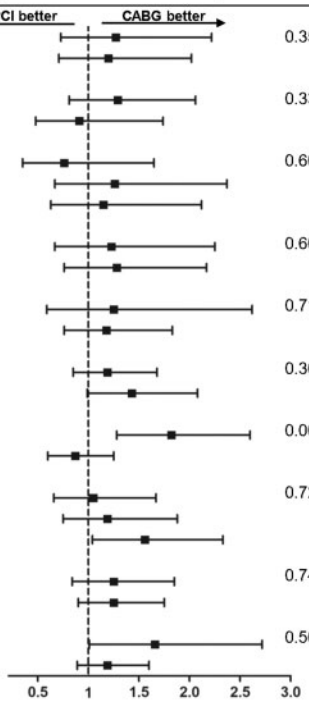


Figure 3 All-cause death at 10 years in the percutaneous coronary intervention and coronary artery bypass grafting arms among diabetic or non-diabetic patients stratified by subgroups.

and non-diabetic patients (Supplementary material online, *Figure S16*). *Figure 4C* shows that for both diabetics (red curves) and non-diabetics (blue curves), the absolute risk difference in mortality (treatment benefit of CABG over PCI) curves was not only well-calibrated, but also largely overlapped in the same range of predicted and observed mortality. Additionally, *Figure 4A and B* displays the absolute risk differences in mortality for each quarter of the diabetic and non-diabetic population together with their respective Kaplan–Meier curves.

Figure 4D shows ranked individual differences ($n = 452$) in predicted mortalities for diabetic patients undergoing either PCI (blue solid line) or CABG (red solid line). Actually, 338 patients have higher predicted mortality after PCI than after CABG, then in the ranking order a crossover point in predicted mortalities (equipoise) is reached: beyond that point, the predicted mortality following PCI of the remaining patients ($n = 114$) becomes lower than the predicted mortality after CABG.

The dashed line in *Figure 4D* depicts in a spline regression (LOESS), the observed mortality either after PCI or CABG. Notably, the dashed lines depicting the observed mortalities following either PCI or CABG crossover around the 200th ranked patient suggesting an equipoised vital prognosis after either PCI or CABG for that specific patient. The remaining 252 patients had higher observed mortality after surgery compared with PCI. In contrast to the neutral 'average treatment effect' observed in diabetics at 10 years with either CABG or PCI, the SYNTAX score II 2020 clearly identifies individuals who derive a treatment survival benefit from either CABG or PCI.

Discussion

The present study was a pre-specified subgroup analysis of the SYNTAXES study, in which we assessed all-cause death at 10 years after PCI with first-generation DES vs. CABG as a function of pharmacologically treated diabetes, with or without insulin (*Graphical abstract*). The main findings are:

(1) The treatment effects of PCI vs. CABG on all-cause death at 10 years were similar irrespective of the presence of diabetes. In this limited sample size with restricted power, insulin-treated patients undergoing PCI had a numerically higher mortality compared with those undergoing CABG.

(2) Compared with non-diabetics, pharmacologically treated diabetics had a higher risk of all-cause death at 10 years after PCI or CABG, with poorer outcomes amongst insulin vs. non-insulin-treated patients. After adjustment for baseline confounders, pharmacologically treated and insulin-treated diabetes were both independent predictors of 10-year mortality.

(3) There was a U-shaped relationship between HbA1c and all-cause death at 10 years in the overall population and the PCI arm, whereas a linear relationship was observed in the CABG arm.

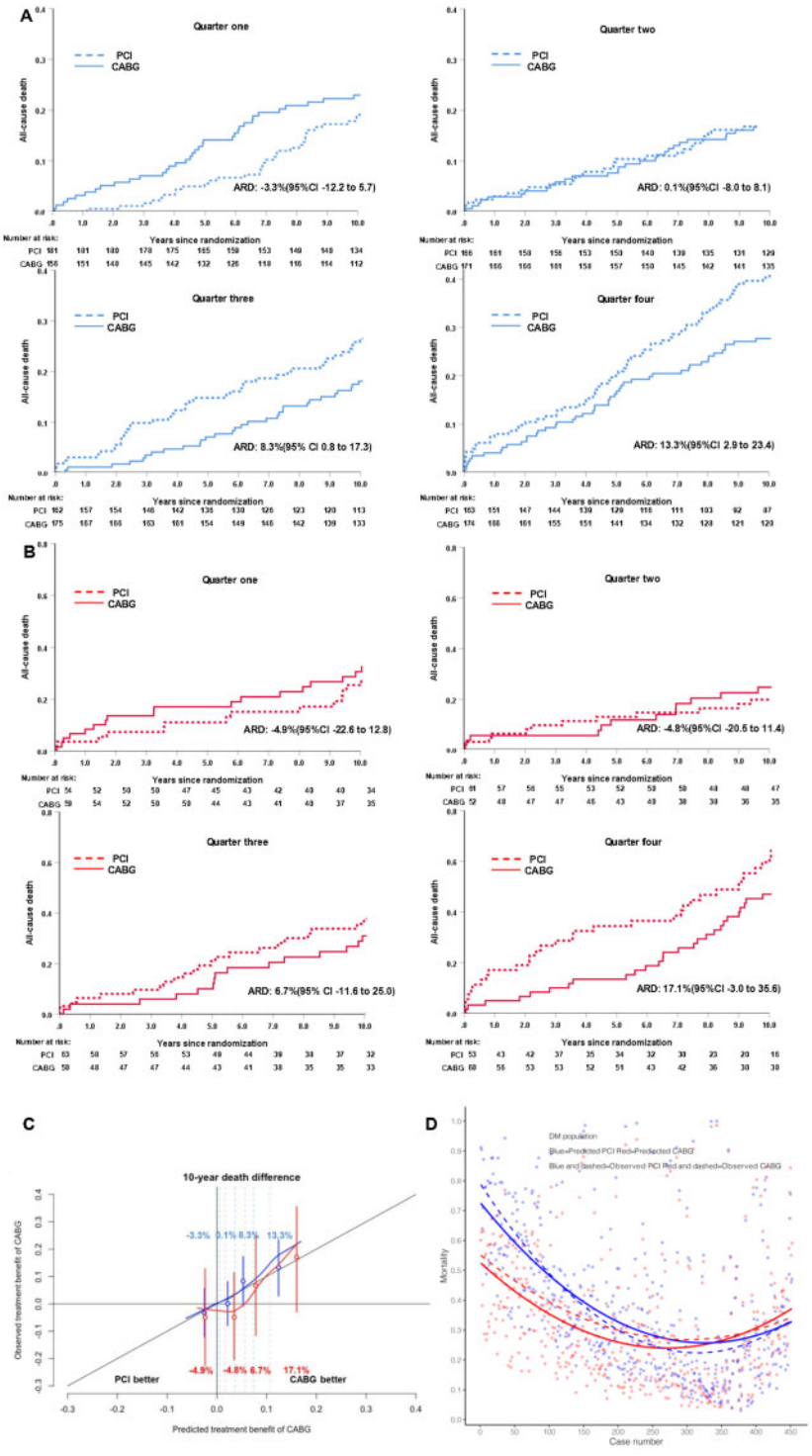


Figure 4 Kaplan–Meier plots showing the observed vs. predicted treatment benefit of coronary artery bypass grafting over percutaneous coronary intervention according to the SYNTAX score II 2020 in predicted benefit quarters in non-diabetic population (*A*) and diabetic population (*B*), and calibration plot (*C*) showing the observed vs. predicted treatment benefit (absolute difference in mortality between coronary artery bypass grafting and percutaneous coronary intervention) in patients with diabetes (red line) and without diabetes (blue line). The percentages in red or blue figuring in the illustration are the absolute risk differences between coronary artery bypass grafting and percutaneous coronary intervention in each quarter for the diabetic and non-diabetic population. Vertical dashed lines represent quartiles, and the solid red or blue lines represent the mean value and 95% CI of the observed absolute risk differences between coronary artery bypass grafting and percutaneous coronary intervention in each quartile. (*D*) The individual difference between the predicted mortality (solid lines) by SYNTAX Score II 2020 after either percutaneous coronary intervention or coronary artery bypass grafting as well as the individual observed mortality (dashed lines) in diabetic patients. Blue solid line represents the predicted mortality after percutaneous coronary intervention; Red solid line represents the predicted mortality after coronary artery bypass grafting; Blue dashed line represents the observed mortality after percutaneous coronary intervention; Red dashed line represents the observed mortality after coronary artery bypass grafting.

(4) Amongst diabetics, there were no significant differences in all-cause death at 10 years between PCI and CABG in any anatomical SYNTAX score tertile.
(5) In patients with diabetes and 3VD, the overall risk of mortality at 10 years was comparable between PCI and CABG; however, it was numerically higher with PCI in the highest (≥33) SYNTAX score tertile.
(6) The SYNTAX score II 2020 further endorses our general contention that—as an 'average treatment effect'—differences in all-cause death between CABG and PCI in diabetic patients at 10 years are minor, whereas individualized predicted and observed mortality clearly identify individuals who benefit either from CABG or PCI.

Previous studies have been unable to conclusively establish whether PCI or CABG offers the best long-term survival for patients with diabetes and multivessel CAD. The BARI trial was the first to report a significant 10-year survival benefit with CABG over PCI with balloon angioplasty amongst 353 diabetic patients with multivessel CAD, however, the benefit diminished somewhat overextended follow-up.[8] In the FREEDOM study, the benefit with CABG over PCI for all-cause death at 5 years was only marginally significant ($P = 0.049$),[4] however, considering that the trial was not powered for all-cause death, this result could be considered hypothesis-generating.[15] In the FREEDOM Follow-On study,[16] which extended follow-up in 943 of the original 1900 patients cohort, the estimated rate of mortality at 8 years was 23.7% and 18.7% in the PCI-DES and CABG group, respectively (unadjusted HR: 1.32, 95% CI: 0.97, 1.78, $P = 0.076$), with the HR remaining unchanged after adjustment.

The greatest variance with our results, which showed no significant difference between PCI and CABG at 10 years amongst diabetics with multivessel CAD, comes from a recent propensity score matching analysis by Tam *et al.*,[17] which reported significantly higher mortality with PCI compared with CABG at 8 years. These conflicting results may be explained by the differences between the trials designs. First, the study cohorts were different as Tam *et al* included patients with two-vessel disease or 3VD, whereas our study only included patients with 3VD and/or LMCAD. Secondly, they included patients with acute coronary syndrome (ACS), while only patients with stable CAD and unstable angina were included in SYNTAXES. Moreover, 22.9% of their patients received bare-metal stents. Finally, the proportion of incomplete revascularization in the PCI arm was higher in their study, which may partly contribute to the higher incidence of all-cause death in their PCI arm.[18–20] In fact, after the exclusion of patients with ACS and those treated with bare-metal stents, Kaplan–Meier curves between PCI and CABG appear to converge, especially after 8 years, suggesting a diminishing treatment difference between PCI and CABG with very long-term follow-up.

At the time of the 5 years report of the SYNTAX study,[12] investigators, surgeons, and interventionists were intuitively convinced that the diverging Kaplan–Meier curves for mortality would keep diverging; however, it now appears that our intuitive assumption was somewhat naïve and partially incorrect. Our landmark analysis showed that after 5 years the Kaplan–Meier survival curve was worse after CABG than PCI, although the differences were not statistically significant (*Figure 2A*). These results suggest that a temporal change in the survival benefit of CABG over PCI in diabetic patients. Notably, within the confines of our limited sample size that may not have adequate power, further research in adequately powered long-term studies are required.

In insulin-treated diabetics, PCI resulted in a numerically higher non-significant mortality at 10 years compared with CABG; however, no significant interaction was established within the limitations of our sample size. Similar results in all-cause death were reported in the insulin-treated diabetic subgroup from the FREEDOM study (PCI vs. CABG: 19% vs. 14.1%, HR: 1.19, 95% CI: 0.76, 1.85, $P_{\text{-interaction}} = 0.64$),[21] indicating that even their sample size of 1850 was too small to detect a differential treatment survival benefit with CABG over PCI between diabetics treated with or without insulin. Patients with insulin-treated diabetes appear to have a longer life expectancy following CABG compared with PCI, although the differences were not statistically significant (8.24 vs. 7.55 years, $P = 0.230$) due to limited sample size ($n = 182$) and restricted power. This reaffirms the need for large sample size investigations in this subset of patients.

In the BARI trial, 10-year survival among diabetic patients was higher following CABG with arterial grafting, compared with CABG using only vein grafts and PCI.[8] However, in our study, no significant difference in all-cause death at 10 years was observed between patients with diabetes receiving PCI or either single or multiple arterial grafts (Supplementary material online, *Figure S15*). These results support our main findings that the survival benefit of CABG over PCI subsides over time (10 years); nevertheless, the convergence of the three survival curves (PCI, CABG with SAG or MAG) is striking. It is also remarkable that the survival curves in the non-diabetic cohort kept diverging over time, at least between patients with MAG and those either treated with PCI, or a combination of SAG and venous grafts. As a matter of fact, this observation is more worrisome than the one made in diabetic patients.

It could be argued that the convergence of Kaplan–Meier curves at 10 years is due to ageing; however, no significant interaction on mortality at 10 years was seen between revascularization mode and age (>70 or ≤70 years old) in patients with and without diabetes. In the entire population of SYNTAXES, a similar lack of significant interaction for age was also reported. Hence the convergence of the two Kaplan–Meier curves at 10 years cannot be solely explained by ageing. This observation could also be attributed to the late attrition of bypass grafts around the 7th year of follow-up affecting both SAG and MAG patients (Supplementary material online, *Figure S15*); however, only the attrition of venous grafts has been widely documented in the literature.[22]

The relationship between HbA1c and mortality following PCI[23,24] or CABG[25,26] is controversial. Currently, several guidelines recommend the assessment of HbA1c to help achieve better clinical outcomes; however, the threshold for implementing more stringent glycaemic control varies substantially.[27] In the present analysis, a U-shaped relationship between HbA1c and mortality at 10 years was observed with PCI, whereas the relationship was linear with CABG. These results suggest that a threshold HbAc1 exists beyond which it should be prognostically unacceptable to treat patients with PCI. Unfortunately, our limited sample size did not permit any strong statistical inference or formal recommendations. High-quality randomized large-scale trials are needed to further investigate this important issue.

Prior studies established that CABG was preferred for those with intermediate or high SYNTAX scores.[5,7,28] Notably, an observation

from the FREEDOM trial was that when CABG is compared with PCI, diabetic status was more determinant of outcomes and vital prognosis, than the extent and complexity of CAD.[29] Our results suggest that the anatomical SYNTAX score is not a determinant factor of fatal prognosis in diabetic patients in the SYNTAX study; however, following multivariable adjustment, it was associated with an increased risk of death in patients who received PCI, but not CABG (Supplementary material online, *Table S2*).

The anatomical SYNTAX score as well as the type of CAD (3VD or LMCAD) are 'modifiers', as labelled by epidemiologists, that have a profound interaction with other clinical characteristics and comorbidities, and deserve to be computed and incorporated into the calculation of the SYNTAX score II 2020.[13] Therefore, if the anatomical SYNTAX score was not integrated into the SYNTAX score II 2020, and just interpreted in isolation, it would have no prognostic value for the Heart Team when deciding the optimal revascularization strategy of diabetic patients with complex CAD. In patients with diabetes and 3VD, the current guidelines recommend that PCI may be considered in patients with a SYNTAX score ≤22 (recommendation IIb for PCI), however, it is not recommended in patients with a SYNTAX score >22 (recommendation III).[30]

Our landmark analysis showed that in diabetic patients with 3VD, PCI compared with CABG had higher all-cause death at 5 years, with a reverse risk seen between 5 and 10 years. These 5-year results were in line with previous studies[6]; however, the survival benefit from CABG was seen to diminish between 5 and 10 years. In patients with diabetes and 3VD, PCI appeared to have a non-significant higher risk of all-cause death at 10 years compared with CABG. Consistent with a prior meta-analysis reporting survival up to 5 years,[6] no significant between-group (PCI vs. CABG) difference in mortality at 5 years was observed in diabetics with LMCAD, with this absence of difference in vital outcome maintained up to 10 years and beyond (Supplementary material online, *Figures S10B* and *S11B*). Notably, with the limited sample size, these subgroup analyses may reduce the power of the analysis and increase the risk of Type 1 and 2 errors.

In non-diabetic patients with 3VD, we observed a higher risk of mortality with PCI over CABG at 5 years, which is inconsistent with the aforementioned meta-analysis.[6] This finding could be due to a play of chance related to the smaller sample size than the pooled patient-level analysis. It could also be due to disparity in follow-up durations, which were a median of 3.8 years in the meta-analysis and 11.2 years in SYNTAXES. Moreover, in the meta-analysis, only 60% of patients had 3VD, unlike the current subgroup analysis where all patients had 3VD. Furthermore, the higher mortality at 10 years with PCI in non-diabetics with 3VD was mainly driven by patients with a SYNTAX score ≥33 (Supplementary material online, *Figure S13A*).

An rSS > 8 has been associated with increased short- and mid-term adverse events, including all-cause death.[31,32] Recently, an observational study found that diabetes and an rSS > 8 contribute independently to late outcomes in STEMI patients with a follow-up of 3.6 years.[33] In our analysis, compared with patients with rSS ≤ 8, patients with rSS > 8 had a significantly higher all-cause death at 10 years both in diabetic and non-diabetic patients. These results were in line with the 5-year results in the SYNTAX trial.[32] Residual SYNTAX score is a post-procedural parameter, and therefore it is difficult to determine the specific risk and outcome a priori; however, if it is unlikely that complete or nearly complete revascularization (rSS ≤ 8) can be achieved, then CABG should be considered.

To further endorse our contention that treatment differences in vital prognosis between diabetic and non-diabetic patients at 10 years are not major, we applied the SYNTAX score II 2020 to the diabetic and non-diabetic population. We found that the ability of the SYNTAX score II 2020 to predict rates of all-cause death at 10 years following PCI or CABG was equally valuable in diabetic and non-diabetic patients. This is not surprising since the score is derived from the outcomes of SYNTAXES, but its applicability and accuracy in diabetics, as well as in non-diabetics, is a form of internal validation. Therefore, the SYNTAX score II 2020 has the capability to support revascularization decision-making in diabetic and non-diabetic patients with 3VD and/or LMCAD. However, we have to acknowledge that due to the limited sample size, the confidence intervals of the absolute risk difference for each quarter in the diabetic population are wide (*Figure 4*).

Although there is equipoise in mortality between diabetics in SYNTAXES treated with PCI and CABG, and theoretically they may seem equally eligible to receive either treatment, the present analysis reflects an 'average treatment effect' based on a singled out comorbidity, namely diabetes. Nowadays, precision medicine tries to individualize the prognosis of patients taking into account multiple co-variables.[34] In the SYNTAX score II 2020,[13] diabetes is included as one of the prognostic indexes predicting the risk of all-cause death at 10 years that is also affected by so-called effect-modifiers (e.g. anatomical SYNTAX score and type of disease: 3VD or LMCAD). The endpoint in SYNTAXES was all-cause death only, and in the absence of data collection of MACCE in the last 5 years of follow-up, caution must be exerted about a simplistic interpretation on the equipoise of mortality. Although all-cause death may for the trialist be the ultimate unbiased comparative assessment between two revascularization approaches,[35] from the patient's viewpoint MACE and quality-adjusted life years (QUALY) are also very relevant outcomes.[36]

Limitations

Although the diabetes subgroup was pre-specified and randomization was stratified by the presence of diabetes,[11] the present analyses did not have adequate statistical power and subgroup analyses may increase the risk of Type 1 and 2 errors. There was no formal correction for multiple testing for subgroup analyses of the trial, taking into account the *post hoc* nature of the analysis.[37] The sophistication and number of the analysis may lead to the likelihood of spurious findings, and all reported findings should be considered strictly as exploratory and hypothesis-generating. To improve statistical efficiency/power, we performed a multivariable analysis in the present study; however, the inability to include all relevant confounders may cause bias that cannot be adjusted. Additionally, the SYNTAX trial enrolled patients with *de novo* 3VD and/or LMCAD, and our findings should not be extrapolated to general CAD patients or in patients with previous revascularization. The endpoint in the SYNTAXES study was all-cause death only, detailed causes for death were not collected. In the elderly patients, the long-term mortality likely includes a sizeable number of non-cardiac death. The therapies received in the last 5 years of follow-up such as revascularization procedures and pharmacological agents, as well as changes in diabetic status were not collected. However, all-cause death has been considered as the most robust and unbiased index for clinical assessment and is less likely to

be affected by ascertainment bias.[38] In the SYNTAXES study, only one measurement of HbA1c was available at enrolment, which cannot accurately reflect prior control of diabetes. Nevertheless, it is remarkable that this single measurement still has a long-term prognostic value. In future studies with larger sample sizes, multiple measurements of HbA1c should be recommended.

Since loss to follow-up may have potentially impacted on estimated treatment effects, it should be acknowledged that vital status was missing in 6% of patients. However, the drop-out rate was comparable between PCI and CABG. Notably, a previous systematic review that included trials published in five top general medical journals found that the median loss to follow-up was also 6% in 191 trials.[39] Another limitation is that the diagnostic criteria of diabetes in the SYNTAX trial (2005–07) did not include HbA1c, which was only adopted by ADA in 2010.[40] Finally, in the SYNTAX study, patients received PCI with first-generation DES, which are no longer commercially available, hence, our results are only partially applicable to contemporary new-generation DES. Obviously, patients did not benefit from new-generation anti-diabetic drugs such as GLP-1 receptor agonists and SGLT2 inhibitors or inhibitors of PCSK 9 which have all been shown to lower the risks of cardiovascular mortality.[41–44] Although the very long-term data from SYNTAXES are important, we have to emphasize that they are not fully applicable to today's patients, and the Task Force drawing future Guidelines should be warned to avoid strict recommendations with legal implications based only on 'old' data, because they are the only data available. Further investigations in dedicated large-scale trials in patients with diabetes on contemporary pharmacologic therapeutic regimens are warranted. 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 from studies with only short-term follow-up.

Conclusions

Diabetes was associated with an increased risk of all-cause death at 10 years in patients with 3VD and/or LMCAD who underwent either PCI or CABG. In diabetic patients with complex CAD, CABG did not lower the risk of all-cause death at 10 years compared with PCI, although diabetic patients on insulin may derive a survival benefit from CABG. The SYNTAX score II 2020 may identify diabetic patients who will benefit from either CABG or PCI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: F.B. reports speaker's fees from Abiomed, Abbott, and Medtronic. S.J.H. reports to work as a full-time employee of Medtronic outside the scope of this work. S.J.'s institution has received research grants from Boston Sc, Abbot, Biotronik, Medtronic, Astra Zeneca, Bayer, Jansen, The MedCo, and has received lecture fees from Biotronik and Astra Zeneca. P.K. reports to work as an employee of Medtronic, outside the submitted work. P.W.S. reports personal fees from Biosensors, Micel Technologies, Sinomedical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. R.-J.v.G. reports grants and personal fees from Boston Scientific, Abbott Vascular, Astra Zeneca, and Amgen and grants from InfraRedx, outside the submitted work. All other authors have no disclosures.

Data availability

Data will be made available upon request in adherence with transparency conventions in medical research and through reasonable requests to the corresponding author.

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