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Impact of left ventricular ejection fraction on 10-year mortality in the SYNTAX trial

Shinichiro Masuda [a,1], Patrick W. Serruys [a,b,*,1], Kai Ninomiya [a], Shigetaka Kageyama [a], Kotoku Nozomi [a], Chao Gao [c,d], Michael J. Mack [e], David R. Holmes [f], Marie-Claude Morice [g], Daniel J.F.M. Thuijs [h], Milan Milojevic [h], Piroze M. Davierwala [i,j,k], Scot Garg [l], Yoshinobu Onuma [a], on behalf of the SYNTAX Extended Survival Investigators

[a] Department of Cardiology, University of Galway, Galway, Ireland
[b] NHLI, Imperial College London, London, United Kingdom
[c] Department of Cardiology, Xijing Hospital, Xi'an, China
[d] Department of Cardiology, Radboud University, Nijmegen, the Netherlands
[e] Department of Cardiothoracic Surgery, Baylor University Medical Center, Dallas, TX, USA
[f] Department of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, MN, USA
[g] Département of Cardiologie, Hôpital privé Jacques Cartier, Générale de Santé Massy, France
[h] Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands
[i] University Department of Cardiac Surgery, Heart Centre Leipzig, Leipzig, Germany
[j] Department of Surgery, University of Toronto, Toronto, Canada
[k] Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada
[l] Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom

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ABSTRACT

Backgrounds: The impact of reduced left ventricular ejection fraction (LVEF) on very long-term prognosis following percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) has been debated. The aim of this study was to investigate the impact of LVEF at baseline on 10-year mortality in the SYNTAX trial.
Methods: Patients (n = 1800) were categorized into three sub-groups: reduced (rEF ≤ 40 %), mildly reduced (mrEF 41–49 %), and preserved LVEF (pEF ≥ 50 %). The SYNTAX score 2020 (SS-2020) was applied in patients with LVEF<50 % and ≥ 50 %.
Results: Ten-year mortalities were 44.0 %, 31.8 %, and 22.6 % (P < 0.001) in patients with rEF (n = 168), mrEF (n = 179), and pEF (n = 1453). Although no significant differences were observed, the mortality with PCI was higher than with CABG in patients with rEF (52.9 % vs 39.6 %, P = 0.054) and mrEF (36.0 % vs. 28.6 %, P = 0.273), and comparable in pEF (23.9 % vs. 22.2 %, P = 0.275). Calibration and discrimination of the SS-2020 in patients with LVEF<50 % were poor, whilst they were reasonable in those with LVEF≥50 %. The proportion of patients eligible for PCI who had a predicted equipoise in mortality with CABG was estimated to be 57.5 % in patients with LVEF≥50 %. CABG was safer than PCI in 62.2 % of patients with LVEF<50 %.
Conclusions: Reduced LVEF was associated with an increased risk of 10-year mortality in patients revascularized either surgically or percutaneously. Compared to PCI, CABG was safe revascularization in patients with LVEF≤40 %. In patients with LVEF≥50 % individualized 10-year all-cause mortality predicted by SS-2020 was helpful in decision-making whilst the predictivity in patients with LVEF<50 % was poor.

1. Introduction

Multivessel coronary artery disease (CAD) can cause left ventricular systolic dysfunction, leading to poor clinical outcomes [1]. Current guidelines on both sides of the Atlantic recommend coronary artery bypass grafting (CABG) as the standard treatment for revascularization in patients with multivessel CAD and a left ventricular ejection fraction

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; LMCAD, left main coronary artery disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

* Corresponding author at: Department of Cardiology, University of Galway, Galway, Ireland.
E-mail address: patrick.serruys@nuigalway.ie (P.W. Serruys).

[1] Equally contributed to the manuscript.

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(LVEF) ≤ 35 % [2,3]; however, the impact of reduced LVEF on very long-term prognosis following percutaneous coronary intervention (PCI) or CABG remains to be established.

Long-term survival benefit following PCI or CABG in patients with impaired LVEF has long been debated [4]. In the EXCEL (Evaluation of Xience versus Coronary artery bypass surgery for the effectiveness of Left Main Revascularization) trial there was no significant difference in the composite endpoint of death, stroke, or myocardial infarction (MI) at three years follow-up following PCI or CABG among patients with impaired LVEF [5]. At 5 years, there was no significant difference between the relative risks of the treatment effects in patients with an LVEF≥50 % and < 50 %. Meta-analyses in patients with impaired LVEF undergoing revascularization suggested superior long-term survival with CABG compared to PCI [6]; however, these studies were limited by the reliance on observational studies with small sample sizes and variable follow-up.

This subgroup analysis aimed to evaluate the impact of baseline LVEF on long-term mortality, and assess the differences in 10-year survival following PCI versus CABG according to LVEF subgroups in the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) Extended Survival (SYNTAXES) trial [7,8]. In this sub-study, we explore the differences between the "average treatment effect "of the two treatment modalities and individualized predicted prognosis that allows a more refined treatment based on personalized data [9,10].

2. Methods

2.1. Ethical statement

The ethics committees approved the SYNTAX and SYNTAXES trials were approved at each investigating center, and all patients provided written informed consent before participation in the SYNTAX trial.

2.2. Study design and population

The study was a *post-hoc* subgroup analysis of the SYNTAXES study (NCT03417050), which investigated 10-year mortality in the SYNTAX trial (NCT00114972) beyond its original follow-up of 5 years [7,8]. The design and the results of the SYNTAX study have been previously reported [7,11]. Briefly, the SYNTAX trial was an international, multicenter, randomized controlled trial performed in 85 hospitals across 18 North American and European countries. From March 2005 through April 2007, a total of 1800 patients with stable de novo three-vessel disease and/or LMCAD, who were considered eligible for both PCI and CABG based on clinical judgement and consensus of a heart team, were randomly enrolled in a 1:1 fashion to receive PCI (n = 903) with the uniform use of TAXUS Express paclitaxel-drug eluting stents (Boston Scientific Corporation, Marlborough, MA, USA) or CABG (n = 897). Patients not eligible for PCI or CABG were entered into two nested registries: CABG (PCI-ineligible patients) or PCI (CABG-ineligible patients) registries.

2.3. LVEF subgroups

In the SYNTAX trial, all the baseline characteristics were collected and reviewed during the Heart Team conference to assess whether the patient is eligible for inclusion [12]. Pre-procedural LVEF was measured by transthoracic echocardiography or left ventriculogram. Out of 1800 patients, LVEF was available as a continuous variable in 1126 patients (62.6 %), and a categorical variable in 1772 patients (98.4 %) being defined as good (≥50 %), moderate (30–49 %), or poor (<30 %) [13]. As described previously, multiple imputations of missing LVEF values were performed to effectively the available data [10]. A total of 20 imputed datasets were generated. The continuous variables were calculated as an average value from the data of 20 imputations. Continuous values were adjusted to not deviate from the range of categorical values. Within each imputed dataset, all patients were categorized into one of three groups according to the current ESC guidelines: reduced LVEF (rEF; LVEF≤40 %), (2) mildly reduced LVEF (mrEF; LVEF 41–49 %), and (3) preserved LVEF (pEF; LVEF≥50 %) [14].

2.4. Study endpoint

The primary endpoint was all-cause mortality at 10 years. All analyses were performed according to the intention-to-treat principle. Vital status and survival data were obtained by electronic medical records or by query of national death registries. An independent clinical events committee adjudicated major adverse cardiac and cerebrovascular events (MACCE) at five years, defined as the composite endpoint of all-cause death, MI, stroke, and any repeat revascularization [8]. Finally, we applied the SYNTAX score 2020 (SS-2020) to patients with an LVEF≥50 % and LVEF<50 % to better refine their respective personalized vital prognosis and assess in a cross-validation the value of the SS-2020 [13], specifically, among patients with reduced LVEF.

2.5. Statistical analysis

All analyses were performed on the intention-to-treat population. Continuous variables were expressed as mean (standard deviation) and unadjusted group comparisons were performed with one-way ANOVA tests. Categorical variables were expressed as percentages with frequency, and unadjusted group comparisons were made using the Pearson chi-square test. The events rate of up to 10 years was estimated according to the Kaplan-Meier method. The log-rank test was performed to examine the differences among LVEF subgroups (rEF, mrEF, and pEF) with confidence intervals for 95 % ratios of the probability of events at 10 years. The hazard ratios (HRs) of PCI versus CABG were assessed by using the Cox proportional hazards models stratified by LVEF subgroups, with an evaluation of the treatment-by-subgroup interaction. Adjusted models included the following baseline variables; age, sex, body mass index, chronic kidney disease, hypertension, dyslipidemia, current smoking, medically treated diabetes, prior MI, prior heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, LMCAD, prior cerebrovascular disease, complete revascularization, any chronic total occlusion and anatomical SYNTAX score, which had been selected based on prior knowledge of the association of these variables with all-cause mortality and MACCE [15,16].

The predicted 10-year mortality for PCI and CABG were calculated using the SS-2020 [13]. The predicted and observed survival benefit of CABG over PCI in each quarter of the whole population was assessed by calibration plot [17]. Calibration plots were generated to evaluate the agreement between predicted and observed rates of 10-year mortality in each treatment arm, with smooth calibration curves based on a Cox model that fitted a restricted cubic spline of the mortality predictions (on the log-hazard scale) to the observed mortality outcomes. Individual absolute risk differences (ARD) between PCI and CABG for mortality at 10-year were calculated by subtracting predicted CABG mortality from predicted PCI mortality and are shown by scatterplot in descending order of magnitude according to the predicted ARD in mortality (survival

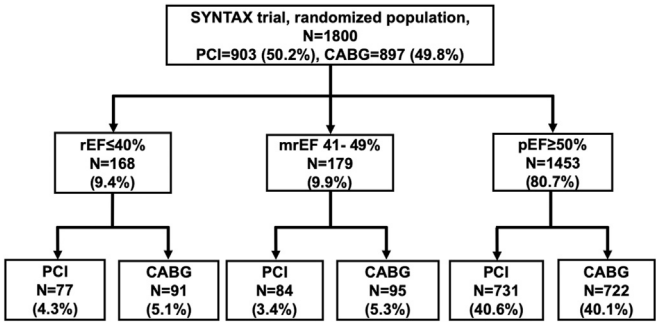


Fig. 1. Study flow chart.
Abbreviations: CABG: coronary artery bypass graft, EF: ejection fraction, PCI: percutaneous coronary intervention, SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery.

Table 1
Baseline patients and procedural characteristics according to left ventricular ejection fraction subgroups.

Characteristics	rEF (N = 168)	mrEF (N = 179)	pEF (N = 1453)	P value
Age	65.0 ± 9.5	67.3 ± 9.7	65.1 ± 9.7	0.007
Male sex (%)	84.5 (142/168)	74.3 (133/179)	77.7 (1398/1453)	0.054
Body mass index (kg/m^2)	28.0 ± 4.7	28.0 ± 5.0	28.0 ± 4.6	0.987
Hypertension (%)	58.3 (98/168)	61.5 (110/179)	68.0 (988/1453)	0.014
Dyslipidemia	69.1 (114/165)	79.2 (141/178)	78.8 (1136/1442)	0.016
Diabetes	32.7 (55/168)	22.3 (40/179)	24.6 (357/1453)	0.046
Insulin use	18.5 (31/168)	9.5 (17/179)	9.2 (134/1453)	<0.001
Current smoking	29.9 (50/167)	17.9 (32/179)	19.4 (281/1447)	0.004
Chronic kidney disease	25.0 (42/168)	15.6 (28/179)	13.3 (193/1453)	0.002
Previous MI	51.5 (84/163)	56.4 (101/179)	27.8 (400/1438)	<0.001
LVEF (%)	33.7 ± 7.0	45.1 ± 2.0	63.1 ± 9.2	<0.001
Previous CVD	19.8 (33/191)	12.8 (23/179)	13.6 (197/1445)	0.086
Stroke	5.5 (9/165)	3.4 (6/179)	4.8 (69/1445)	0.620
Transient ischemic attack	4.2 (8/191)	5.8 (9/156)	4.8 (69/1452)	0.785
Carotid artery disease	11.3 (19/168)	8.9 (16/179)	7.8 (113/1453)	0.269
Previous heart failure	15.2 (25/164)	9.0 (16/178)	2.9 (42/1436)	<0.001
PVD	13.7 (23/168)	9.5 (17/179)	9.4 (137/1453)	0.211
COPD	10.1 (17/168)	8.9 (16/179)	8.3 (121/1453)	0.721
Clinical presentation				0.034
Silent ischemia	20.2 (34/168)	11.7 (21/179)	14.1 (205/1453)	
Stable angina	48.8 (82/168)	54.2 (97/179)	58.4 (848/1453)	
Unstable angina	31.0 (52/168)	34.1 (61/179)	27.5 (400/1453)	
Euro score	5.4 ± 2.8	5.4 ± 2.6	3.4 ± 2.5	<0.001
Parsonnet score	10.9 ± 6.3	11.5 ± 8.0	7.8 ± 7.0	<0.001
Number of lesions	4.3 ± 1.7	4.5 ± 1.8	4.3 ± 1.8	0.735
SYNTAX score	31.0 ± 11.2	30.3 ± 28.3	28.3 ± 11.6	0.002
SYNTAX score tercile				0.010
Low (<23)	23.6 (39/165)	24.6 (44/179)	34.0 (491/1445)	
Intermediate (23–32)	36.4 (60/165)	36.3 (65/179)	33.6 (485/1445)	
High (>32)	40.0 (66/165)	39.1 (70/179)	32.5 (469/1445)	
10-year predicted mortality of PCI (SS-2020) (%)	44.1 ± 24.6	36.2 ± 20.7	22.6 ± 18.2	<0.001
10-year predicted mortality of CABG (SS-2020) (%)	36.8 ± 22.8	29.7 ± 18.0	22.3 ± 15.9	<0.001
ARD (%)	7.7 ± 7.1	6.5 ± 6.6	4.3 ± 6.1	<0.001
Any total occlusion	30.2 (59/165)	37.4 (56/179)	20.8 (300/1443)	<0.001
Any bifurcation lesion	77.6 (128/165)	72.6 (130/179)	72.2 (1042/1443)	0.341
Disease type				0.020
Left main disease	29.8 (50/168)	36.9 (66/179)	40.5 (589/1453)	
Three vessel disease	70.2 (118/191)	63.1 (113/156)	59.5 (864/1453)	
Disease type				0.066
LMD only	3.7 (6/167)	1.9 (4/179)	5.6 (81/1453)	
LMD + 1VD	5.2 (9/167)	5.8 (10/179)	8.2 (119/1453)	
LMD + 2VD	9.4 (14/167)	10.3 (20/179)	12.7 (184/1453)	
LMD + 3VD	12.6 (21/167)	18.6 (32/179)	14.1 (205/1453)	
2VD (No LMCAD)	0.6 (1/167)	1.9 (3/156)	2.2 (32/1453)	
3VD (No LMCAD)	69.5 (116/167)	61.5 (110/156)	57.3 (832/1453)	
Procedural characteristics				
PCI				
Number of stents	4.8 ± 2.2	5.0 ± 2.3	4.54 ± 2.3	0.134
Total length of the stents (mm)	89.9 ± 48.3	97.7 ± 55.8	83.6 ± 46.6	0.020
Use of IABP	***11.8 (9/76)***	***4.3 (4/94)***	***4.1 (30/726)***	***0.011***
CABG				
Operation time (min)	224.2 ± 66.6	214.9 ± 57.6	208.0 ± 65.7	0.012
Use of IABP	***10.5 (9/86)***	***1.2 (1/84)***	***2.1 (15/700)***	***<0.001***
Off-pump CABG	15.3 (13/85)	8.3 (7/74)	15.8 (110/695)	0.192
Number of total conduits	2.66 ± 0.66	2.90 ± 0.63	2.75 ± 0.72	0.068
LIMA graft use	80.0 (68/85)	85.7 (72/84)	86.8 (604/696)	0.234
RIMA graft use	22.4 (19/85)	11.9 (10/84)	30.3 (211/696)	<0.001
Bilateral IMA use	22.4 (18/85)	11.9 (10/84)	29.9 (208/696)	0.001
Arterial conduit	1.29 ± 0.63	1.23 ± 0.59	1.42 ± 0.66	0.013
Venous conduit	1.36 ± 0.86	1.68 ± 0.85	1.33 ± 0.92	0.004

Continuous variables were expressed as mean ± standard deviation and were compared with a one-way ANOVA test.
Categorical variables were expressed as percentages with frequency, and are compared with the chi-square test.
Absolute risk differences (ARD) were calculated by subtracting predicted CABG mortality from predicted PCI mortality.
Hypertension was defined as blood pressure ≥130/85 mmHg.
Chronic kidney disease was defined as creatinine clearance <60 mL/min.
The SYNTAX score reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease; a low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33.
Abbreviations: ARD: absolute risk difference; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary artery disease; CVD: cerebrovascular disease; ***IABP: intra-aortic balloon pumping***; IMA: internal mammary artery; LMCAD: left main coronary artery disease; LMD: left main disease; LIMA: left internal mammary artery LVEF: left ventricular ejection fraction; MI myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; RIMA: right internal mammary artery; SS: syntax score; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; VD: vessel disease.

benefit) for each patient. Each patient only received either PCI or CABG and the outcome was binary (dead or alive), therefore, observed mortality after PCI or CABG needed to be estimated in small groups. The observed mortality after PCI or CABG was estimated by calculating the mortality in a small group of 10 % of the population nearest to each patient. The dots in the scatter plots were connected with the use of locally weighted smoothing (LOESS) spline curves [9,10]. According to an external validation in a large contemporary registry, an individual predicted ARD in all-cause death at five-year of <4.5 % and ≥ 4.5 % offers a sensible cut-off for "equipoise of PCI and CABG" or "CABG better," respectively [10].

Statistical significance was defined as a two-sided *p*-value ≤0.05. All analyses were performed using SPSS Statistics version 27 (IBM Corp., Armonk, 281 N.Y., USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline and procedural characteristics

The entire randomized population was categorized into rEF (n = 168, 9.4 %), mrEF (n = 179, 9.9 %), and pEF (n = 1453, 80.7 %) (Fig. 1). Baseline patient and procedural characteristics are shown in Table 1. Patients with rEF had a higher prevalence of insulin-treated diabetes, chronic kidney disease, and current smoking. Mean LVEF was 33.7 % vs. 45.1 % vs. 63.1 % in patients with rEF, mrEF, and pEF, respectively (P < 0.001), with a significant difference in rates of previous MI (51.5 % vs. 56.5 % vs. 27.8 %, respectively; P < 0.001). Patients with rEF had a significantly higher prevalence of three-vessel disease (59.5 % vs. 63.1 % vs. 70.2 %, P = 0.020) compared to patients with mrEF and pEF. The number of bifurcation lesions was comparable between the three groups; however, the prevalence of total occlusion was significantly different (30.2 % vs. 37.4 % vs. 20.8 %, P < 0.001).

Regarding procedural characteristics, the total number of stents implanted at PCI was similar between the three groups, whereas the total stent length was significantly different (rEF 88.9 mm vs. mrEF 97.7 mm vs. pEF 83.6 mm; P = 0.020). Operation time was the longest in patients with rEF (rEF 224.2 min vs. mrEF 214.9 min vs. pEF 208.0 min; P = 0.019). The rate of off-pump CABG and total conduit numbers were comparable among the three groups. The status of the medication up to five years of follow-up is shown in Supplementary Table 1.

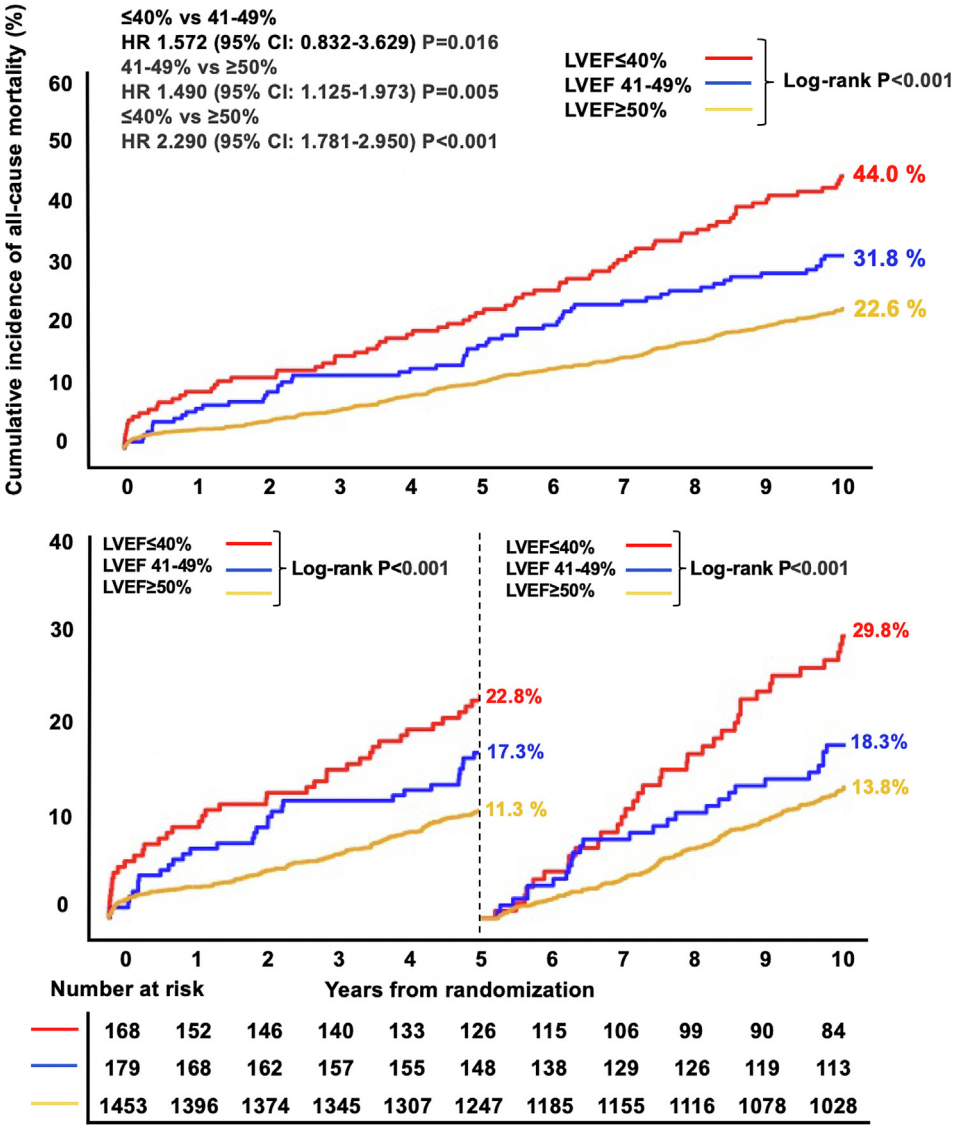


Fig. 2. Cumulative incidences of all-cause mortality up to 10 years for each left ventricular ejection fraction subgroup.
Landmark analysis shows a continuous and significant divergence in the cumulative incidence of mortality beyond five years.
Abbreviations: HR: hazard ratio; LVEF: left ventricular ejection fraction.

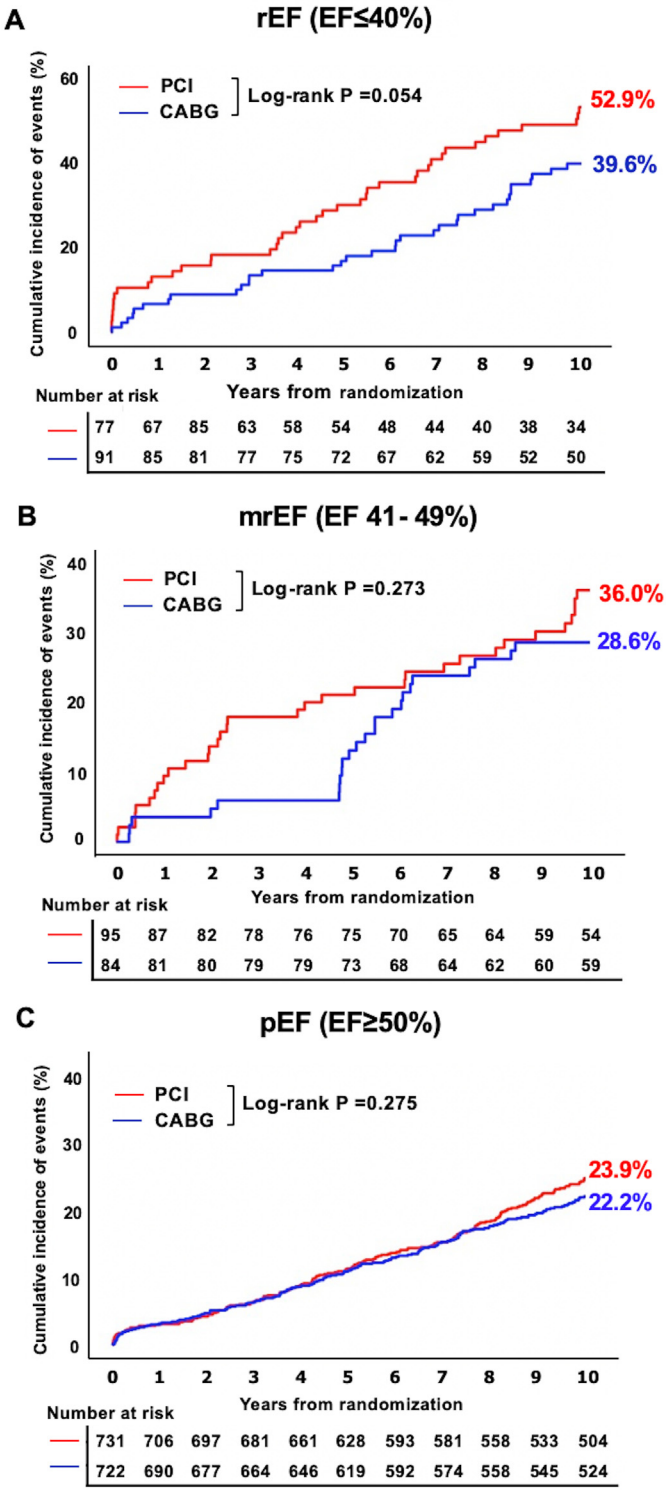


Fig. 3. Ten-year all-cause death after percutaneous coronary intervention and coronary artery bypass graft.
(A) Reduced ejection fraction.
(B) Mildly reduced ejection fraction.
(C) Preserved ejection fraction.
Abbreviations: CABG: coronary artery bypass graft, EF: ejection fraction, PCI: percutaneous coronary intervention.

3.2. Clinical outcomes

At 10 years, the all-cause mortality rate was 44.0 % vs. 31.8 % vs. 22.6 %, in patients with rEF, mrEF, and pEF, respectively (P < 0.001, Fig. 2); overall, patients with an LVEF<50 % had a poorer prognosis than those with pEF. The significant differences in mortality observed at 5-year follow-up persisted at 10 years. Ten-year mortality in patients with rEF was higher with PCI than in CABG, but this difference was not statistically significant presumably due to the small sample size (52.9 % vs 39.6 %, P = 0.054). In patients with mrEF, there was numerical higher mortality with PCI versus CABG (36.0 % vs. 28.6 %, P = 0.273), whilst in patients with pEF, all-cause mortality was comparable (23.9 % vs. 22.2 %, P = 0.275) (Fig. 3). The all-cause mortality in patients with quantitative assessment of LVEF at baseline was shown in Supplemental Fig. 1. A significant interaction was seen for mortality between the three subgroups and treatment modality at 5 years; however, this interaction was no longer seen at 10-year follow-up (Table 2).

3.3. Assessment of the SS-2020 and treatment benefit in patients treated with PCI or CABG according to LVEF subgroup (LVEF<50 % versus LVEF≥50 %)

Calibration plots (four quartiles) between the observed and predicted mortality in patients with an LVEF<50 % and LVEF≥50 % undergoing CABG or PCI are shown in Supplemental Fig. 2. The calibration plots have reasonable intercepts and slopes; discrimination in patients with an LVEF≥50 % was helpful (C index: CABG 0.732, PCI 0.731), whilst in patients with an LVEF<50 % was borderline (C index: CABG 0.691, PCI 0.675) [18,19]. Fig. 4 shows scatter plots of "individual predicted mortality" (PCI: blue dots, CABG: red dots) according to the SYNTAX score versus observed mortality at 10 years after PCI (dashed blue line) or CABG (dashed red line) in the LVEF<50 % (Fig. 4A) and LVEF≥50 % groups (Fig. 4B). In patients with an LVEF<50 %, PCI was preferred to CABG in 15 % of the population with an ARD<0 %; however, in those with an LVEF≥50 %, the recommendation for PCI increased to 22.9 %. CABG was recommended using in 42.5 % and 62.2 % of the population with an LVEF≥50 % and LVEF<50 %, respectively. In patients with LVEF<50 %, above the threshold of 4.5 % the individual predicted mortality (in about 216 patients) following PCI and CABG tended to underestimate the observed mortalities; in the first 52 patients, the prediction was inaccurate with the predicted mortality for PCI underestimated and for CABG, overestimated. The individual scatter plots would suggest that at least two-thirds of patients (62.2 %) with EF < 50 % have a better-predicted prognosis (solid line in Fig. 4A) with CABG. The observed mortality at 10 years only partially confirmed that prediction, since the dashed lines (observed mortality following PCI or CABG) are far from being superimposed with the solid lines (predicted mortality following PCI or CABG) in approximately a quarter of patients (Kaplan-Meier curve of the fourth quartile in the Supplemental Fig. 2). Conversely in at least one-third of individuals with an EF < 50 %, observed mortality is at variance with predicted mortality as indicated by calibration plots of predicted vs observed mortality and calibration plots of treatment benefit. The Scatter plot showing the relationship between ranked ARD and LVEF in the SYNTAX study population is shown in Supplementary Fig. 3. Baseline and procedural characteristics in patients with LVEF≥50 % and LVEF<50 % are shown in Supplemental Table 2.

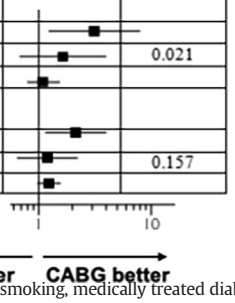
4. Discussion

The main findings of this study were:

1. Ten-year all-cause mortality was significantly different among patients with rEF, mrEF and pEF with the significant difference first emerging at 5-year follow-up.
2. Among the patients with rEF (≤40 %) and mrEF (41–49 %), 10-year all-cause mortality was lower after CABG than PCI, but failed to be statistically different presumably due to the small sample size. Mortalities of PCI versus CABG were comparable in pEF.

Table 2
Hazard risks for long-term clinical outcomes calculated with the ratios of the percutaneous coronary intervention arm compared to the coronary artery bypass graft arm.

	Overall (n=1800)	PCI (n=903)	CABG (n=897)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	Adjusted P value	P value for interaction
5-year all-cause death								
rEF (≤40%)	22.6 (38/168)	29.9 (23/77)	16.5 (15/91)	1.932 (1.008-3.703)	0.047	3.124 (1.231-7.933)	0.017	
mrEF (41-49%)	17.3 (31/179)	21.1 (20/95)	13.1 (11/84)	1.738 (0.833-3.629)	0.141	1.640 (0.680-3.960)	0.271	0.021
pEF (≥50%)	11.1 (162/1453)	11.4 (83/731)	10.9 (79/722)	1.028 (0.756-1.400)	0.551	1.084 (0.797-1.528)	1.104	
10-year all-cause death								
rEF (≤40%)	44.0 (74/168)	51.9 (40/77)	37.4 (34/91)	1.562 (0.988-2.467)	0.056	2.140 (1.148-3.990)	0.017	
mrEF (41-49%)	31.8 (57/179)	34.7 (33/95)	28.6 (24/84)	1.341 (0.746-2.268)	0.275	1.195 (0.644-2.219)	0.573	0.157
pEF (≥50%)	22.6 (329/1453)	23.9(175/731)	21.3 (154/722)	1.128 (0.886-1.401)	0.275	1.231 (0.976-1.551)	0.079	



Adjusted models included the following baseline variables; age, sex, body mass index, chronic kidney disease, hypertension, dyslipidemia, current smoking, medically treated diabetes, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, prior heart failure, complete revascularization, any total occlusion, left main disease, prior cerebrovascular disease, and anatomical SYNTAX score.
Abbreviations: CABG: coronary artery bypass graft; EF: ejection fraction; MACCE: major adverse cardiac or cerebrovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention.

3. PCI would be a relatively safe modality of revascularization in 57.5 % of patients with an EF ≥ 50 %, but these "legitimate" candidates for PCI must be individually identified using the SS-2020.
4. In two-thirds of patients with an EF < 50 % (n = 216), CABG was safer than PCI in terms of predicted and observed mortality; whilst in the remaining third (n = 131) the predicted mortality was unreliable.

4.1. Impact of LVEF on 10 years all-cause mortality

Cumulative evidence confirms the detrimental effect of an altered LVEF on long-term (three to five years) mortality after CABG or PCI in patients with LMCAD and/or three-vessel disease [5,20]. Previous randomized LE MANS and PRECOMBAT studies showed comparable mortality after CABG or PCI in patients with LMCAD; however, given the small number of patients with impaired LVEF, its impact on outcomes could not be adequately examined [21,22]. In the present study, patients with an LVEF<50 % had a worse prognosis than those with preserved LVEF. Similar to previous studies, these patients had significantly more adverse cardiovascular risk profiles and comorbidities, including chronic kidney disease and previous MI, which contribute to the progression of cardiovascular disease and influences prognosis [23]. Although data on major adverse events beyond 5 years after randomization are unavailable in the SYNTAXES trial, the significantly higher rate of cardiac death in patients with an LVEF<50 % was already evident at 5-years (Supplemental Fig. 4). Our results therefore highlight that a baseline LVEF<50 % is a warning signal for clinicians and the heart team that should trigger a more comprehensive and holistic assessment using a validated personalized risk/benefit score.

4.2. Impact of LVEF on 10 years all-cause mortality (PCI versus CABG)

Our results suggested that CABG was safer than PCI for patients with reduced EF (≤40 %) at 10-year follow-up. Although statistical significance was not reached due to the small sample size, it might be inferred from the results of the present sub-study that recommendations favouring surgery in the current ESC guidelines are valid long-term. The potential advantages of CABG over PCI in patients with multivessel CAD are mainly based on the higher rate of complete revascularization and less need for repeat revascularization [24]. CABG overcomes the overall burden of complex and diffuse atherosclerotic disease by constructing the graft anastomosis distal to diseased segments whereas PCI only treats topically flow-limiting lesions without providing "protection" against a plaque rupture in the coronary segment proximal to the stent [25]. These advantages may be even more prominent in patients presenting with complex lesions and a high anatomical SYNTAX score or patients with insulin-dependent diabetes mellitus which is a strong predictor of repeat revascularization. Further investigations will be needed to clarify which of the two different treatment strategies is safer considering patient-level personalized risk differences.

4.3. "Average treatment effect" vs "personalized treatment benefit" in patients with left ventricular dysfunction

Sub-group analysis showed that mortality was higher with PCI versus CABG in all categories of LVEF. However, the absolute risk difference fell from 13.3 % to 7.4 % and then 1.7 % in patients with rEF, mrEF and pEF, respectively. Therefore, as an "average treatment effect" these results imply that CABG is overall a safer revascularization procedure than PCI particularly in patients with an LVEF<50 %. Traditionally, when making decisions clinicians consider the "average treatment effect (or treatment benefit)" stemming from Kaplan-Meier estimates established in large randomized trials and endorsed by guidelines of clinical societies; however, the question remains whether an "average treatment effect" can/should be systematically and blindly applied to every individual. Indeed, from the patient's point of view, it is essential to have a personalized assessment of risk and benefit by combining multiple independent determinants of outcome while integrating their mutual interactions.

The current analysis reports an average treatment effect related to a specific parameter—LVEF. However, it is critical to identify among a heterogeneous population with an LVEF<50 % who will benefit, not be helped or be harmed by CABG or PCI. Instead of a conventional subgroup analysis searching for interactions between isolated baseline characteristics and outcomes or traditional statistical adjustments for confounding factors affecting the average treatment, we opted for a personalized prediction outcome using a novel probabilistic model validated in a randomized trial and contemporary registry [9,10].

To further refine individual decision-making with respect to vital prognosis at 10-year in patients with a baseline LVEF<50 % or ≥50 %, we utilised the SS-2020. The sample size of patients with an LVEF<50 % was small, thereby having less statistical discriminative capability when compared to the larger group of patients with an LVEF≥50 % [10]. In two-third of patients (n = 216) with an LVEF<50 %, CABG was safer than PCI in terms of predicted and observed all-cause mortality whilst in the remaining third (n = 131), the risk score did not permit an accurate prediction of mortality. The use of individual predicted ARD of 0 % with the SS-2020 seems to be too stringent and restrictive, as it leads to the recommendation of CABG in the majority of patients with 3VD with or without LMCAD.

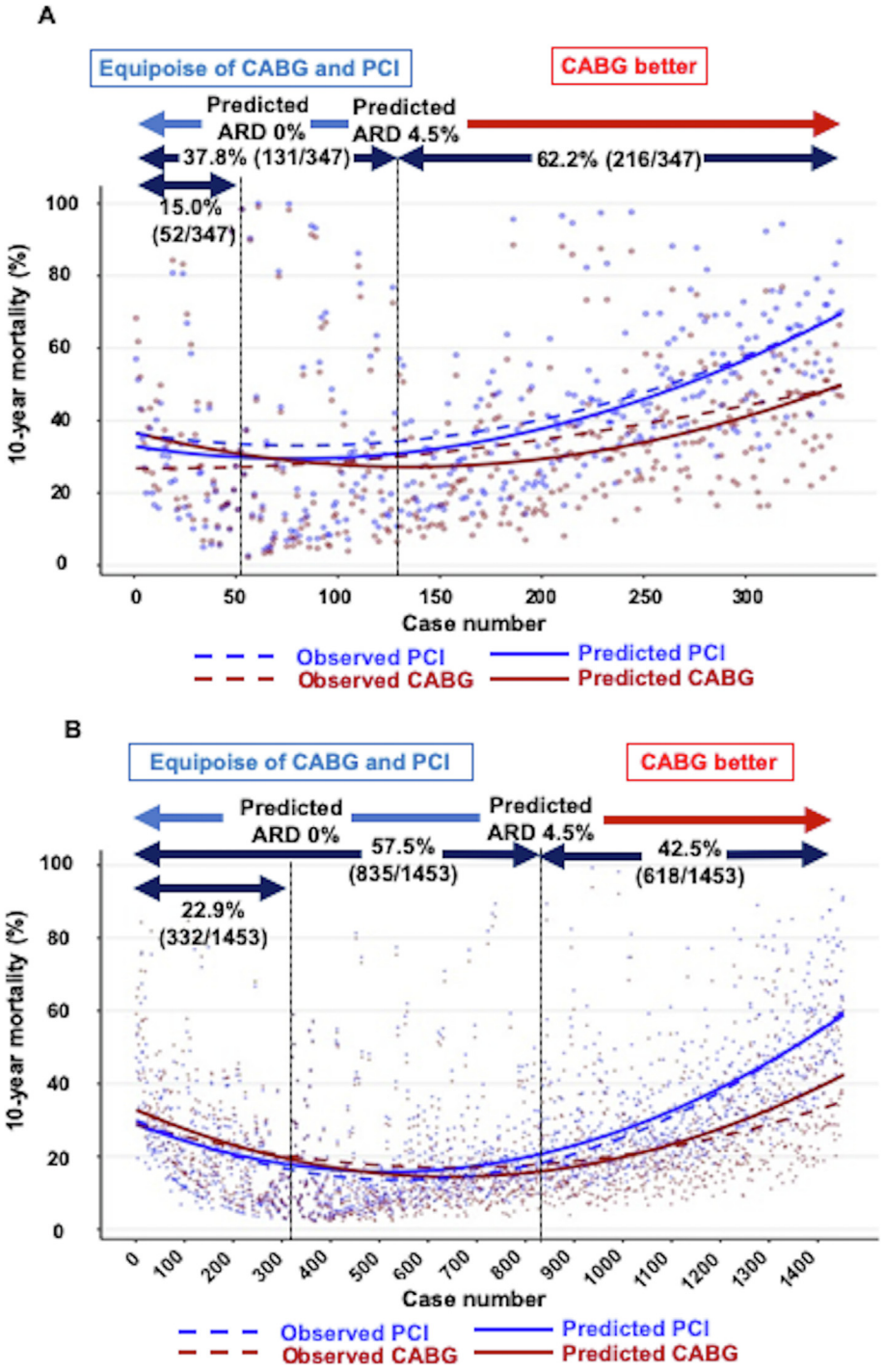


Fig. 4. Individual scatter plots of predicted and observed mortality at ten years according to SYNTAX score 2020.
Left ventricular ejection fraction<50 % (A) and ≥50 % (B). Left ventricular ejection fraction (LVEF) < 50 % (A) and ≥ 50 % (B). In patients with LVEF<50 %, CABG is recommended for 62.2 % of the population if an absolute risk difference (ARD) of 4.5 % in mortality is applied. If an ARD of 0 % is applied, CABG recommended population increases to 85 %. Similarly, in patients with LVEF≥50 %, CABG is recommended for 42.5 % of the population if an ARD of 4.5 % in mortality is applied. If an ARD of 0 % is applied, CABG recommended population increases to 77.1 %.
Predicted mortality after PCI; blue solid line.
Observed mortality after PCI; blue dashed line.
Predicted mortality after CABG; red solid line.
Observed mortality after CABG; red dashed line.
Abbreviations: ARD: absolute risk difference, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the SYNTAX II trial in which all the lesions were treated with contemporary PCI technology (e.g. physiological guidance with pressure wire, chronic total occlusion expertise, intravascular imaging, thin struts stent of the third generation) there was a significant reduction in 5-year all-cause mortality compared with the SYNTAX I PCI cohort (8.1 % vs 13.8 %) [26]. This is probably the reason why the threshold of equipoise in mortality at 5 years moved from 0 % to an ARD of 4.5 % in the external validation of the CREDO-Kyoto cohort 2 and 3 [10].

Further studies are needed to develop a score incorporating additional risk factors, such as biomarkers, physical and mental states, active malignancy, frailty, and severe co-morbid conditions that are strong predictors, but not accounted for in the SS-2020. Surgical ineligibility in itself is an independent predictor of increased mortality even after adjustment for important surgical risk scores such as the EuroSCORE or the Society of Thoracic Surgeons (STS) score, indicating that these surgical risk scores may be insufficient for determining surgical ineligibility [27].

4.4. Limitations

First, LVEF was not qualitatively assessed by echocardiography or ventriculogram at baseline in all patients. Although, multiple imputations were performed to adjust categorical to continuous values within a range that did not deviate from the values that had been categorized, we acknowledged the potential bias was unavoidable. Second, LVEF, the parameter specifically singled out in this analysis, is an independent determinant already incorporated in the probabilistic formula of the SS-2020 predicting 10-year mortality in the SYNTAXES trial. To apply the score to discriminate individuals and predict their personalized vital prognosis seems to be potentially fraught with "self-prediction." However, recent experience among investigators of trials prospectively collecting the decision-making of their Heart Teams has shown that clinicians are largely under-using validated and personalized risk scores in their daily practice. Ultimately, they need alerting and specific warning signals such as insulin-dependent diabetes, presence of bifurcation, heavy calcification, and low LVEF before taking the pain to consult a comprehensive and personalized risk score [9,15,28]. Finally, the original SYNTAX trial was conducted >10 years ago. The patients underwent PCI with the first-generation DES, which is no longer commercially available. Furthermore, current clinical guidelines have recommended contemporary pharmacological therapy (e.g. sodium-glucose co-transporter 2 receptor inhibitor and sacubitril/valsartan) which was not available in the trial to improve clinical outcomes in patients with reduced EF [29]; therefore, these pharmacological advantages were not applied in this sub-study. The technological improvements of PCI devices as well as medical treatment strategies may limit the generalizability of our findings to current clinical practice, although external validation of the SS-2020 in the most contemporary cohort of the CREDO-Kyoto registry has shown the persisting actuality and accuracy of the probabilistic model [10].

5. Conclusion

Impaired LVEF was associated with an incremental risk of ten-year all-cause mortality in patients with multivessel and/or left main disease revascularized either surgically or percutaneously. In patients with impaired LVEF, CABG seems to be safer than PCI as an average treatment effect and also on the basis of personalized probabilistic decision-making.

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CRediT authorship contribution statement

Shinichiro Masuda: Formal analysis, Writing – original draft, Writing – review & editing. **Patrick W. Serruys:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Kai Ninomiya:** Formal analysis, Writing – review & editing. **Shigetaka Kageyama:** Writing – review & editing. **Kotoku Nozomi:** Writing – review & editing. **Chao Gao:** Writing – review & editing. **Michael J. Mack:** Writing – review & editing. **David R. Holmes:** Writing – review & editing. **Marie-Claude Morice:** Writing – review & editing. **Daniel J.F.M. Thuijs:** Writing – review & editing. **Milan Milojevic:** Writing – review & editing. **Piroze M. Davierwala:** Writing – review & editing. **Scot Garg:** Writing – review & editing. **Yoshinobu Onuma:** Supervision, Methodology, Writing – review & editing.

Data availability

All relevant data are stored on a secure private server; it is accessible with relevant.

Declaration of competing interest

Dr. Masuda reports a grant from TERUMO corporation outside the submitted work.

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All other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2023.06.031.

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