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RESEARCH ARTICL

Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularization: results from the randomized EXCEL trial

Daniel J.F.M. Thuijs[1]*, Milan Milojevic[1], Gregg W. Stone[2,3], John D. Puskas[4], Patrick W. Serruys[5], Joseph F. Sabik 3rd[6], Ovidiu Dressler[3], Aaron Crowley[3], Stuart J. Head[1], and A. Pieter Kappetein[1]

[1]Department of Cardiothoracic Surgery, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands; [2]Division of Cardiology, New York-Presbyterian Hospital/Columbia University Medical Center, New York, NY, USA; [3]Clinical Trials Center, Cardiovascular Research Foundation, New York, NY, USA; [4]Department of Cardiovascular Surgery, Mount Sinai Heart at Mount Saint Luke's, New York, NY, USA; [5]Department of Cardiology, Imperial College London, London, UK; and [6]Department of Surgery, UH Cleveland Medical Center, Cleveland, OH, USA

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Aim

To evaluate the impact of left ventricular ejection fraction (LVEF) on 3-year outcomes in patients with left main coronary artery disease (LMCAD) undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the EXCEL trial.

Methods and results

The EXCEL trial randomized patients with LMCAD to PCI with everolimus-eluting stents ($n = 948$) or CABG ($n = 957$). Among 1804 patients with known baseline LVEF, 74 (4.1%) had LVEF <40% [heart failure with reduced ejection fraction (HFrEF)], 152 (8.4%) LVEF 40–49% [heart failure with mid-range ejection fraction (HFmrEF)] and 1578 (87.5%) LVEF ≥50% (heart failure with preserved ejection fraction). Patients with HFrEF vs. HFmrEF vs. preserved LVEF experienced a longer postoperative hospital stay (9.0 vs. 7.0 vs. 6.0 days, $P = 0.02$) with greater peri-procedural complications after CABG, while hospital stay after PCI was unaffected by LVEF (1.5 vs. 2.0 vs. 1.0 days, $P = 0.20$). The composite primary endpoint of death, stroke, or myocardial infarction at 3 years was 29.3% (PCI) vs. 27.6% (CABG) in patients with HFrEF, 16.2% vs. 15.0% in patients with HFmrEF, and 14.5% vs. 14.6% in those with preserved LVEF, respectively ($P_{interaction} = 0.90$). Smoothing spline analysis demonstrated that the 3-year risk of all-cause death increased when LVEF decreased, both in patients undergoing CABG and PCI.

Conclusion

In the EXCEL trial, the composite rate of death, stroke or myocardial infarction at 3 years was significantly higher in patients with HFrEF compared with HFmrEF or preserved LVEF, driven by an increased rate of all-cause death. No significant differences after PCI vs. CABG were observed among patients with HFrEF, HFmrEF and preserved LVEF. Longer-term follow-up could provide important insights on differences in clinical outcomes that might emerge over time.

Clinical Trial Registration: ClinicalTrials.gov ID NCT01205776.

Keywords

Coronary artery bypass grafting • Percutaneous coronary intervention • Left main coronary artery disease • Left ventricular ejection fraction • Left ventricular function • Heart failure with reduced ejection fraction

*Corresponding author. Department of Cardiothoracic Surgery, Erasmus MC, University Medical Centre, Dr. Molewaterplein 40, 3015GD, P.O. Box 2040, Rotterdam, 3000 CA, The Netherlands. Tel: +31 10 7038341, Email: d.thuijs@erasmusmc.nl

Introduction

Coronary artery bypass surgery is generally recommended for patients with extensive multivessel coronary artery disease (CAD) and severely impaired left ventricular ejection fraction (LVEF) (<35%).[1,2] However, whether coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is preferred in patients with left main CAD (LMCAD) and impaired LVEF (<50%) is unclear. Whereas randomized trials of patients with impaired LVEF undergoing CABG vs. medical therapy have been performed,[3] most trials comparing PCI with CABG have excluded patients with severely impaired LVEF (≤35%). Insights related to myocardial revascularization in patients with impaired LVEF are thus mainly limited to observational studies. A recent systematic review of mainly observational studies ($n = 16\,191$), compared myocardial revascularization with medical therapy and reported an overall survival benefit of CABG over PCI in 8782 patients with LVEF ≤40% [hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.75–0.90].[4] However, the results varied widely between the individual studies ($I^2 = 47\%$), possibly in part because follow-up ranged from 12–180 months. Moreover, only a limited number of patients with LMCAD and impaired LVEF was included in the analysis.

In the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, PCI with drug-eluting stents was shown to be an acceptable alternative to CABG in selected patients with LMCAD at 3-year follow-up.[5–7] The current pre-specified EXCEL sub-study aims to estimate the impact of LVEF, defined according to the European Society of Cardiology heart failure terminology,[8] on 3-year outcomes and evaluates differences in treatment effect of PCI with everolimus-eluting stents vs. CABG according to LVEF in patients with LMCAD in the EXCEL trial.

Methods

Study design

The design of the EXCEL trial and the main outcomes have been reported previously.[9,10] In brief, 1905 patients with LMCAD and a site-determined SYNTAX score of ≤32 were randomized to PCI with everolimus-eluting stents ($n = 948$) and CABG ($n = 957$). Among those, baseline data on LVEF were available for 1804 patients (94.7%) and were assessed within 14 days after randomization. In 226 out of 1804 patients (12.5%) LVEF was <50%. These 226 patients were classified according to the European Society of Cardiology heart failure terminology; heart failure with reduced ejection fraction (HFrEF; LVEF <40%) and heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%). The HFrEF group consisted of 74 patients, and of those 43 were randomized to PCI and 31 to CABG. There were 152 patients in the HFmrEF group, of which 68 were randomized to PCI and 84 to CABG. LVEF was preserved (≥50%) in 1578 out of 1804 patients (87.5%), of whom 782 were randomized to PCI and 796 to CABG. The aim of the present pre-specified analysis was to evaluate the association of LVEF on 3-year clinical outcomes among patients with LMCAD undergoing PCI or CABG.

All patients reached 3-year follow-up at the time of this post-hoc analysis. An independent clinical events committee monitored and adjudicated adverse events. Informed consent was signed by all patients prior to randomization. The EXCEL trial complies with the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01205776).

Endpoints

The primary endpoint consisted of the composite rate of all-cause death, stroke, or myocardial infarction (MI),[11] at 3 years in subgroups of patients with HFrEF, HFmrEF and preserved LVEF, randomized to either PCI or CABG. Secondary powered endpoints included the primary endpoint measure at 30 days and the composite rate of all-cause death, stroke, MI, or ischaemia-driven revascularization at 3 years in subgroup of patients with HFrEF, HFmrEF and preserved LVEF, randomized to PCI or CABG. Additional endpoints consisted of the individual components of the primary and secondary endpoints at 3 years and 30 days.[9,10]

Statistical analyses

All analyses were performed according to the intention-to-treat principle. Discrete variables were expressed as percentages with frequencies and compared with the χ^2 test or Fisher exact test when the expected frequency in any cell was <5. Continuous variables were summarized as mean ± standard deviation and were compared by independent samples *t*-test if normally distributed, or the Wilcoxon rank-sum test when non-normally distributed. Event rates up to 3 years were estimated according to the Kaplan–Meier method, and differences between baseline LVEF subgroups (HFrEF, HFmrEF, and preserved),and PCI vs. CABG, were assessed using the log-rank test. Any differences in baseline characteristics between subgroups of patients with HFrEF, HFmrEF and preserved LVEF were adjusted using a multivariable Cox proportional hazard model, correcting for pre-specified important clinical and statistical variables. The association of LVEF as a continuous variable on the 3-year hazard of all-cause death was analysed by smoothing spline analysis with a linear Cox proportional hazards regression model. Baseline characteristics of patients with and without known baseline LVEF were compared to check for potential attrition bias. All reported *P*-values are 2-sided, and $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

The baseline characteristics of the overall cohort of patients classified as HFrEF ($n = 74$), HFmrEF ($n = 152$) and those with preserved LVEF ($n = 1578$) are provided in *Table 1*. LVEF was assessed by cardiac ultrasound in 1051 patients (58.3%) and contrast left ventriculography in 715 patients (39.6%). Magnetic resonance or nuclear imaging were used in 38 patients (2.1%). Mean LVEF was 31.6% vs. 43.6% vs. 59.6% in patients with HFrEF vs. HFmrEF vs. preserved LVEF, respectively ($P = <0.001$). Patients with HFrEF and HFmrEF vs. preserved LVEF had a significantly worse cardiovascular risk profile and had a higher pre-operative risk reflected by increased predicted risk of mortality STS risk scores (1.11 vs. 0.96 vs. 0.86, respectively; $P = 0.02$). More patients with HFrEF had a high SYNTAX score (≥33, core laboratory analysis) compared to those with HFmrEF and preserved

Table 1 Baseline characteristics according to left ventricular ejection fraction

Characteristics % (n/N)	LVEF <40% (HFrEF) (*n* = 74)	LVEF 40–49% (HFmrEF) (*n* = 152)	Preserved LVEF ≥50% (*n* = 1578)	*P*-value
Age (years)	67.0 ± 9.3	66.7 ± 9.3	65.9 ± 9.6	0.42
Female sex	21/74 (28.4)	20/152 (13.2)	380/1578 (24.1)	0.006
LVEF (%)	31.6 ± 4.2	43.6 ± 2.6	59.6 ± 6.6	<0.001
CAD risk factors				
Hypertension[a]	54/74 (73.0)	112/152 (73.7)	1169/1578 (74.1)	0.97
Hyperlipidaemia	45/74 (60.8)	100/151 (66.2)	1116/1577 (70.8)	0.11
Diabetes mellitus[a]	24/74 (32.4)	57/152 (37.5)	449/1578 (28.5)	0.05
Current or former smoker	53/74 (71.6)	103/151 (68.2)	962/1566 (61.4)	0.06
Family history of CAD	45/64 (70.3)	92/125 (73.6)	868/1323 (65.6)	0.16
NYHA class, known	23/74 (31.1)	23/152 (15.1)	73/1573 (4.6)	<0.001
I	4/74 (5.4)	3/152 (2.0)	16/1573 (1.0)	0.003
II	6/74 (8.1)	15/152 (9.9)	33/1573 (2.1)	<0.001
III	12/74 (16.2)	5/152 (3.3)	23/1573 (1.5)	<0.001
IV	1/74 (1.4)	0/152 (0.0)	2/1573 (0.1)	0.04
Pre-operative risk factors				
History of stroke	6/74 (8.1)	8/152 (5.3)	50/1577 (3.2)	0.04
History of TIA	2/74 (2.7)	4/151 (2.6)	47/1569 (3.0)	0.96
Recent myocardial infarction[b]	18/74 (24.3)	34/151 (22.5)	219/1574 (13.9)	0.001
Chronic kidney disease[c]	24/73 (32.9)	39/149 (26.2)	231/1550 (14.9)	<0.001
Dialysis	0/74 (0.0)	2/152 (1.3)	3/1578 (0.2)	0.04
Peripheral vascular disease	14/72 (19.4)	23/152 (15.1)	133/1572 (8.5)	0.004
Chronic obstructive pulmonary disease	14/74 (18.9)	17/152 (11.2)	113/1575 (7.2)	0.004
History of carotid artery disease	13/74 (17.6)	12/150 (8.0)	125/1574 (7.9)	0.01
Body mass index (kg/m^2)	28.9 ± 6.4	28.7 ± 4.9	28.7 ± 4.9	0.93
< 20: cachectic	2/74 (2.7)	2/152 (1.3)	24/1578 (1.52)	0.52
> 30: obese	25/74 (33.8)	47/152 (30.9)	514/1578 (32.6)	0.85
History of anaemia[d]	8/74 (10.8)	23/152 (15.1)	146/1572 (9.3)	0.07
Lesions per patient	2.7 ± 1.5 (42)	2.9 ± 1.5 (66)	2.5 ± 1.3 (773)	0.051
Diffuse disease or small vessels	4/73 (5.5)	18/146 (12.3)	85/1555 (5.5)	0.004
Critical pre-operative state[e] STS risk scores				
PROM score	1.11 ± 1.0	0.96 ± 0.93	0.86 ± 0.78	0.02
Stroke score	0.97 ± 0.82	0.82 ± 0.61	0.75 ± 0.56	0.004
Reop. score	4.00 ± 1.63	3.64 ± 1.41	3.51 ± 1.34	0.007
SYNTAX score (site-assessed)	21.0 ± 5.7	22.4 ± 5.7	20.4 ± 6.2 (1576)	0.004
Low (≤22)	41/74 (55.4)	77/152 (50.7)	967/1576 (61.4)	0.03
Intermediate (23–32)	33/74 (44.6)	75/152 (49.3)	609/1576 (38.6)	0.03
High (≥33)	0/74 (0.0)	0/152 (0.0)	0/1576 (0.0)	–
SYNTAX score (core laboratory-assessed)	28.4 ± 9.7	27.6 ± 9.2	26.3 ± 9.3 (1526)	0.06
Low (≤22)	24/72 (33.3)	37/144 (25.7)	563/1526 (36.9)	0.03
Intermediate (23–32)	21/72 (29.2)	76/144 (52.8)	600/1526 (39.3)	0.001
High (≥33)	27/72 (37.5)	31/144 (21.5)	363/1526 (23.8)	0.021

Values are mean ± standard deviation, or *n* (%).

CAD, coronary artery disease; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association heart failure classification; PROM, Predicted Risk Of Mortality; STS, Society of Thoracic Surgeons; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TIA, transient ischaemic attack.

[a]Medically treated.

[b]Within 7 days of randomization.

[c]Estimated glomerular filtration rate < 60 mL/min.

[d]World Health Organization criteria: Hematocrit <13 g/dL (male) and < 12 g/dL (female).

[e]Ventricular tachycardia, ventricular fibrillation, or aborted sudden death; preoperative cardiac massage; preoperative ventilation before anesthetic room; preoperative inotropes or intra-aortic balloon pump; preoperative acute renal failure (anuria or oliguria <10 mL/h).

Table 2 Procedural characteristics and discharge medication according to left ventricular ejection fraction and revascularization assignment

	CABG (n = 911)				PCI (n = 893)			
	LVEF <40% (HFrEF) (n = 31)	LVEF 40–49% (HFmrEF) (n = 84)	Preserved LVEF ≥50% (n = 796)	P-value	LVEF <40% (HFrEF) (n = 43)	LVEF 40–49% (HFmrEF) (n = 68)	Preserved LVEF ≥50% (n = 782)	P-value
Assigned treatment received	28/31 (90.3)	81/84 (96.4)	774/796 (97.2)	0.098	42/43 (97.7)	66/68 (97.1)	773/782 (98.9)	0.22
Procedure duration[a] (min)	231 [215–305]	239 [200–291]	235 [195–280]	0.39	66 [51–101]	83 [65–109]	73 [51–106]	0.59
Bypass time (min)	80 [59–87]	73 [62–94]	74 [57–97]	0.77	–	–	–	–
Off-pump CABG	10/28 (35.7)	23/81 (28.4)	225/774 (29.1)	0.74	–	–	–	–
BITAs used	4/28 (14.3)	25/80 (31.3)	219/771 (28.4)	0.22	–	–	–	–
No. of distal anastomoses	2.5 ± 0.6	2.6 ± 0.8	2.7 ± 0.8	0.83	–	–	–	
No. of grafts used	3.0 [2.0–3.0]	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.32	–	–	–	–
No. of stents implanted	–	–	–	–	2.0 [1.0–4.0]	3.0 [2.0–3.0]	2.0 [1.0–3.0]	0.004
Total stent length (mm)	–	–	–	–	35.0 [26.0–76.0]	52.0 [30.0–84.0]	38.0 [23.0–61.0]	0.003
Intubation > 48 h	2/29 (6.9)	5/82 (6.1)	21/787 (2.7)	0.12	1/42 (2.4)	0/67 (0.0)	3/778 (0.4)	0.15
Renal failure[b]	4/29 (13.8)	4/82 (4.9)	15/787 (1.9)	0.001	2/42 (4.8)	0/67 (0.0)	4/778 (0.5)	0.004
Major arrhythmia	9/29 (31.0)	17/82 (20.7)	108/787 (13.7)	0.011	1/42 (2.4)	1/67 (1.5)	14/778 (1.8)	0.94
Post-operative hospital stay (days)	9.0 [5.0–13.0]	7.0 [5.0–10.0]	6.0 [5.0–9.0]	0.02	1.5 [1.0–3.0]	2.0 [1.0–3.0]	1.0 [1.0–2.0]	0.20
Discharge medications								
Aspirin	26/27 (96.3)	79/79 (100.0)	752/760 (98.9)	0.26	42/42 (100.0)	66/66 (100.0)	760/766 (99.2)	0.65
$P2Y_{12}$ inhibitor	7/27 (25.9)	22/79 (27.8)	259/765 (33.9)	0.40	42/42 (100.0)	65/66 (98.5)	754/769 (98.0)	0.64
DAPT	7/27 (25.9)	22/79 (27.8)	254/765 (33.2)	0.48	42/42 (100.0)	65/66 (98.5)	748/769 (97.3)	0.47
Statin	25/27 (92.6)	70/79 (88.6)	709/765 (92.7)	0.43	40/42 (95.2)	66/66 (100.0)	741/769 (96.4)	0.26
Beta-blocker	26/27 (96.3)	74/79 (93.7)	704/765 (92.0)	0.64	40/42 (95.2)	57/66 (86.4)	634/769 (82.4)	0.08
ACE-inhibitor or ARB	12/27 (44.4)	37/79 (46.8)	311/765 (40.7)	0.54	26/42 (61.9)	39/66 (59.1)	428/769 (55.7)	0.65
Calcium-channel blockers	0/27 (0.0)	9/79 (11.4)	53/765 (6.9)	0.12	0/42 (0.0)	1/66 (1.5)	48/769 (6.2)	0.07
Diuretics	7/27 (25.9)	18/79 (22.8)	185/765 (24.2)	0.94	2/42 (4.8)	2/66 (3.0)	26/769 (3.4)	0.88

Values are n (%), median [interquartile range], or mean ± standard deviation.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BITA, bilateral internal thoracic artery; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
[a]Time from start of anaesthesia to procedure end (e.g. for CABG this is the time of skin closure).
[b]Serum creatinine increase by ≥1 mg/dL from baseline or need for dialysis.

LVEF (37.5% vs. 21.5% vs. 23.8%, respectively; $P = 0.02$). The specific cardiovascular risk profile of patients with HFrEF, HFmrEF and preserved LVEF randomized to PCI vs. CABG are reported in online supplementary *Table S1*. No differences between baseline characteristics among those patients with vs. those without known baseline LVEF were identified (online supplementary *Table S2*).

Procedural characteristics

Surgical techniques used for CABG were similar among patients with HFrEF, HFmrEF and preserved LVEF (*Table 2*). Off-pump CABG was performed in 35.7% of patients (n = 10/28) with HFrEF, in 28.4% of patients (n = 23/81) with HFmrEF and in 29.1% of patients (n = 225/774) with preserved LVEF. Bilateral internal thoracic arteries were used less frequently in patients with HFrEF (14.3%; n = 4/28) vs. in those with HFmrEF (31.3%; n = 25/80) and preserved LVEF (28.4%; n = 219/771). The number of distal anastomoses did not differ among patients with HFrEF, HFmrEF and preserved LVEF. The duration of the PCI procedure was similar among patients with HFrEF, HFmrEF and preserved LVEF (*Table 2*), while the number of implanted stents and the total stent length differed significantly between patients with HFrEF, HFmrEF and preserved LVEF.

After CABG, patients with HFrEF vs. HFmrEF vs. preserved LVEF had a longer post-operative hospital stay (median 9.0 vs. 7.0 vs. 6.0, $P = 0.02$), and more often experienced renal failure and arrhythmias (*Table 2*). Following PCI, no differences were identified in hospital stay, however patients with HFrEF more often had post-operative renal failure. No statistical differences were noted in medical treatment at the time of discharge after CABG or PCI according to LVEF status.

Thirty-day outcomes

Overall, the event rates for the primary endpoint, as well as for the individual endpoints, were relatively low. The composite endpoint of death, stroke, or MI occurred more frequently in patients with preserved LVEF that underwent CABG compared with those that underwent PCI (7.9% vs. 5.1%; HR 0.65, 95% CI 0.44–0.97; online supplementary *Table S3*). No treatment-by-subgroup interaction was identified between LVEF status (HFrEF, HFmrEF and preserved LVEF) and revascularization strategy (PCI vs. CABG) among any of the clinical endpoints.

Three-year outcomes

The composite of death, stroke, or MI was 28.3% vs. 15.7% vs. 14.5% according to HFrEF, HFmrEF and preserved LVEF status ($P = 0.02$) (*Figure 1A*). All-cause death occurred in 19.5% vs. 9.6% vs. 6.2%, respectively ($P < 0.001$) (*Figure 1B*). Smoothing spline analysis showed a gradually increasing risk of all-cause death with decreasing LVEF below 50% after PCI (*Figure 2*) (HR 1.15, 95% CI

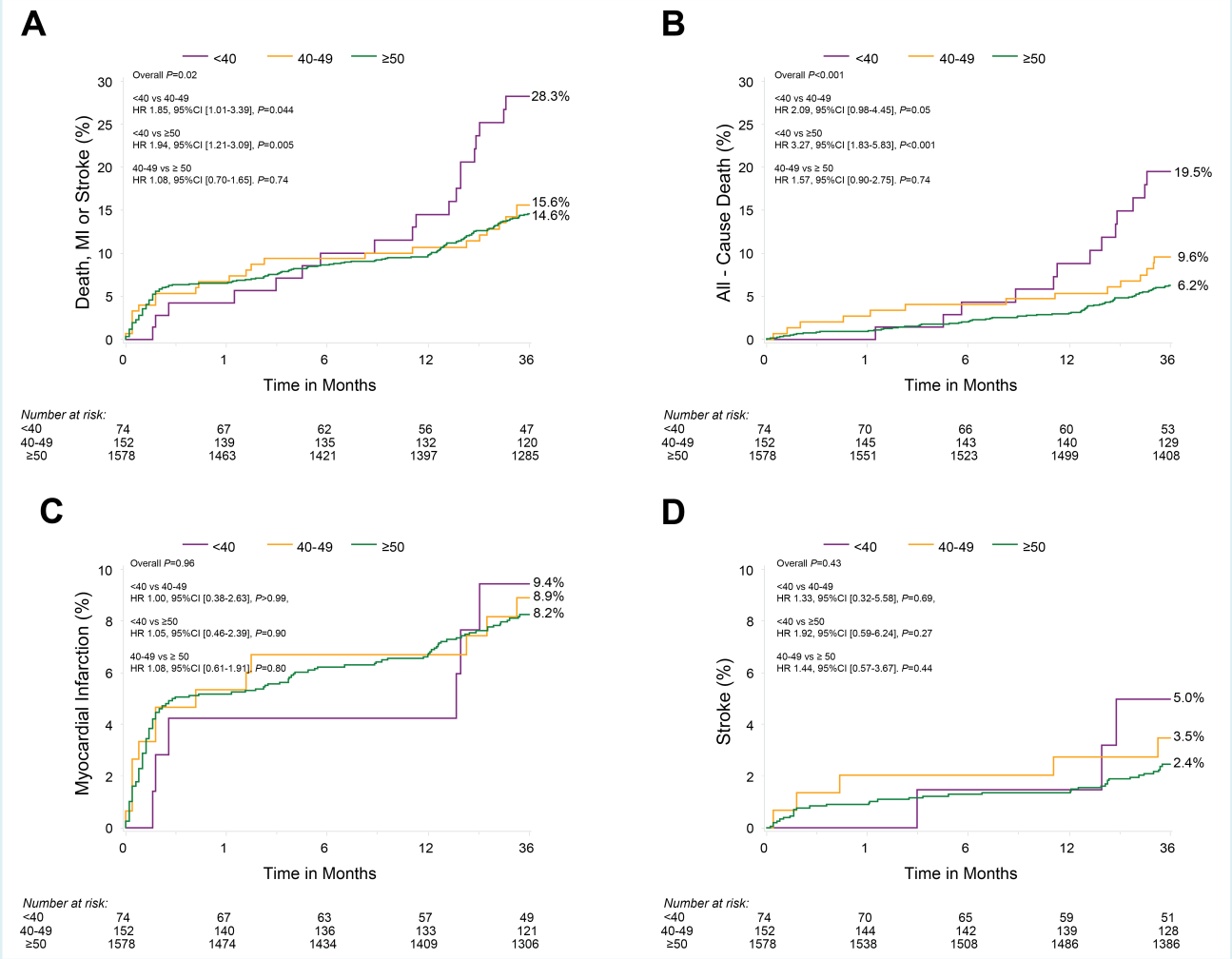

Figure 1 Three-year clinical endpoints in the overall cohort of patients with heart failure with reduced, mid-range and preserved left ventricular ejection fraction. Kaplan–Meier estimates of (*A*) the composite primary endpoint of all-cause death, stroke, or myocardial infarction (MI) and individual components of the composite primary endpoint; all-cause death (*B*), MI (*C*) and stroke (*D*) in pre-specified subgroups of patients with heart failure with reduced, mid-range (orange curve) and preserved left ventricular ejection fraction. *P*-values were generated by the log-rank test. CI, confidence interval; HR, hazard ratio.

0.95–1.39) and CABG (HR 1.90, 95% CI 1.05–3.43). Patients with HFrEF, HFmrEF and preserved LVEF had comparable rates of stroke and MI (*Figure 1C* and *D*).

The rates of the 3-year composite primary endpoint were similar between PCI and CABG across groups of patients with HFrEF (29.3% after PCI vs. 27.6% after CABG: $P = 0.90$), those with HFmrEF (16.2% vs. 15.0%; $P = 0.93$) and preserved LVEF (14.5% vs. 14.6%; $P = 0.95$) (*Table 3* and *Figure 3*). The individual rates of all-cause death, stroke, MI and ischaemia-driven revascularization were not statistically different between PCI and CABG in patients with HFrEF or HFmrEF. Any repeat revascularization occurred more often after PCI vs. CABG in those patients with preserved LVEF (HR 1.68, 95% CI 1.22–2.30), driven by increased rates of ischaemia-driven revascularization. No treatment-by-subgroup interaction existed according to baseline LVEF and revascularization strategy. Adjusted outcomes from the full multivariable adjusted Cox proportional hazard model were similar to unadjusted outcomes (*Table 3*).

Discussion

In the current pre-specified sub-study from the EXEL trial, the largest randomized study to date comparing PCI vs. CABG in selected patients with LMCAD, the composite rate of death, stroke, or MI at 3-year follow-up was significantly higher in patients with impaired (<50%; $n = 74$) vs. preserved LVEF (≥50%; $n = 1730$), driven by an increased rate of all-cause death in those with HFrEF ($n = 74$, LVEF<40%). Mortality furthermore progressively increased with decreasing LVEF. Nonetheless, baseline LVEF did not influence the relative 30-day or 3-year treatment outcomes in patients with LMCAD randomly allocated to PCI vs. CABG. Since data on the influence of HFrEF and HFmrEF on

Table 3 Three-year unadjusted and adjusted clinical outcomes stratified according to left ventricular ejection fraction status and revascularization strategy

Clinical outcomes	PCI frequency, *n* (%)	CABG frequency, *n* (%)	Unadjusted HR (95% CI), *P*-value	$P_{interaction}$	Adjusted HR (95% CI)
Death, stroke or MI					
HFrEF	11 (29.3)	8 (27.6)	1.04 (0.46–2.35), 0.90		1.05 (0.42–2.61)
HFmrEF	11 (16.2)	12 (15.0)	0.96 (0.38–2.38), 0.92	0.90	1.06 (0.40–2.80)
Preserved LVEF	113 (14.6)	113 (14.5)	0.99 (0.76–1.28), 0.89		1.05 (0.79–1.38)
Death, stroke, MI or IDR					
HFrEF	12 (31.9)	9 (31.0)	1.22 (0.59–2.52), 0.82		1.18 (0.53–2.66)
HFmrEF	15 (22.1)	14 (17.4)	0.92 (0.39–2.19), 0.59	0.78	1.03 (0.41–2.56)
Preserved LVEF	173 (22.4)	147 (18.9)	1.18 (0.95–1.47), 0.16		1.24 (0.98–1.56)
All-cause death					
HFrEF	7 (18.6)	6 (20.7)	0.63 (0.21–1.87), 0.78		0.53 (0.16–1.81)
HFmrEF	5 (7.4)	9 (11.5)	0.85 (0.29–2.54), 0.40	0.20	0.77 (0.23–2.55)
Preserved LVEF	57 (7.4)	39 (5.0)	1.47 (0.98–2.20), 0.08		1.50 (0.98–2.31)
Cardiovascular death					
HFrEF	5 (13.5)	5 (17.8)	0.38 (0.08–1.88), 0.62		0.15 (0.02–1.28)
HFmrEF	2 (3.0)	6 (7.8)	0.73 (0.21–2.51), 0.22	0.26	0.70 (0.18–2.81)
Preserved LVEF	29 (3.8)	23 (3.0)	1.27 (0.73–2.19), 0.40		1.40 (0.79–2.48)
Stroke					
HFrEF	2 (5.5)	1 (4.2)	0.75 (0.13–4.49), 0.74		1.43 (0.19–10.69)
HFmrEF	2 (3.0)	3 (3.8)	1.49 (0.13–16.39), 0.77	0.49	-
Preserved LVEF	14 (1.9)	23 (3.0)	0.61 (0.31–1.19), 0.14		0.67 (0.34–1.32)
MI					
HFrEF	3 (8.9)	3 (10.3)	1.00 (0.34–2.97), 0.62		0.95 (0.29–3.19)
HFmrEF	6 (9.0)	7 (8.7)	0.69 (0.14–3.41), 0.99	0.78	1.02 (0.17–6.29)
Preserved LVEF	62 (8.1)	65 (8.4)	0.95 (0.67–1.35), 0.79		0.99 (0.69–1.44)
Repeat revascularization, any					
HFrEF	4 (11.9)	2 (7.5)	2.30 (0.58–9.19), 0.68		1.91 (0.45–8.10)
HFmrEF	6 (9.3)	3 (3.8)	1.43 (0.26–7.82), 0.37	0.96	2.77 (0.31–25.02)
Preserved LVEF	100 (13.2)	61 (8.1)	1.68 (1.22–2.30), 0.001		1.72 (1.23–2.39)
Ischaemia-driven revascularization					
HFrEF	4 (11.9)	2 (7.5)	2.30 (0.57–9.18), 0.68		1.86 (0.44–7.88)
HFmrEF	6 (9.3)	3 (3.8)	1.43 (0.26–7.82), 0.37	0.95	2.82 (0.31–25.56)
Preserved LVEF	98 (12.9)	60 (8.0)	1.67 (1.21–2.30), 0.002		1.72 (1.23–2.40)

CABG, coronary artery bypass grafting; CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IDR, ischaemia-driven revascularization; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
The event rates are Kaplan–Meier estimates (*n* events) with unadjusted and adjusted HR and 95% CI. A full multivariable Cox proportional hazards model using was constructed to provide adjusted outcomes for the primary and secondary endpoints. Significance levels of 0.10 for both addition and removal from the model were used. Adjusted models include the following covariates: age, sex (female), body mass index >30 kg/m^2, medically treated hypertension, hyperlipidaemia and diabetes, history of MI, history of stroke or transient ischaemic attack, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200 μmol/L, recent MI, history of anaemia, diffuse or small vessel disease, LVEF (as continuous variable), unstable angina, SYNTAX score (as continuous variable), New York Heart Association class < II, and revascularization strategy (PCI vs. CABG).

clinical outcomes after PCI and CABG are limited, especially in those patients with left main disease, a strength of the present study is that it provides important insights into clinical outcomes during 3-year follow-up in this high-risk patient population. These insights can aid clinical decision making in determining the optimal treatment strategy in such a specific patient population requiring revascularization.

In the overall cohort, patients with HFrEF or HFmrEF had a significantly more complex cardiovascular risk profile, compared with those with preserved LVEF. The detrimental cardiovascular risk profile especially in patients with HFrEF and LMCAD, in concert with less viable myocardium, likely drives the increased all-cause death rate in this specific subgroup.[12,13] While no significant interactions were noted between clinical outcomes 3 years after PCI and CABG as a function of LVEF, patients with impaired LVEF (HFrEF and HFmrEF) experienced a longer post-operative hospital stay after CABG due to more frequent post-operative arrhythmias and renal failure. In contrast, post-PCI complications and length of stay were not significantly increased in patients with impaired LVEF. The clinical outcomes in patients with HFmrEF were essentially similar to the outcomes in patients with preserved LVEF; findings that contribute to the better understanding of the impact of heart failure and the preferred treatment modalities in those patients with LMCAD and LVEF 40–49% and >50%.[14,15] Moreover,

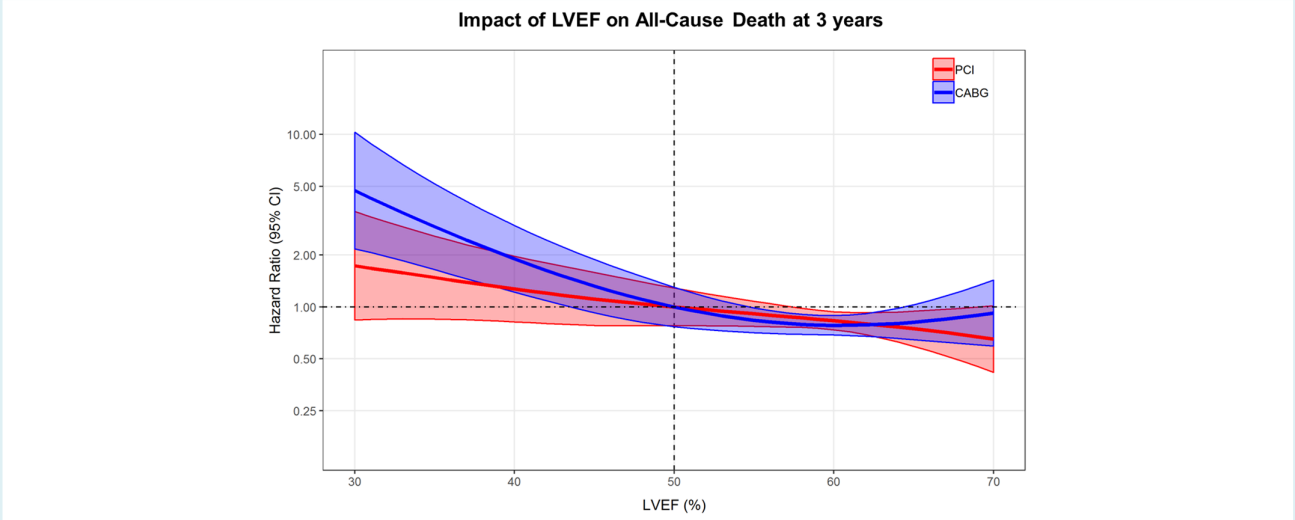

Figure 2 The influence of Left Ventricular Ejection Fraction (LVEF) on all-cause death at 3 years in patients undergoing left main coronary artery revascularization by either Percutaneous Coronary Intervention (PCI) versus Coronary Artery Bypass Grafting (CABG). CI, confidence interval.

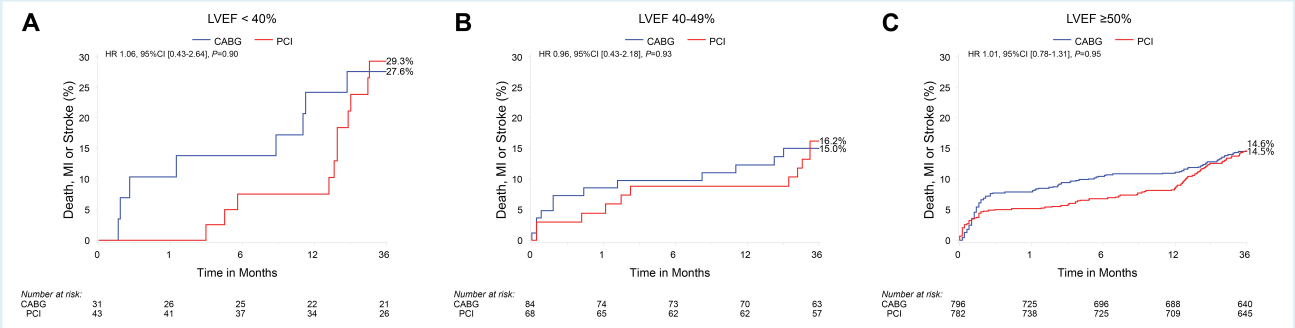

Figure 3 Three-year primary endpoint after percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) in patients with heart failure with reduced, mid-range and preserved left ventricular ejection fraction (LVEF). Kaplan–Meier estimates of the composite primary endpoint of all-cause death, stroke, or myocardial infarction (MI) after PCI vs. CABG in patients with heart failure with reduced (*A*), mid-range (*B*) and preserved LVEF (*C*). *P*-values were generated by the log-rank test. CI, confidence interval; HR, hazard ratio.

all peri-procedural outcomes should be considered along with the potential short- and long-term clinical benefits of both revascularization strategies in patients with impaired LVEF during structured multidisciplinary heart team meetings.

No treatment interactions were observed between PCI and CABG according to baseline LVEF status for 3-year outcomes. Nonetheless, impaired LVEF (<50%) was strongly associated with 3-year all-cause death in the overall cohort. To date, conflicting evidence has been published on the preferred revascularization modality in patients with CAD and impaired LVEF, with limited randomized data to provide guidance. The observational CREDO-Kyoto PCI/CABG Registry Cohort 2 (LVEF ≤50% vs. LVEF >50%) reported that PCI in patients with impaired LVEF was associated with higher rates of all-cause death after 5 years compared to CABG (33.2% vs. 23.4%; $P < 0.01$).[16] The observational, propensity-matched analysis by Nagendran *et al.*[17] ($n = 1738$) showed lower rates of major adverse cardiac and cerebrovascular events and improved 5-year survival with CABG compared with PCI in patients with diabetes and impaired LVEF (35–49% and <35%). Nonetheless, the largest pooled analysis of individual patient-level data from 11 randomized trials found no interaction for mortality between treatment strategy (PCI vs. CABG) and different LVEF cut-off values (<30%, 30–49% and ≥50%; $P_{interaction} = 0.65$).[18]

Finally, in the present study the rate of the composite of death, stroke, or MI at 3 years was significantly higher in patients with HFrEF (28.3%) compared with those patients with HFmrEF (15.7%) or preserved LVEF (14.5%) ($P = 0.02$) (*Figure 1A*). This finding was driven by an increased rate of all-cause death and cardiovascular death in those patients whom are at higher-risk for adverse events (e.g. patients with HFrEF). Moreover, in a smoothing spline analysis, the risk of mortality continued to increase when LVEF decreased

below 50%. Nonetheless, no significant differences in clinical outcomes were found between CABG or PCI in patients with LVEF <40% at 3-year follow-up. The propensity-matched analysis by Shah *et al.*[19] ($n = 134$) reported that patients with coronary artery disease and LVEF <30% experienced an increased risk of mortality when undergoing PCI vs. CABG at 8-year follow-up (multivariable adjusted HR 3.29, 95% CI 1.78–6.10; $P < 0.001$). However, only 32% of patients in the study by Shah *et al.* had LMCAD, with the majority having three-vessel disease. Longer-term follow-up from the EXCEL trial is required to determine if differences in survival between the PCI and CABG groups might emerge over time.

Limitations

Although the present analysis was pre-specified, the number of patients with impaired LVEF was modest, especially those with HFrEF ($n = 74$), limiting statistical interaction testing. Furthermore, the EXCEL trial excluded patients with high site-assessed SYNTAX scores (>32), and thus the present results might not apply to the particularly high-risk group with more complex CAD in whom CABG is considered standard of care. Finally, patient follow-up in the EXCEL trial is prolonged up to 5 years; however, even this follow-up duration may not be long enough to determine a potential benefit of either revascularization strategy.

Conclusions

At 3-year follow-up in the EXCEL trial, the composite rate of death, stroke, or MI was significantly higher in patients with HFrEF compared with HFmrEF or preserved LVEF, driven by an increased rate of all-cause death. No significant differences in clinical outcomes after PCI vs. CABG were observed among patients with HFrEF, HFmrEF and preserved LVEF. Prolonged follow-up could provide important insights on differences in clinical outcomes that might emerge over time.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics according to left ventricular ejection fraction and revascularization assignment

Table S2. Baseline characteristics for those patients with versus without known baseline LVEF

Table S3. Thirty-day clinical outcomes according to left ventricular ejection fraction and revascularization assignment

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