ORIGINAL RESEARCH

Association of Body Mass Index and Extreme Obesity With Long-Term Outcomes Following Percutaneous Coronary Intervention

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***Background*—**Previous studies have reported a protective effect of obesity compared with normal body mass index (BMI) in patients undergoing percutaneous coronary intervention (PCI). However, it is unclear whether this effect extends to the extremely obese. In this large multicenter registry-based study, we sought to examine the relationship between BMI and long-term clinical outcomes following PCI, and in particular to evaluate the association between extreme obesity and long-term survival after PCI.

***Methods and Results*—**This cohort study included 25 413 patients who underwent PCI between January 1, 2005 and June 30, 2017, who were prospectively enrolled in the Melbourne Interventional Group registry. Patients were stratified by World Health Organization–defined BMI categories. The primary end point was National Death Index–linked mortality. The median length of follow-up was 4.4 years (interquartile range 2.0-7.6 years). Of the study cohort, 24.8% had normal BMI (18.5-24.9 kg/m^2), and 3.3% were extremely obese (BMI ≥40 kg/m^2). Patients with greater degrees of obesity were younger and included a higher proportion of diabetics (P<0.001). After adjustment for age and comorbidities, a J-shaped association was observed between different BMI categories and adjusted hazard ratio (HR) for long-term mortality (normal BMI, HR 1.00 [ref]; overweight, HR 0.85, 95% CI 0.78-0.93, P<0.001; mild obesity, HR 0.85, 95% CI 0.76-0.94, P=0.002; moderate obesity, HR 0.95, 95% CI 0.80-1.12, P=0.54; extreme obesity HR 1.33, 95% CI 1.07-1.65, P=0.01).

***Conclusions*—**An obesity paradox is still apparent in contemporary practice, with elevated BMI up to 35 kg/m^2 associated with reduced long-term mortality after PCI. However, this protective effect appears not to extend to patients with extreme obesity. **(*J Am Heart Assoc*. 2019;8:e012860. DOI: 10.1161/JAHA.119.012860.)**

Key Words: long-term outcome • obesity • percutaneous coronary intervention

Obesity is a growing health concern worldwide, particularly in developed countries, where there has been an unprecedented rise in the proportion of overweight and obese individuals in the population.[1,2] Obesity is associated with numerous adverse health outcomes including coronary artery disease, stroke, heart failure, and diabetes mellitus and has also been linked to higher rates of mortality.[3,4] Despite this, several studies in the past have described an "obesity paradox" whereby obesity appears to confer a protective effect compared with normal body mass index (BMI), in a variety of medical conditions.[5–9] This was also described in the setting of percutaneous coronary intervention (PCI), where overweight and obese patients were shown to have lower rates of short-term mortality compared with normal-BMI individuals.[10–12] A meta-analysis of over 200 000 patients with myocardial infarction also reported that obese patients have a 30% to 40% lower mortality compared with individuals with normal BMI over a 1- to 3-year follow-up period.[13]

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012860

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Clinical Perspective

What Is New?

- This study shows that the obesity paradox persists in contemporary percutaneous coronary intervention practice, whereby overweight and obese patients have better post–percutaneous coronary intervention long-term survival than those with normal body mass index.
- However, our study demonstrates that this protective effect does not extend to patients with extreme obesity.

What Are the Clinical Implications?

- Our study demonstrates that there is a threshold effect to the obesity paradox, which is important for clinicians to recognize when risk-stratifying patients.
- We also show that patients with normal body mass index are less likely to receive appropriate secondary prevention therapy compared with their higher body mass index counterparts.
- More attention needs to be paid to reducing this treatment gap in clinical practice, which may help improve outcomes in patients with normal body mass index.

However, more recent studies in patients in the contemporary era of PCI have produced conflicting results.[14–18] In particular, despite extreme obesity (BMI≥40 kg/m^2) increasing in prevalence among patients undergoing PCI, few studies have examined long-term clinical outcomes in this group.[19,20] Studies examining in-hospital mortality of patients undergoing PCI have suggested that although lesser degrees of obesity may be protective, this effect does not extend to patients with extreme obesity.[12,19] However, very few earlier studies have assessed mortality rates beyond 12 months in patients with extreme obesity undergoing PCI for both stable angina and acute coronary syndromes.

In this study we therefore sought to determine whether an obesity paradox persists in contemporary PCI practice over long-term follow-up and, in particular, to further evaluate the association between extreme obesity and long-term clinical outcomes after PCI.

Methods

Due to the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Ms Angela Brennan of Monash University at angela.brennan@monash.edu.

This was a cohort study of patients undergoing PCI between January 1, 2005 and June 30, 2017 inclusive, enrolled prospectively in the MIG (Melbourne Interventional Group) registry. All consecutive adult patients undergoing PCI were eligible for inclusion. We excluded patients in whom height and/or weight was not recorded at the time of PCI, and therefore BMI could not be calculated. Patients who could not be considered for linkage to the Australian NDI (National Death Index) mortality database due to incomplete case information at the time the registry data were sent for linkage were also excluded (n=267).

For all patients included in this study, BMI was calculated by dividing weight (in kilograms) by the square of the height (in meters). Patients were classified into the following 6 groups by their BMI as per the World Health Organization Classification System: underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), class I obese (BMI 30-34.9 kg/m^2), class II obese (BMI 35-39.9 kg/m^2), and class III obese (BMI≥40 kg/m^2).[21] However, due to the very small sample size in the underweight group (n=232), which is likely to make comparisons with the other groups imprecise, these patients were excluded in deriving our final study cohort.

The MIG registry is a multicenter Australian PCI registry that collects data from 6 participating hospitals, 4 of which are located in metropolitan Melbourne, and 2 hospitals are located in large regional centers.[22] Baseline demographic, clinical, procedural, and in-hospital outcome data are prospectively recorded on case-report forms using standardized definitions for all fields (Table S1). Relevant information for 30-day outcomes was obtained through telephone follow-up with further review of medical records performed in patients who reported any events.[23] In addition, mortality data were obtained by linkage to the Australian NDI, a database housed at the Australian Institute of Health and Welfare that contains records of all deaths occurring in Australia since 1980. The censoring date for linkage with the NDI in this study was August 1, 2017. Successful matching of patients through this linkage process was achieved in 99.0% of all patients in the study cohort. The MIG registry has an "opt-out" consent process as previously described and has been granted ethics approval by the ethics committee at The Alfred Hospital (approval number 92/04) as well as by committees at each participating hospital.[22,23]

Baseline and procedural characteristics, as well as in-hospital and 30-day outcomes, were compared among the groups. The primary end point was NDI-linked long-term mortality. Secondary end points included death (all-cause mortality and cardiac mortality), myocardial infarction, target vessel revascularization and major adverse cardiovascular events at 30-day follow-up. Major adverse cardiovascular events were defined as a composite of death, myocardial infarction, and target vessel revascularization. Major bleeding was defined as a fall in hemoglobin by >3.0 g/dL and/or requiring transfusion. Use of antiplatelet

therapy, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and cholesterol-lowering therapies (statins, fibrates, and ezetimibe) at 30 days after the index PCI was also compared among the groups. Prescription of postdischarge medications was at the discretion of the treating physician according to contemporary guidelines.

Continuous variables are expressed as mean±SD and were compared using a Kruskal-Wallis equality-of-populations rank test. Categorical data are expressed as numbers and percentages and compared using the Pearson chi-squared test or Fisher exact test as appropriate. The Kaplan-Meier method was used to estimate post-PCI survival rates, and the log-rank test was used for survival comparisons. Cox proportional hazard modeling was used to identify independent predictors of the primary end point of NDI-linked long-term mortality. In this model in addition to BMI group, 28 other clinically relevant variables such as sex, cardiovascular risk

Table 1. Baseline Characteristics

	BMI 18.5 to 24.9 kg/m^2	BMI 25.0 to 29.9 kg/m^2	BMI 30.0 to 34.9 kg/m^2	BMI 35.0 to 39.9 kg/m^2	BMI ≥40 kg/m^2	*P* for Trend
N (%)	6305 (24.6)	10 608 (41.4)	5780 (22.5)	1874 (7.3)	846 (3.3)	
Mean age±SD, y	67.0±12.4	64.4±11.8	62.7±11.6	61.0±10.7	59.2±10.7	<0.001
Age >80 years	966 (15.3)	944 (8.9)	340 (5.9)	56 (3.0)	19 (2.3)	<0.001
Female	1664 (26.4)	1967 (18.5)	1281 (22.2)	586 (31.3)	354 (41.8)	<0.001
Diabetes mellitus	1022 (16.2)	2419 (22.8)	1735 (30.0)	784 (41.8)	381 (45.0)	<0.001
Hypertension	3731 (59.2)	6848 (64.6)	4233 (73.3)	1475 (78.8)	675 (79.8)	<0.001
Dyslipidemia	3836 (61.0)	7081 (66.9)	4140 (71.6)	1385 (74.0)	611 (72.4)	<0.001
Current or past smoker	4016 (64.7)	6975 (66.7)	4001 (70.5)	1262 (68.4)	585 (70.1)	<0.001
Family history of coronary artery disease	2096 (34.7)	3939 (38.9)	2236 (40.6)	726 (40.7)	370 (46.1)	<0.001
eGFR >60 mL/min per 1.73 m^2	4594 (75.9)	8019 (79.0)	4346 (77.7)	1400 (77.7)	602 (74.1)	0.694
eGFR 30 to 60 mL/min per 1.73 m^2	1242 (20.5)	1864 (18.4)	1108 (19.8)	355 (19.7)	181 (22.3)	
eGFR <30 mL/min per 1.73 m^2	216 (3.6)	262 (2.6)	143 (2.6)	48 (2.7)	30 (3.7)	
Chronic obstructive pulmonary disease	505 (8.0)	545 (5.1)	341 (5.9)	109 (5.8)	53 (6.3)	<0.001
Obstructive sleep apnea	98 (1.6)	305 (2.9)	366 (6.3)	245 (13.1)	175 (20.7)	<0.001
Peripheral vascular disease	439 (7.0)	547 (5.2)	347 (6.0)	109 (5.8)	36 (4.3)	0.007
Previous stroke	427 (6.8)	547 (5.2)	320 (5.5)	108 (5.8)	51 (6.0)	0.072
Previous myocardial infarction	1563 (24.8)	2717 (25.6)	1600 (27.7)	535 (28.6)	236 (28.0)	<0.001
Previous percutaneous coronary intervention	1543 (24.5)	2734 (25.8)	1610 (27.9)	533 (28.4)	227 (26.8)	<0.001
Previous coronary artery bypass graft surgery	457 (7.3)	880 (8.3)	488 (8.4)	179 (9.6)	49 (5.8)	0.107
Clinical presentation						
Stable angina	1832 (29.1)	3597 (33.9)	2075 (35.9)	708 (37.8)	264 (31.2)	<0.001
Unstable angina	513 (8.1)	870 (8.2)	448 (7.8)	163 (8.7)	66 (7.8)	0.856
NSTEMI	1778 (28.2)	2821 (26.6)	1700 (29.4)	569 (30.4)	291 (34.4)	<0.001
STEMI	2180 (34.6)	3318 (31.3)	1554 (26.9)	434 (23.2)	224 (26.5)	<0.001
Cardiogenic shock	257 (4.1)	286 (2.7)	145 (2.5)	32 (1.7)	21 (2.5)	<0.001
Out-of-hospital cardiac arrest	200 (3.2)	315 (3.0)	148 (2.6)	38 (2.0)	18 (2.1)	0.001
Mean LV ejection fraction±SD	52.2±11.0	52.8±10.4	53.2±9.9	53.4±9.8	53.5±9.9	<0.001
LV ejection fraction <30%	130 (2.3)	157 (1.7)	62 (1.2)	22 (1.4)	8 (1.1)	<0.001
LV ejection fraction 30% to 45%	1295 (2.3)	157 (1.7)	62 (1.2)	22 (1.4)	8 (1.1)	
LV ejection fraction >45%	4236 (74.8)	7318 (77.8)	4001 (79.5)	1289 (80.9)	598 (81.7)	

Data expressed as mean±SD or numbers (%).
BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LV, left ventricular; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 2. Procedural Characteristics

	BMI 18.5 to 24.9 kg/m^2	BMI 25.0 to 29.9 kg/m^2	BMI 30.0 to 34.9 kg/m^2	BMI 35.0 to 39.9 kg/m^2	BMI ≥40 kg/m^2	*P* for Trend
Lesion characteristics						
Multivessel disease	3712 (59.0)	6248 (59.0)	3383 (58.6)	1085 (58.1)	461 (54.6)	0.054
Left main lesion	89 (1.2)	135 (1.1)	76 (1.1)	22 (1.0)	7 (0.7)	0.243
Chronic total occlusion lesion	229 (3.1)	480 (3.8)	269 (4.0)	98 (4.5)	37 (3.7)	0.003
ACC/AHA type B2/C lesion	4221 (56.2)	7075 (56.2)	3804 (56.1)	1304 (59.2)	566 (56.3)	0.206
Procedural details						
Radial access	1434 (22.7)	2675 (25.2)	1594 (27.6)	549 (29.3)	290 (34.3)	<0.001
Femoral access	4871 (77.3)	7932 (74.8)	4186 (72.4)	1325 (70.7)	556 (65.7)	
Arterial access closure device used	645 (10.2)	1123 (10.6)	587 (10.2)	223 (11.9)	121 (14.3)	0.004
Balloon angioplasty only	411 (6.5)	657 (6.2)	410 (7.1)	130 (6.9)	56 (6.6)	0.001
Bare metal stent	2471 (39.2)	4035 (38.0)	2089 (36.1)	628 (33.5)	308 (36.4)	
Drug-eluting stent	3423 (54.3)	5916 (55.8)	3281 (56.8))	1116 (59.6)	482 (57.0)	
Intra-aortic balloon pump use	136 (2.2)	177 (1.7)	82 (1.4)	17 (0.9)	9 (1.1)	<0.001
Thrombectomy device used	520 (8.0)	884 (8.0)	406 (6.8)	105 (5.4)	49 (5.4)	<0.001
Glycoprotein IIb/IIIa inhibitors	1854 (29.4)	2991 (28.2)	1441 (25.0)	431 (23.0)	197 (23.3)	<0.001
Complications						
Dissection	339 (4.5)	533 (4.2)	265 (3.9)	84 (3.8)	32 (3.2)	0.004
Perforation	24 (0.3)	39 (0.3)	12 (0.2)	5 (0.2)	0 (0.0)	0.011
Transient/persistent no-reflow	280 (3.9)	350 (2.9)	200 (3.1)	58 (2.7)	32 (3.3)	0.019
Unsuccessful PCI	334 (5.3)	514 (4.9)	310 (5.4)	102 (5.4)	48 (5.7)	0.440

Data expressed as mean±SD, or numbers (%).
ACC/AHA indicates American College of Cardiology/American Heart Association; BMI, body mass index; PCI, percutaneous coronary intervention.

factors including diabetes mellitus, hypertension, and renal impairment, history of previous myocardial infarction and/or previous stroke, disease extent on angiography, and type of stent used were considered. Aside from the BMI group, only variables with a $P<0.10$ on univariate analysis that were not collinear were entered into a stepwise backward selection modeling process for multivariable assessment. Complete case analysis was performed for purposes of multivariable modeling (ie, patients with missing values were excluded). The proportion of missing variables was <1% for all variables except smoking status (1.6%), estimated glomerular filtration rate (3.9%), family history of coronary artery disease (4.5%), 30-day medications (7.3%), and left ventricular ejection fraction (11.7%).

All statistical analyses were performed using Stata 13.1 software (StataCorp LP, College Station, TX). $P<0.05$ was considered to be statistically significant.

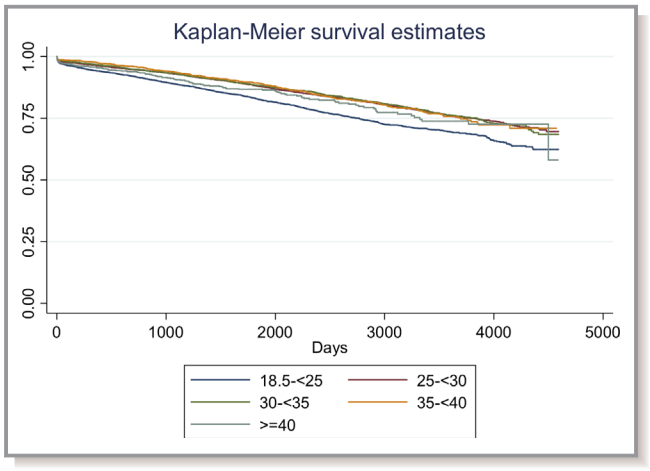

Figure 1. Kaplan-Meier curves of long-term survival by body mass index group.

Results

In total, 25 413 patients were included in this analysis. Of these, 6305 (24.6%) were in the normal BMI category, 10 608 (41.4%) were overweight, 5780 (22.5%) had mild (class I) obesity, 1874 (7.3%) had moderate (class II) obesity, and 846 (3.3%) had extreme (class III) obesity. The mean age of the whole study cohort was 64.2±12.0 years, and 23.0% were female.

Baseline Characteristics

Table 1 shows the baseline characteristics of the study cohort stratified by BMI groups. With increasing BMI, patients were younger and had more cardiovascular risk factors such as diabetes mellitus (all $P<0.001$). The proportion of women was highest at both extremes of BMI and lowest in the overweight group. With increasing BMI, the proportion of patients who presented with non–ST-elevation acute coronary syndromes increased, whereas the proportion of patients who presented with ST-elevation myocardial infarction, out-of-hospital cardiac arrest, and cardiogenic shock decreased ($P\leq0.001$).

Procedual characteristics are shown in Table 2. As BMI increased, there was more radial access and less femoral access use ($P<0.001$). There were no significant differences in extent of coronary artery disease or lesion complexity by BMI group. Drug-eluting stents were more frequently implanted in the higher BMI groups ($P<0.001$). Procedural complications such as coronary dissection and perforation were overall infrequent, but less common in the higher BMI groups (both $P<0.04$), although the overall proportion of unsuccessful PCIs was similar across the BMI groups ($P=0.440$). There was also a reduction in the proportion of patients with severe left ventricular systolic dysfunction (left ventricular ejection fraction <30%) at the time of PCI, with increasing BMI ($P<0.001$).

Clinical Outcomes

In-hospital and 30-day outcomes are shown in Table 3. A 30-day follow-up was completed in 99.6% of the study cohort. There was a J-shaped association between BMI and both in-hospital and 30-day mortality, with a steady fall in mortality from the normal BMI group to the moderate obesity group, followed by a substantial rise in mortality in the extreme obesity group ($P<0.001$). A similar pattern of association was also seen with in-hospital and 30-day major adverse cardiovascular events. With increasing BMI, there was a significant stepwise reduction in in-hospital bleeding ($P<0.001$). There were no significant differences in 30-day readmission rates across the BMI groups.

All-cause mortality data beyond 30 days were obtained using linkage with the NDI database. Median length of follow-up was 4.4 years (IQR 2.0-7.6 years) overall and similar in all the

Table 3. Clinical Outcomes

	BMI 18.5 to 24.9 kg/m^2	BMI 25.0 to 29.9 kg/m^2	BMI 30.0 to 34.9 kg/m^2	BMI 35.0 to 39.9 kg/m^2	BMI ≥40 kg/m^2	*P* for Trend
In-hospital outcomes						
Death	142 (2.3)	175 (1.6)	74 (1.3)	20 (1.1)	16 (1.9)	<0.001
Cardiac death	113 (1.8)	144 (1.4)	58 (1.0)	18 (1.0)	11 (1.3)	0.799
Periprocedural myocardial infarction	76 (1.2)	113 (1.1)	60 (1.0)	20 (1.1)	6 (0.7)	0.208
Heart failure	263 (4.2)	357 (3.4)	188 (3.3)	52 (2.8)	38 (4.5)	0.041
Acute kidney injury	111 (1.8)	191 (1.8)	87 (1.5)	21 (1.1)	23 (2.7)	0.591
Major bleeding	208 (3.3)	196 (1.9)	107 (1.9)	24 (1.3)	10 (1.2)	<0.001
Stroke	24 (0.4)	22 (0.2)	22 (0.4)	4 (0.2)	1 (0.1)	0.380
Target vessel revascularization	77 (1.2)	115 (1.1)	69 (1.2)	19 (1.0)	11 (1.3)	0.931
MACE	265 (4.2)	374 (3.5)	181 (3.1)	58 (3.1)	31 (3.7)	0.007
30-day outcomes						
Death	177 (2.8)	211 (2.0)	95 (1.7)	24 (1.3)	21 (2.5)	<0.001
Cardiac death	133 (2.1)	161 (1.5)	71 (1.2)	21 (1.1)	13 (1.5)	0.774
Myocardial infarction	129 (2.1)	175 (1.7)	104 (1.8)	30 (1.6)	8 (1.0)	0.045
Stroke	38 (0.6)	33 (0.3)	25 (0.4)	8 (0.4)	1 (0.1)	0.084
Target vessel revascularization	146 (2.3)	234 (2.2)	133 (2.3)	52 (2.8)	20 (2.4)	0.452
Any readmission	751 (12.3)	1084 (10.5)	653 (11.6)	219 (12.0)	93 (11.3)	0.610
MACE	375 (6.0)	527 (5.0)	276 (4.8)	88 (4.7)	42 (5.0)	0.008
NDI-linked mortality						
No. of deaths	1195 (19.2)	1423 (13.5)	751 (13.1)	225 (12.2)	118 (14.1)	<0.001
Median follow-up time (IQR), y	4.4 (2.0-7.5)	4.5 (2.0-7.7)	4.4 (2.0-7.6)	4.1 (2.0-7.0)	3.9 (1.5-6.9)	0.047

Data expressed as median (IQR) or numbers (%). BMI indicates body mass index; IQR, interquartile range; MACE, major adverse cardiovascular events; NDI, national death index.

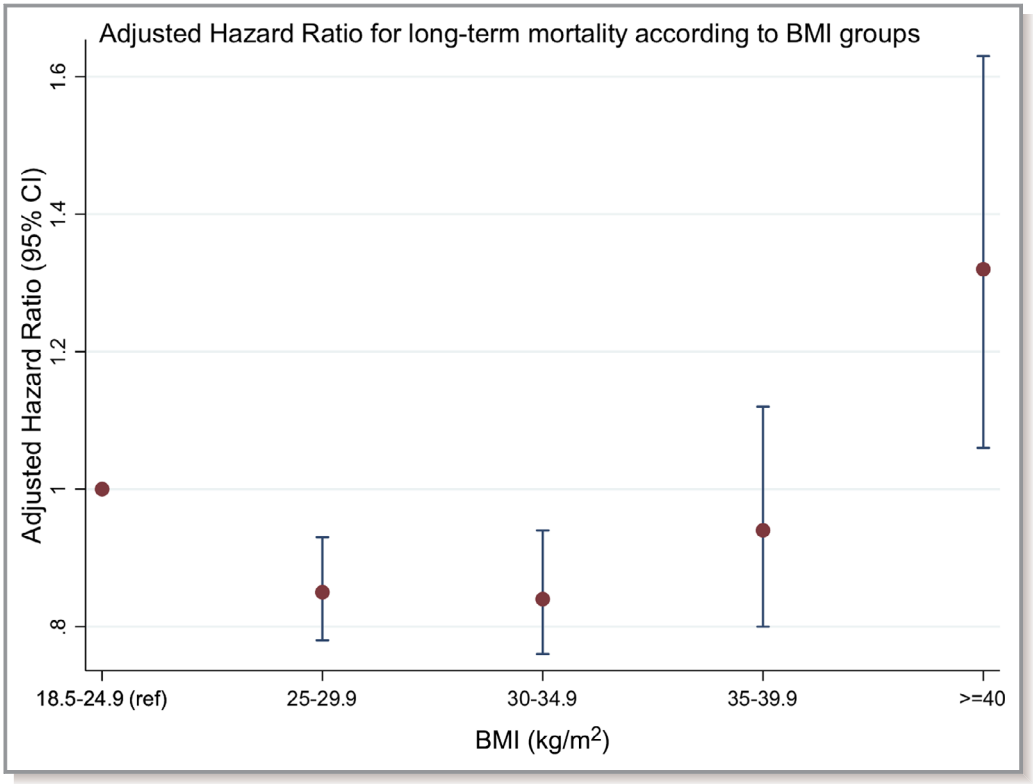

Figure 2. Adjusted hazard ratios for NDI-linked mortality according to body mass index groups. BMI indicates body mass index; NDI, National Death Index.

groups (P=0.047). Patients with moderate obesity had the lowest mortality rate (12.2%), whereas patients both with normal BMI and extreme obesity were found to have a higher mortality rate (19.2% and 14.1% respectively). The Kaplan-Meier survival curves for the 5 BMI groups are shown in Figure 1, and they confirm that patients with extreme obesity had significantly lower long-term survival, compared to the other groups (log rank P<0.001). Using Cox-proportional hazards modelling with the normal BMI group as the reference category, a J-shaped association between BMI and adjusted hazard ratio for NDI-linked long-term mortality was observed (Figure 2). The adjusted hazard ratio (HR) was highest for patients with extreme obesity (HR 1.33, 95% CI 1.07-1.65). Being overweight and having mild obesity both appeared to be protective for long-term NDI-linked mortality, with the latter group having the lowest adjusted hazard ratio. The 3 strongest independent predictors of NDI-linked long-term mortality were stage 4 to 5 chronic kidney disease, cardiogenic shock, and severe left ventricular systolic dysfunction (HR 3.46, 2.98 and 2.50 respectively; all P<0.001) (Table 4).

Secondary Prevention Therapy

At 30 days post PCI, there were no significant differences in use of aspirin, a second antiplatelet agent, or statins across the BMI groups (all P>0.05) (Table 5). However, patients with normal BMI were significantly less likely to receive a β-blocker or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker compared with the other BMI groups (P=0.003 and P<0.001 respectively).

Discussion

In this large, multicenter study evaluating the relationship between BMI and long-term mortality in patients undergoing PCI, we observed a J-shaped association between different BMI groups and adjusted mortality risk, with patients at the extremes of BMI experiencing the highest risk. Although an obesity paradox was present with underweight patients having the highest mortality out of all of the groups, it only extended as far as patients with mild obesity. Therefore, patients with extreme obesity remain at significantly increased risk of long-term mortality compared with their healthy weight and less obese counterparts.

The results of our study provide important additional insights to the literature regarding outcomes after PCI in patients with varying BMI. Our results are in accordance with several large studies that have demonstrated a similar association between in-hospital mortality and BMI group.[12,17,19] A feature of our study is that very few earlier studies have assessed mortality rates beyond 12 months in extremely obese patients undergoing PCI for both stable

Table 4. Multi-Variable Cox-Proportional Hazards Modeling for NDI-Linked Mortality

	Hazard Ratio	95% CI	*P* Value
eGFR			
eGFR >60 mL/min per 1.73 m^2	1 (ref)		
eGFR 30 to 60 mL/min per 1.73 m^2	1.45	1.33 to 1.58	<0.001
eGFR <30 mL/min per 1.73 m^2	3.46	3.03 to 3.95	<0.001
Cardiogenic shock	2.98	2.57 to 3.44	<0.001
Left ventricular ejection fraction			
Left ventricular ejection fraction >45%	1 (ref)		
Left ventricular ejection fraction 30% to 45%	1.57	1.44 to 1.70	<0.001
Left ventricular ejection fraction <30%	2.50	2.12 to 2.94	<0.001
Chronic obstructive airways disease	2.11	1.90 to 2.34	<0.001
Out-of-hospital cardiac arrest	1.76	1.47 to 2.10	<0.001
BMI category			
BMI 18.5 to 24.9 kg/m^2	1 (ref)		
BMI 25.0 to 29.9 kg/m^2	0.85	0.78 to 0.93	<0.001
BMI 30.0 to 34.9 kg/m^2	0.85	0.76 to 0.94	0.002
BMI 35.0 to 39.9 kg/m^2	0.95	0.80 to 1.12	0.543
BMI ≥40.0 kg/m^2	1.33	1.07 to 1.65	0.010
Diabetes mellitus	1.45	1.34 to 1.57	<0.001
Peripheral vascular disease	1.44	1.29 to 1.60	<0.001
Obstructive sleep apnea	1.39	1.19 to 1.63	<0.001
Previous coronary artery bypass graft surgery	1.37	1.17 to 1.60	<0.001
Previous stroke	1.35	1.21 to 1.51	<0.001
Left main disease	1.31	1.04 to 1.64	0.023
Multivessel disease	1.25	1.16 to 1.36	<0.001
Previous myocardial infarction	1.19	1.10 to 1.30	<0.001
Hypertension	1.11	1.01 to 1.22	0.034
Age (per year increase)	1.06	1.05 to 1.06	<0.001
Drug-eluting stent use	0.79	0.73 to 0.85	<0.001

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; NDI, National Death Index.

angina and acute coronary syndromes. Holroyd et al evaluated mortality up to 5 years after PCI in over 300 000 patients and also found that patients who were overweight and obese (BMI >30 kg/m^2) had reduced mortality risk up to 5 years compared with those with normal BMI.[16] However, the authors did not further subdivide obese patients further into degrees of obesity, and therefore no conclusions can be made as to whether extreme obesity remains protective. Interestingly, a subgroup analysis on 15 603 patients who underwent PCI and were enrolled in the Canadian APPROACH registry with a median follow-up of 46 months showed that whereas underweight patients had the highest adjusted mortality risk and moderate obesity was protective, those with extreme obesity had very similar adjusted mortality risk to their normal weight counterparts.[20] It is however difficult to make comparisons with our study to understand reasons behind this difference in outcomes as baseline or procedural characteristics of the PCI subgroup were not presented separately, and medication use data were only available for 12% of the whole cohort (including those not treated with PCI). However, a similar neutral effect of severe obesity (defined as BMI ≥35 kg/m^2) compared with normal weight on cardiovascular mortality risk after percutaneous or surgical revascularization was also seen in a recent meta-analysis by Sharma et al, suggesting that further large studies in this area are required.[24]

Several possible mechanisms for the obesity paradox have been postulated. In accordance with previous studies, our data show that there was a linear relationship between BMI and the prevalence of comorbidities such as diabetes mellitus, hypertension, and dyslipidemia. However, patients with higher BMI may be more likely to have been screened earlier and aggressively treated for these cardiovascular risk factors, thereby leading to better long-term outcomes despite obesity.[25] Overweight and mild-to-moderately obese patients were also less likely to present with cardiogenic shock and post–out-of-hospital cardiac arrest, factors that are usually associated with poorer outcomes.[26,27] Similar to other studies, in-hospital major bleeding complications were also lower in overweight and obese patients, which is likely at least in part due to the increased use of radial access in these patients.[16] Excess dosing of anticoagulant and antiplatelet drugs is also potentially less likely to occur in more obese patients, which may also reduce their bleeding risk. Bleeding has been shown to be independently associated with worse short- and long-term mortality and therefore may explain our results to some extent.[28]

In our study we also found that increased BMI up to the level of moderate obesity was associated with an increased use of guideline-based medical therapy, in particular β-blockers, renin-angiotensin-system blockers, and statins. Previous studies have shown that increased use of evidence-based cardiovascular medications is associated with lower long-term mortality after PCI.[29] Nonpharmacological measures such as smoking cessation, dietary counseling, and cardiac rehabilitation referral have been shown to be employed more frequently in overweight and obese patients

Table 5. Medication Use at 30-Day Follow-Up

	BMI 18.5 to 24.9 kg/m^2	BMI 25.0 to 29.9 kg/m^2	BMI 30.0 to 34.9 kg/m^2	BMI 35.0 to 39.9 kg/m^2	BMI ≥40 kg/m^2	*P* for Trend
Aspirin	5688 (97.7)	9690 (97.4)	5299 (97.6)	1733 (98.1)	758 (96.3)	0.628
Clopidogrel/prasugrel/ticagrelor	5592 (96.1)	9590 (96.4)	5188 (95.5)	1688 (95.6)	751 (95.6)	0.045
β-Blocker	4494 (77.7)	7827 (79.2)	4295 (80.0)	1410 (80.5)	617 (79.4)	0.003
ACEi/ARB	4340 (75.0)	7792 (78.8)	4424 (82.2)	1491 (85.1)	647 (83.3)	<0.001
Statin	5450 (94.2)	9403 (95.1)	5096 (94.5)	1673 (95.3)	747 (95.5)	0.119

Data expressed as numbers (%). ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index.

as well, which could also account for the improved outcomes.[30,31]

With an increase in the proportion of overweight and obese individuals in the general population as well as in those undergoing PCI, it has also been proposed that the worse prognosis observed in patients with normal BMI may be due to the effect of residual confounding.[17,19] Given that 67% of the Australian population are overweight or obese, even having a normal BMI may potentially reflect the presence of unmeasured serious comorbidities that carry substantial mortality hazard.[32] Previous studies have indeed shown that patients with low BMI have higher rates of noncardiac mortality.[33,34] In our study we also observed an inverse relationship between BMI and the presence of comorbidities such as chronic obstructive pulmonary disease and peripheral vascular disease. However, we were unable to account for the prevalence of serious conditions such as cancer, dementia, malnutrition, and overall measures of frailty, which could explain the higher mortality in patients even with normal BMI.[35]

Finally, there is also evidence that adipose tissue may itself have potentially cardioprotective effects by producing hormones such as leptin and adiponectin.[36] These hormones have anti-inflammatory and antiapoptotic properties and might reduce infarct size.[37,38] Obesity-inducing high-fat diets in rats have also been shown to be cardioprotective.[39] Obesity may also be protective against malnutrition following a major cardiac event or procedure.[40] However, the increase in mortality seen in patients with extreme, class III obesity suggests that there is likely a threshold effect. Therefore, as BMI increases to over 40 kg/m^2, the protective effects of milder degrees of obesity may be abrogated by the deleterious effects of extreme obesity including alterations in cardiac structure and function, potentiation of an inflammatory and prothrombotic state, and increased noncardiovascular mortality.[41-43] This may explain why the obesity paradox did not extend to the extremely obese in several studies including ours.[17,44]

Limitations

Our study has several limitations. First, due to the retrospective design of this study, we were unable to account for all potential confounding factors such as socioeconomic status, noncardiac comorbidities such as cancer, as well as measures of frailty, which can all potentially affect post-PCI short- and long-term mortality. Second, BMI measured at the time of PCI might not necessarily reflect BMI at the time of linkage with the NDI, which was on average 4 years after the index PCI procedure. It is also not known how dynamic weight changes might impact clinical outcomes among patients whose weight had changed between the index PCI and the time of NDI linkage. Third, we did not capture measures of central adiposity such as waist circumference and waist-to-hip ratio, which have been shown to be better predictors of cardiovascular outcomes than BMI alone.[45,46] However, BMI is the measurement used and endorsed by the World Health Organization to classify obesity worldwide given its simple and easily quantifiable nature, and it was therefore chosen for this study. Finally, we did not have data on the use of guideline-recommended secondary prevention therapy beyond 30 days after PCI, which might also have explained some of the differences in mortality among BMI groups.[40]

Conclusions

In conclusion, there remains an obesity paradox with regard to long-term mortality in patients undergoing PCI in contemporary practice, with mildly obese patients having the lowest adjusted mortality hazard. However, this protective effect does not extend to patients with extreme obesity. Factors behind this phenomenon are likely multifactorial and require further mechanistic and epidemiological studies.

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Supplemental Material

Table S1. Data dictionary for variables in Melbourne Interventional Group Registry.

Variable	Definition
Baseline characteristics	
Body mass index	Calculated from weight (in kilograms in light clothing) and height (in metres in bare feet), using formula: weight / height^2
Diabetes mellitus	Documented history of diabetes regardless of duration of disease or need for anti-diabetic agents
Hypertension	Must have one of the following documented findings - History of hypertension diagnosed and treated with medication, diet and/or exercise. - Blood pressure >140 systolic or >90 diastolic on at least 2 occasions. - Currently on antihypertensive medication.
Dyslipidemia	Must have one of the following documented findings - History of dyslipidemia diagnosed and/or treated by a physician.

	- Cholesterol > 5.0 mmol/L, HDL < 1.0mmol/L or Triglycerides > 2.0mmol/L.
Smoking status	History confirming any form of tobacco use in the past. This includes cigarettes, cigar and/or pipe. Choose from: - Currently smoking - within 1 month of this admission - Previously smoked - more than 1 month prior to this admission - Never smoked
Family history of coronary artery disease	Any first-degree relatives of the patient (parents, siblings, children) who have any of the following at age <60 years: - Coronary artery disease (angina, previous CABG or PCI) - MI - Sudden cardiac death without an obvious cause
Estimated glomerular filtration rate	Calculated using Cockroft-Gault formula using last serum creatinine level recorded prior to the current PCI

Chronic obstructive pulmonary disease	Documented history of chronic obstructive pulmonary disease - a slowly progressive disease that is characterized by a gradual loss of lung function. Includes chronic bronchitis, chronic obstructive bronchitis, or emphysema, or combinations of these conditions. Diagnosis of COPD is confirmed by the presence of airway obstruction on testing with spirometry.
Obstructive sleep apnea	Patient reports knowledge of, or has previously been diagnosed with obstructive sleep apnoea
Peripheral vascular disease	Evidence of either chronic or acute PVD. The presence of PVD must be demonstrated by vascular reconstruction or amputation for arterial insufficiency, bypass surgery or percutaneous intervention.
Previous stroke	History of stroke or cerebrovascular accident (CVA), resulting from an ischaemic or intracerebral haemorrhagic event ONLY where the patient suffered a loss of neurological function with residual symptoms remaining for at least 72 hours
Previous myocardial infarct (MI)	At least one documented MI greater than 7 days prior to admission. An MI is evidenced by any of the following.

	1. A rise and fall of cardiac biomarkers (Troponin, CK or CK-MB) with at least one value in an abnormal range for that laboratory above the upper reference limit (URL) of normal (i.e. above the 99th percentile of the URL measured with a coefficient of variation ≤10%). In partnership with at least one of the following manifestations of myocardial ischemia. a. Ischemic symptoms. b. ECG changes indicative of new ischemia (new ST-T changes, new left bundle branch block (LBBB) or loss of R wave voltage. c. Development of pathological Q waves in two or more contiguous leads on the ECG (or equivalent findings for true posterior MI) d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

	e. Documentation in the medical record of the diagnosis of acute myocardial infarction based on the cardiac biomarker pattern in the absence of any items enumerated in a-d due to conditions that may mask their appearance (e.g. peri-operative infarct when the patient cannot report ischemic symptoms, baseline LBBB or ventricular pacing). 2. ECG changes associated with prior MI can include the following (with or without prior symptoms): a. Any Q wave in leads V2-V3 ≥ 0.02sec or QS complex in leads V2 & V3. b. Q wave ≥ 0.03 sec & ≥ 0.1mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF). c. R-wave ≥ 0.04 sec in V1-V2 and R/S ≥ 1 with a concordant positive T wave in the absence of a conduction defect.

	3. Imaging evidence of a region with new loss of viable myocardium at rest in the absence of non-ischemic cause. This can be manifested as: a. Echocardiographic, computed tomography (CT), magnetic resonance (MR), ventriculographic or nuclear imaging evidence of left ventricular (LV) thinning or scarring and failure to contract (i.e., hypokinesis, akinesis, or dyskinesis) b. Fixed (non-reversible) perfusion defects on nuclear radioisotope imaging (e.g. MIBI, Thallium) 4. Medical records documentation of prior MI.
Previous percutaneous coronary intervention	Patient has had a prior Percutaneous Transluminal Coronary Angioplasty, Coronary Atherectomy, and/or coronary stent done at any time prior to the current PCI procedure (this may have included a PCI performed during the current admission)
Previous coronary artery bypass graft surgery	Patient has undergone a previous Coronary Artery Bypass (CABG) surgery prior to the current PCI procedure
Presentation and PCI characteristics	

Stable angina	Angina without a change in frequency or pattern for the 6 weeks prior to presentation/procedure. Angina is controlled by rest and/or sublingual/oral/transcutaneous medications.
Unstable angina	Symptoms must include at least one of the following: 1. Angina that occurred at rest and was prolonged, usually lasting >20 mins 2. New-onset angina of at least CCS class III severity 3. Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class (to at least CCS class III)
Non ST-elevation myocardial infarction (NSTEMI)	At least one of the following biomarkers for detecting myocardial necrosis must be present: 1. Troponin T or I: Maximal concentration of Troponin T or I greater than the MI diagnostic limit on at least one occasion within 24 hours from the index clinical event; 2. CK-MB: Maximal value of CK-MB >2x the upper limit of normal (ULN) on one occasion during the first hours after the

	index clinical event; OR Maximal value of CK-MB (preferable CK-MB mass) > ULN on two successive samples. 3. Total CK: Only where Troponin or CK-MB assays are unavailable, total CK >2x the ULN (or the B fraction of CK) may be employed. AND one of the following: 1. Either ST segment depression or T wave abnormalities in the ECG; or 2. Ischaemic symptoms in the presence or absence of chest discomfort. Ischaemic symptoms may include: unexplained nausea and vomiting or persistent shortness of breath secondary to left ventricular failure or unexplained weakness, dizziness, light-headedness, or syncope.
ST-elevation myocardial infarction (STEMI)	At least one of the following biomarkers for detecting myocardial necrosis must be present:

	1. Troponin T or I: Maximal concentration of Troponin T or I greater than the MI diagnostic limit on at least one occasion within 24 hours from the index clinical event; 2. CK-MB: Maximal value of CK-MB >2x the upper limit of normal (ULN) on one occasion during the first hours after the index clinical event; OR Maximal value of CK-MB (preferable CK-MB mass) > ULN on two successive samples. 3. Total CK: Only where Troponin or CK-MB assays are unavailable, total CK >2x the ULN (or the B fraction of CK) may be employed. AND one of the following: 1. ST-segment elevation: New or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points ≥ 0.2mV in leads V1, V2, or V3, or ≥0.1 mV in other leads. 2. Development of any Q wave in leads V1 through V3, or the development of a Q-wave ≥ 30ms (0.03s) in leads I, II, aVL,

	aVF, V4, V5, or V6. (Q wave changes must be present in any two contiguous leads, and be ≥1mm in depth).
Out-of-hospital cardiac arrest at presentation	Patient has experienced an out of hospital cardiac arrest (i.e. the lack of effective cardiac output) including if the person was under cardiac arrest at the time of presentation to the hospital.
Cardiogenic shock	All of the following must apply at the time of index PCI: 1. Sustained (>30 minutes) episode of systolic blood pressure <90 mm Hg (or vasopressors required to maintain BP >90 mm Hg); AND 2. Evidence of elevated filling pressures (e.g. pulmonary congestion on examination or chest radiograph); AND 3. Evidence of end organ hypoperfusion (e.g. urine output 30mL/hour; or cold/diaphoretic extremities; or altered mental status, etc.).
Left ventricular ejection fraction	Left ventricular ejection fraction measured immediately post PCI with angiography or prior to discharge with echocardiography
Multi-vessel disease	Lesion of ≥50% stenosis in 2 or more coronary systems.

	Coronary systems are defined as: left anterior descending (LAD)-Diagonal / left circumflex-marginal (Cx-OM) / right coronary artery (RCA). LAD-Diagonal is one coronary system as is Cx-OM and the RCA. Left main coronary artery (LMCA) is 2 coronary systems as it gives rise to the LAD & Cx systems, therefore is multi-vessel disease.
Left main disease	Lesion of ≥50% stenosis in the left main coronary artery.
Chronic total occlusion	Lesion treated was presumed to be a CTO defined as being >3 months old and/or bridging collaterals
AHA/ACC class B2/C lesion	Lesion type according to ACC/AHA guidelines: - B2: more than one type B characteristic (lesion moderately complex, tubular (10- 20mm), eccentric, moderately tortuosity of proximal segments, lesion in moderately angulated segment (>45 degrees but < 90 degrees), irregular contour, moderate to heavy calcification, total occlusions less than 3 months old, ostial in location, bifurcation lesions requiring double guide wires, some thrombus present).

	- C: severely complex diffuse (>20mm), excessive tortuosity of proximal segment, lesion in extremely angulated segment > 90 degrees, total occlusion greater than 3 months old or bridging collaterals, inability to protect major side branches, degenerated vein graft with friable lesions.
PCI complications:	
- **Dissection**	If a dissection > 5 mm was observed during the PCI procedure for the treated segment (or for a significant side branch). Dissection is defined as the appearance of contrast materials outside of the expected luminal dimensions of the target vessel and extending longitudinally beyond the length of the lesion.
- **Perforation**	If a coronary perforation occurred during the procedure for the treated segment. A coronary artery perforation occurs when there is angiographic or clinical evidence of a dissection or intimal tear that extends through the full thickness of the arterial wall. This does not include pre-existing AV fistula and other coronary anomalies.

- **Transient no-reflow**	If there was a period of temporary lack of flow distal to the treated segment during the PCI procedure
- **Persistent no-reflow**	If there was persistent lack of flow distal to the treated segment during the PCI procedure
Unsuccessful PCI	>50% residual stenosis for a lesion treated by balloon angioplasty only OR >20% residual stenosis for stented lesion
In-hospital outcomes	
Death	Patient died in hospital during or after the index PCI procedure, but prior to discharge
Cardiac death	Primary cause of death was cardiac i.e. sudden death, myocardial infarction, heart failure or arrhythmia
Myocardial infarction	New presence of a peri-procedural MI during the cath lab visit or after lab visit until discharge (or before any subsequent lab visits) as documented by at least 1 of the following criteria: - Evolutionary ST-segment elevations, development of new Q-waves in 2 or more contiguous ECG leads, or new or presumably new LBBB pattern on the ECG.

	- Biochemical evidence of myocardial necrosis. This can be manifested as: a) CK-MB > 3x the upper limit of normal or, if CK-MB not available b) Total CK > 3x upper limit of normal. (Because normal limits of certain blood tests may vary, please check with your lab for normal limits for CK-MB and total CK). Note: Must be distinct from the index event
Heart failure	Patient experienced documented new onset HF or an acute reoccurrence of HF which necessitated new or increased pharmacologic therapy during the cath lab visit or after lab visit until discharge (or before any subsequent lab visits). HF can be diagnosed based on careful history and physical exam, or by one of the following criteria: - Paroxysmal nocturnal dyspnoea (PND) and/or fatigue - Dyspnoea on exertion (DOE) due to heart failure

	- Chest X-Ray (CXR) showing pulmonary congestion - Pedal oedema or dyspnoea treated with medical therapy for heart failure
Acute kidney injury	Patient experienced new acute or worsening renal failure after the cardiac catheter lab visit but prior to discharge, defined as an absolute rise of serum creatinine $\geq$ 44.2 mmol/L OR > 25% up to 5 days after the index PCI, when compared to baseline creatinine immediately prior to PCI
Major bleeding	Bleeding that occurred during or after the cath lab visit until discharge. The bleeding should require a transfusion and/or prolong the hospital stay and/or cause a drop in haemoglobin > 3.0 g/dL.
Stroke	The patient experienced a stroke or new central neurologic deficit (persisting for > 72 hours) during the cardiac catheter lab visit, after the lab visit, but prior to discharge and/or any subsequent lab visits. Stroke is evidenced by persistent loss of neurological function caused by an ischaemic or haemorrhagic event.
Target vessel revascularisation	

Major adverse cardiovascular events (MACE)	Composite endpoint of death, myocardial infarction and target vessel revascularization (any revascularisation due to restenosis/occlusion within the target coronary artery and/or the same arterial branch that was treated during the index PCI. This includes any percutaneous revascularisation within the same arterial branch treated during the index PCI, regardless of whether the index PCI was successful).
30-day outcomes	
Death	Patient died in hospital during or after the index PCI procedure, but prior to discharge
Cardiac death	Primary cause of death was cardiac i.e. sudden death, myocardial infarction, heart failure or arrhythmia
Myocardial infarction	Readmission with primary reason documented as acute myocardial infarction (STEMI or NSTEMI)
Stroke	Readmission with primary reason documented as stroke (loss of neurological function persisting for >72 hours caused by an ischaemic or haemorrhagic event)

Target vessel revascularisation	Readmission with primary reason documented as revascularization by PCI or CABG
Readmission	Any overnight stay in hospital since discharge from the index PCI
MACE	Composite endpoint of death, myocardial infarction and target vessel revascularization (any revascularisation due to restenosis/occlusion within the target coronary artery and/or the same arterial branch that was treated during the index PCI. This includes any percutaneous revascularisation within the same arterial branch treated during the index PCI, regardless of whether the index PCI was successful).
Beta-blocker	Patients on any of the following medications: metoprolol, atenolol, carvedilol, propranolol, bisoprolol, sotalol, labetolol, oxprenolol, nebivolol
Angiotensin converting enzyme inhibitor / angiotensin II receptor blocker	Patients on any of the following medications: perindopril, lisinopril, ramipril, enalapril, fosinopril, captopril, quinapril, trandalopril, candesartan, telmisartan, irbesartan, losartan, olmesartan, valsartan, eprosartan

Statin	Patient on any of the following medications: atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin