Comparison of Long-Term Outcomes After Percutaneous Coronary Intervention in Patients With Insulin-Treated Versus Non-Insulin Treated Diabetes Mellitus

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There are conflicting data on whether patients with insulin-treated diabetes mellitus (ITDM) have poorer outcomes compared with non-insulin treated diabetic (non-ITDM) patients following percutaneous coronary intervention (PCI). We therefore compared clinical outcomes following PCI in ITDM versus non-ITDM patients. We prospectively collected data on 4,579 patients with diabetes underwent PCI between 2005 and 2014 in a large multicenter registry and dichotomized them as having ITDM (n = 1,111) or non-ITDM (n = 3,468). The non-ITDM group was further divided into diet control only (diet-DM; n = 786) and those taking oral hypoglycemic agents (OHG-DM; n = 2,639), and clinical outcomes were compared with ITDM patients. Median follow-up for long-term mortality was 4.2 years (IQR 2.0 to 6.6 years). ITDM patients were more likely to be female, obese, and have severe renal impairment (all p <0.001). Procedural characteristics were similar other than a greater use of drug-eluting stents in ITDM patients. On multivariable analysis, ITDM was an independent predictor of 12-month major adverse cardiovascular and cerebrovascular events (MACCE; OR 1.26, 95% CI 1.02 to1.55, p = 0.03). Dividing the non-ITDM group further by treatment, a progressively higher rate of 12-month MACCE across the 3 groups was observed (13.5% vs 17.9% vs 21.8%; p <0.001). Long-term mortality was similar in the diet-DM and OHG-DM groups, but significantly higher in the ITDM group on Kaplan-Meier analysis (log-rank p <0.001). In conclusion, there is a clear gradient of adverse outcomes with escalation of therapy from diet control to OHGs to insulin. **(Am J Cardiol 2021;148:36−43)**

Diabetes mellitus (DM) is an important risk factor for the development and progression of coronary artery disease. Coronary artery lesions in patients with diabetes are more often diffuse and involve multiple vessels with small luminal diameters.[1] Patients with DM have also been consistently shown to have worse cardiovascular outcomes after percutaneous coronary intervention (PCI) compared with nondiabetics.[2, 3, 4] However, the results of studies comparing clinical outcomes in patients with insulin-treated DM (ITDM) with patients with non-insulin treated DM (non-ITDM) have been inconsistent. Patients with ITDM often have had a more prolonged duration of disease, a greater burden of co-morbidities, as well as poorer glycemic control, and therefore may be expected to have worse outcomes.[5] A recent meta-analysis comparing PCI outcomes in ITDM with non-ITDM patients showed that both short- and long-term mortality was higher in the ITDM group.[6] However, data from a large German drug-eluting stent (DES) registry and from the secondary analysis of the Taxus Element versus Xience Prime in a Diabetic Population trial, both showed a similar incidence of major adverse cardiovascular events (MACE) at 12 months following PCI regardless of insulin treatment.[7, 8] Given the conflicting data in the published literature, we sought to compare clinical outcomes following PCI in patients with diabetes mellitus according to their treatment status in a large, multicenter Australian registry.

Methods

We analyzed data from consecutive patients with diabetes underwent PCI from January 1, 2005 to December 31,

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2014 enrolled prospectively in the Melbourne Interventional Group (MIG) registry. Patients were divided into two groups based on whether they were on insulin (ITDM group) or not on insulin (non-ITDM group). Diabetic status and treatment were determined at the time of PCI by the interventional cardiologist through assessment of medical records and medication charts, and recorded on a prespecified registry case report form.

The MIG registry is a multicenter Australian PCI registry and has been previously described in detail.[9] Briefly, it collects data from 6 participating hospitals located in metropolitan Melbourne and regional Victoria, that all have 24-hour cardiac catheterization laboratory services. The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics; an independent research body within the School of Public Health and Preventive Medicine at Monash University (Melbourne, Australia). Demographic, clinical, procedural and in-hospital outcome data are prospectively recorded on case-report forms using standardized definitions for all fields.[10] Thirty-day and 12-month outcomes are obtained through telephone follow-up and medical records were reviewed to verify events. Long-term mortality data were obtained by linkage to the Australian National Death Index (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 30 July, 2014. Successful matching of patients through this linkage process was achieved in 99.4% of all patients in the MIG registry. The primary ethics approval has been granted by the ethics committee at The Alfred Hospital (approval number 92/04), and also approved by each participating hospital, including the use of "opt-out" consent as previously described.[9, 10]

Baseline and procedural characteristics, as well as in-hospital, 30-day and 12-month clinical outcomes were compared between the groups. The primary end point was a composite end point of major adverse cardiovascular and cerebrovascular events (including all-cause mortality, myocardial infarction (MI), target vessel revascularization (TVR) and stroke; MACCE) at 12 months. Secondary end points included 30-day and 12-month mortality, MI, stroke and TVR, as well as long-term NDI-linked mortality. MI was defined using the Third Universal Definition of Myocardial Infarction.[11] Post-PCI major bleeding was defined as any bleeding requiring a transfusion and/or prolonging the hospital stay and/or causing a fall in hemoglobin > 3.0 g/dl. We also performed a sensitivity analysis of outcomes by diabetes treatment status in patients according to the generation of drug-eluting stent (DES) received (first vs second generation DES). First generation DES were defined as Taxus (Boston Scientific Corporation, Natick, Massachusetts) and Cypher (Cordis Corporation, Miami Lakes, Florida) stents while all other DES were defined as second generation DES. Patients who received >1 DES from >1 generation were excluded from this analysis. Further subgroup analyses were also performed comparing 12-month outcomes in patients treated with diet-control only (diet-DM), oral hypoglycemic agents only (OHG-DM) and insulin (ITDM).

Continuous variables are expressed as mean ± standard deviation and were compared using Kruskal-Wallis equality-of-populations rank test. Categorical data are expressed as numbers and percentages and were compared using Pearson's Chi-square test or Fisher's exact test as appropriate. The Kaplan-Meier method was used to evaluate 12-month MACCE-free survival rates and long-term NDI-linked mortality rates, while the log-rank test was used for survival comparisons. Multiple logistic regression analysis was used to identify independent predictors of 12-month MACCE. In this model, in addition to diabetes treatment status, 26 other clinically relevant variables were considered (Supplementary Table 1). Those with a p value of <0.1 on univariate analysis that were not co-linear were entered into a stepwise backward selection modelling process for multivariable assessment. Complete case analysis was performed for purposes of multivariable modelling (i.e., patients with missing values were excluded). The proportion of missing data were <1% for all variables. However, out of the non-ITDM group, 43 patients (1.3%) did not have their specific treatment for diabetes (i.e., whether on oral hypoglycemic agents or diet-control alone) recorded and therefore were excluded from analysis. All statistical analyses were performed using Stata 13.1 software (StataCorp LP, College Station, Texas). p values of <0.05 were considered to be statistically significant.

Results

In total, 4,579 patients were included in this study, of which 1,111 patients (24.3%) were in the ITDM group, and 3,468 (75.7%) were in the non-ITDM group.

Table 1 shows the baseline characteristics of the 2 groups. ITDM patients tended to be slightly younger and were more likely to be female and obese (defined by body mass index ≥30 kg/m^2) than non-ITDM patients (all p

Table 1
Baseline characteristics

Variable	Non-ITDM (n = 3,468)	ITDM (n = 1,111)	p value
Mean age ± SD (years)	67.1 ± 11.2	65.2 ± 11.3	< 0.001
Male	2,531 (73.0%)	741 (66.7%)	< 0.001
Mean body mass index (kg/m^2) ± SD	29.7 ± 5.5	30.8 ± 6.2	< 0.001
Body mass index ≥ 30 kg/m^2	1,305 (42.0%)	522 (51.0%)	< 0.001
Hypertension	2,875 (83.0%)	947 (85.3%)	0.06
Hypercholesterolemia	2,833 (81.8%)	930 (83.8%)	0.13
Current smoker	578 (16.9%)	179 (16.6%)	0.79
Peripheral vascular disease	307 (8.9%)	185 (16.7%)	< 0.001
Previous myocardial infarction	1,161 (33.5%)	485 (43.7%)	< 0.001
Previous coronary artery bypass graft surgery	431 (12.4%)	199 (17.9%)	< 0.001
Previous stroke	261 (7.5%)	134 (12.1%)	<0.001
Family history of coronary artery disease	1,234 (37.3%)	374 (35.9%)	0.42
eGFR (ml/min/1.73m^2)			
> 60	2,404 (71.1%)	595 (54.7%)	< 0.001
30 – 60	852 (25.2%)	344 (31.6%)	
< 30	124 (3.7%)	149 (13.7%)	

Abbreviations: non-ITDM = non-insulin treated diabetes mellitus; ITDM = insulin-treated diabetes mellitus; eGFR = estimated glomerular filtration *rate*

<0.001). They were also more likely to have stage 4 to 5 chronic kidney disease (defined as estimated glomerular filtration rate <30 ml/min/1.73m^2), peripheral vascular disease, and a history of MI or coronary artery bypass graft surgery (CABG) (all p <0.001).

Presentation and procedural characteristics of the 2 groups are shown in Table 2. ITDM patients were more likely to have PCI to the left main coronary artery (2.3% vs 1.2%; p = 0.004), receive a drug-eluting stent (64.5% vs 60.9%; p=0.002) and require rotational atherectomy (2.9% vs 1.9%; p = 0.03) than their non-ITDM counterparts. Mean total stent length was also slightly longer in the ITDM group (20.0 ± 9.6 vs 19.2 ± 8.7 mm; p = 0.04). ITDM patients were also more likely to have moderate-severe or severe left ventricular dysfunction (defined as a left ventricular ejection fraction 30% to 45% and <30%; 27.7% vs 21.6% and 4.0% vs 2.7% respectively; both p <0.001)

Table 2
Presentation and Procedural characteristics

Variable	Non-ITDM (n = 3,468)	ITDM (n=1,111)	p value
Clinical presentation			
ST elevation myocardial infarction	751 (21.7%)	221 (19.9%)	0.17
Non-ST elevation myocardial infarction	1,046 (30.2%)	334 (30.1%)	
Unstable angina pectoris	375 (10.8%)	105 (9.5%)	
Stable angina pectoris	1,293 (37.3%)	450 (40.5%)	
Cardiogenic shock at presentation	102 (2.9%)	41 (3.7%)	0.21
Post-out-of-hospital cardiac arrest at presentation	59 (1.7%)	18 (1.6%)	0.86
Left ventricular ejection fraction			
>45%	2,252 (75.7%)	640 (68.4%)	< 0.001
30-45%	643 (21.6%)	259 (27.7%)	
<30%	81 (2.7%)	37 (4.0%)	
Radial access	658 (19.1%)	222 (20.0%)	0.49
Femoral access	2,793 (80.9%)	887 (80.0%)	
Single vessel coronary disease	1,131 (32.7%)	298 (26.9%)	<0.001
Multi-vessel coronary disease	2,328 (67.3%)	809 (73.1%)	
Coronary Vessel treated			
Left main	51 (1.2%)	31 (2.3%)	0.004
Left anterior descending	1,427 (34.0%)	426 (31.8%)	0.15
Left circumflex	533 (12.7%)	193 (14.4%)	0.10
Right	1,303 (31.0%)	417 (31.2%)	0.93
Bypass graft	191 (4.6%)	65 (4.9%)	0.64
AHA/ACC B2/C lesion	2,318 (55.2%)	759 (56.7%)	0.33
PCI to chronic total occlusion	185 (4.4%)	62 (4.6%)	0.73
PCI to bifurcation lesion	483 (11.5%)	141 (10.5%)	0.33
PCI to in-stent restenosis	253 (6.0%)	98 (7.3%)	0.09
Glycoprotein IIb/IIIa inhibitor used	842 (24.3%)	226 (20.4%)	0.007
Rotational atherectomy used	80 (1.9%)	39 (2.9%)	0.03
Drug eluting stent implanted	2,113 (60.9%)	717 (64.5%)	0.002
Bare-metal stent implanted	1,114 (32.1%)	299 (26.9%)	
Balloon angioplasty only	241 (7.0%)	95 (8.6%)	
Mean total stent length (mm) ± SD	19.2 ± 8.7	20.0 ± 9.6	0.04
Pre-PCI TIMI flow 0-1	941 (22.5%)	255 (19.3%)	< 0.001
Post PCI TIMI flow 3	4,019 (95.8%)	1,266 (94.8%)	0.21
PCI complications:			
Acute closure	17 (0.4%)	6 (0.5%)	0.83
Transient no-reflow	89 (2.3%)	26 (2.1%)	0.59
Persistent no-reflow	27 (0.7%)	12 (1.0%)	
Unsuccessful PCI	194 (5.6%)	73 (6.6%)	0.23

Abbreviations: non-ITDM = non-insulin treated diabetes mellitus; ITDM = insulin-treated diabetes mellitus; AHA/ACC = American Heart Association/American College of Cardiology; TIMI = Thrombolysis in Myocardial Infarction' PCI = percutaneous coronary intervention

Table 3
Comparison of outcomes between ITDM and non-ITDM groups

Variable	Non-ITDM (n = 3,468)	ITDM (n = 1,111)	p value
In-hospital outcomes:			
Death	89 (2.6%)	39 (3.5%)	0.10
Myocardial infarction	39 (1.1%)	18 (1.6%)	0.20
Stroke	15 (0.4%)	6 (0.5%)	0.64
Unplanned CABG	27 (0.8%)	14 (1.3%)	0.14
Major Bleeding	64 (1.9%)	25 (2.3%)	0.40
MACCE	162 (4.7%)	76 (6.8%)	0.005
30-day outcomes			
Death	116 (3.3%)	47 (4.2%)	0.17
Myocardial infarction	78 (2.3%)	31 (2.8%)	0.30
Stroke	17 (0.5%)	8 (0.7%)	0.37
Target vessel revascularisation	84 (2.4%)	35 (3.2%)	0.18
Stent thrombosis	11 (0.4%)	1 (0.1%)	0.17
MACCE	251 (7.2%)	102 (9.2%)	0.04
12-month outcomes			
Death	222 (6.4%)	96 (8.6%)	0.01
Death due to primarily cardiac diagnosis	132 (3.8%)	59 (5.3%)	0.04
Myocardial infarction	203 (5.9%)	91 (8.2%)	0.006
Stroke	31 (0.9%)	17 (1.5%)	0.07
Target vessel revascularisation	266 (7.7%)	101 (9.1%)	0.13
MACCE	583 (16.8%)	242 (21.8%)	< 0.001
NDI-linked mortality			
Long-term mortality	536 (18.7%)	236 (27.7%)	<0.001
Median time to NDI-linked mortality data (IQR, years)	4.3 (2.1 − 6.9)	3.7 (1.7 − 5.9)	<0.001

All values expressed as number (percentage) unless stated otherwise

Abbreviations: non-ITDM = non-insulin treated diabetes mellitus; ITDM = insulin-treated diabetes mellitus; CABG = coronary artery bypass graft surgery; MACCE = major adverse cardiovascular and cerebrovascular events; NDI = National Death Index

A comparison of clinical outcomes between the 2 groups is shown in Table 3. In-hospital and 30-day MACCE rates were both significantly higher in the ITDM group compared with the non-ITDM group (6.8% vs 4.7%; p = 0.005 and 9.2% vs 7.2%; p = 0.04 respectively). There were no differences in rates of death, MI or stroke during the index admission or at 30-day follow-up, between the two groups (all p >0.05). However, by 12-month follow-up, mortality (8.6% vs 6.4%; p = 0.01), MI (8.2% vs 5.9%; p = 0.006) and MACCE rates (21.8% vs 16.8%; p <0.001) were all significantly higher in the ITDM group compared with the non-ITDM group. Similarly, long-term NDI-linked mortality was higher in the ITDM group (27.7% vs 18.7%; p<0.001). These differences in 12-month and long-term outcomes between the ITDM and non-ITDM groups persisted regardless of the type of initial clinical presentation (stable angina vs acute coronary syndrome) (all p <0.05) (Supplementary Table 2).

Kaplan-Meier survival curves for MACCE-free survival are shown in Figure 1 and demonstrate inferior 12-month MACCE-free survival in ITDM patients (log rank p <0.001). Additionally, Kaplan-Meier survival curves for NDI-linked mortality demonstrate worse long-term survival in the ITDM group, with the survival curves diverging early (log rank p <0.001) (Supplementary Figure 1). No significant differences in 30-day or 12-month medications were

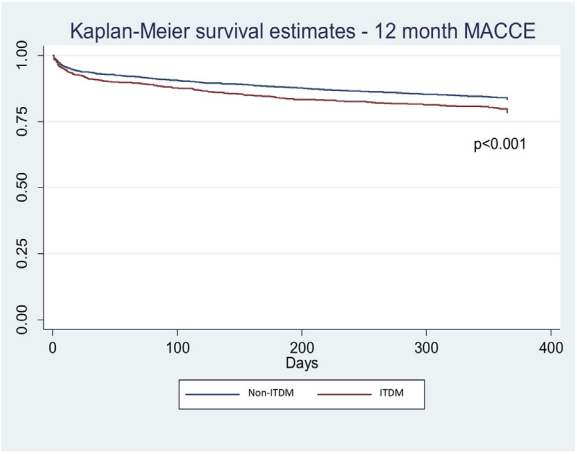

Figure 1. Kaplan-Meier survival curves of 12-month MACCE-free survival by treatment type for diabetes.

observed between the 2 groups except for a slightly lower use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers in the ITDM group (Supplementary Table 3)

On logistic multivariable regression analysis, ITDM was found to be an independent predictor of 12-month MACCE (OR 1.30; 95% CI 1.04 to 1.63; p = 0.02) (Table 4). The 3 strongest predictors of 12-month MACCE were found to be cardiogenic shock at presentation, severe left ventricular systolic dysfunction (ejection fraction < 30%) and a history of stage 4 to 5 chronic kidney disease (eGFR < 30 ml/min/1.73m^2) (OR 4.41, 2.22 and 2.21 respectively). Age (per year increase) was also shown to be a strong predictor of 12-month MACCE (OR 1.01, 95% CI 1.01 to 1.02; p <0.001). Of note, DES use was associated with a lower risk of MACCE (OR 0.37, 95% CI 0.30 to 0.45, p <0.001).

A sensitivity analysis comparing 12-month outcomes by diabetes treatment status and generation of DES received was also performed (Supplementary Table 3). For first generation DES, there were no significant differences in the outcomes of mortality, MACCE and TVR between ITDM and non-ITDM patients (all p >0.05). However, in the 2,059 patients receiving second generation DES, 12-month MACCE was significantly higher in ITDM patients (7.2% vs 3.7%, p <0.001), driven by higher 12-month mortality (16.6% vs 10.5% p <0.001). There was no significant difference in rates of TVR between the 2 groups (5.4% vs 4.3%; p =0.29).

Dividing the non-ITDM group further by treatment, there were 2,639 patients in the OHG-DM and 786 patients in the diet-DM groups. A comparison of selected baseline characteristics and 12-month outcomes between these 2 groups and the ITDM group is shown in Supplementary Table 5. With increasing diabetes treatment intensity, there was an increasing proportion of female patients (25.8% vs 27.3% vs 33.3%; p <0.001) as well as drug-eluting stent use (56.1% vs 62.5% vs 64.5%; p = 0.001). There was a clear rising gradient of risk from the diet-DM group to the ITDM group with a progressively higher rate of 12-month MACCE across the 3 groups (13.5% vs 17.9% vs 21.8%; p <0.001). This was mainly driven by a higher 12-month

Table 4.
Multivariable logistic regression analysis for 12-month MACCE

	Odds ratio	95% CI	p
Cardiogenic shock at presentation	4.41	2.65 – 7.35	<0.001
Left ventricular ejection fraction			
>45%	1 (ref)		
30-45%	1.62	1.30 – 2.01	<0.001
<30%	2.22	1.35 – 3.66	0.002
Estimated glomerular filtration rate (ml/min/1.73m^2)			
>60	1 (ref)		
30-60	1.27	1.01 – 1.55	0.04
<30	2.21	1.53 – 3.17	<0.001
In-stent restenosis	2.09	1.53 – 2.87	<0.001
Post-out-of-hospital cardiac arrest at presentation	1.81	1.07 – 3.63	0.03
PCI to bypass graft lesion	1.76	1.17 – 2.64	0.007
AHA/ACC B2/C lesion	1.46	1.19 – 1.79	<0.001
Acute coronary syndrome presentation	1.38	1.12 – 1.71	0.003
Peripheral vascular disease	1.32	0.99 – 1.77	0.06
Diabetes treatment status			
Non-insulin treated	1 (ref)		
Insulin-treated	1.30	1.04 – 1.63	0.02
Previous myocardial infarction	1.19	1.03 – 1.47	0.02
PCI to left anterior descending artery	1.26	1.02 – 1.55	0.03
Age (per year increase)	1.01	1.01 – 1.02	0.01
Body mass index (kg/m^2)			
20 – 24.9	1 (ref)		
<20	0.92	0.40 – 2.10	0.84
25 – 29.9	0.75	0.57 – 0.98	0.04
>30	0.87	0.66 – 1.14	0.31
Drug-eluting stent use	0.37	0.30 – 0.45	<0.001

Abbreviations: AHA/ACC = American Heart Association/American College of Cardiology; MACCE = major adverse cardiovascular and cerebrovascular events; PCI = percutaneous coronary intervention

mortality in the ITDM group compared with the diet-DM and OHG-DM groups (p <0.001). Kaplan-Meier analysis for 12-month MACCE-free survival similarly showed inferior outcomes in the ITDM group (log-rank p <0.001) (Figure 2). There was also a progressive increase in long-term NDI-linked mortality with increasing treatment intensity (16.3% vs 19.4% vs 27.7%; p <0.001). Kaplan-Meier survival curves for NDI-linked mortality demonstrated similar long-term survival in the diet-DM and OHG-DM groups, but significantly poorer survival in the ITDM group (log-rank p <0.001) (Figure 3). On multivariable logistic regression analysis to identify independent predictors for 12-month MACCE, there was again an increasing gradient of risk with increasing treatment intensity (diet-DM: OR 1.00 (ref), OHG-DM: OR 1.38 (95% CI 1.06 to 1.82), ITDM: OR 1.62 (95% CI 1.19 to 2.21)) (Table 5).

Discussion

This study evaluated clinical outcomes of patients with diabetes underwent PCI stratified by their therapy for diabetes at both medium- and long-term follow-up. We found that among patients with diabetes underwent PCI, those treated with insulin had significantly worse 12-month

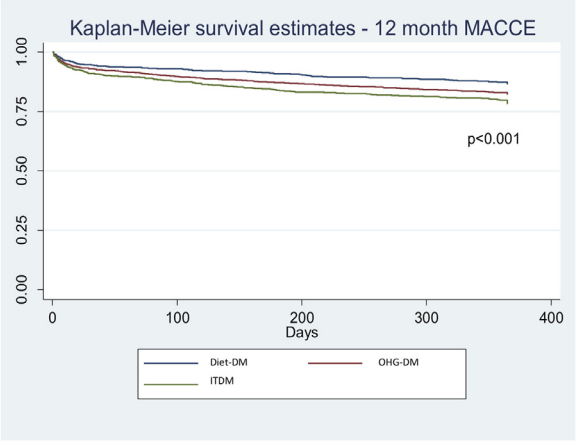

Figure 2. Kaplan-Meier survival curves of 12-month MACCE-free survival by diet control, oral hypoglycaemic therapy and insulin treatment for diabetes.

MACCE and long-term mortality compared with patients not requiring insulin. Even after adjustment for other factors, ITDM remained an independent risk factor for 12-month MACCE. When the non-ITDM group was further divided by their treatment (diet control or OHG), there appeared to be a gradient of risk with a significant increase in 12-month MACCE with escalation of therapy for diabetes from diet control only to OHG and finally insulin. However, long-term mortality was similar in those on diet control and OHG, though significantly worse in those on insulin.

Worldwide, approximately 1 in 3 to 1 in 4 diabetic patients are on insulin therapy.[12, 13] ITDM patients have generally had a longer duration of DM. Particularly among type 2 DM patients, insulin tends to be initiated at a more advanced stage of diabetes.[14] Therefore, ITDM patients tend to have more comorbid cardiovascular risk factors, which may in themselves be expected to lead to worse cardiovascular outcomes following PCI.[15] This was observed to an extent in our study where the ITDM group had a higher proportion of patients with peripheral vascular

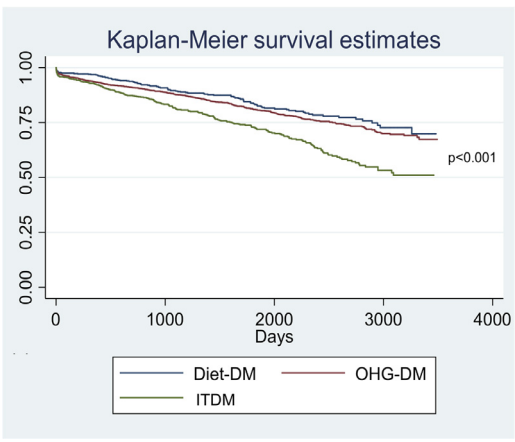

Figure 3. Kaplan-Meier survival curves of long-term NDI-linked mortality by diet control, oral hypoglycaemic therapy and insulin treatment for diabetes.

Table 5
Multivariable logistic regression analysis for 12-month MACCE by diet control, oral hypoglycemic therapy and insulin treatment for diabetes

	Odds ratio	95% CI	p
Cardiogenic shock at presentation	4.02	2.54 – 6.37	<0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)			
>60	1 (ref)		
30-60	1.10	0.88 – 1.36	0.41
<30	2.24	1.59 – 3.17	<0.001
Left ventricular ejection fraction			
>45%	1 (ref)		
30-45%	1.59	1.29 – 1.95	<0.001
<30%	2.09	1.32 – 3.31	0.002
PCI to in-stent restenosis lesion	2.09	1.53 – 2.82	<0.001
Post-out-of-hospital cardiac arrest at presentation	2.01	1.06 – 3.81	0.03
PCI to bypass graft lesion	1.76	1.20 – 2.59	0.004
Diabetes treatment			
Diet control only	1 (ref)		
Oral hypoglycaemic agents only	1.39	1.06 – 1.82	0.02
Insulin	1.62	1.19 – 2.21	0.002
AHA/ACC B2/C lesion	1.55	1.28 – 1.88	<0.001
Previous stroke	1.47	1.10 – 1.95	0.008
Acute coronary syndrome presentation	1.37	1.12 – 1.68	0.002
PCI to left anterior descending artery	1.28	1.05 – 1.56	0.01
Peripheral vascular disease	1.27	0.97 – 1.68	0.08
Previous myocardial infarction	1.17	0.96 – 1.44	0.12
Age (per year increase)	1.01	1.00 – 1.02	0.002
Drug-eluting stent use	0.38	0.31 – 0.46	<0.001

AHA/ACC = American Heart Association/American College of Cardiology; MACCE = major adverse cardiovascular and cerebrovascular events; PCI = percutaneous coronary intervention

disease, previous MI, prior CABG and stage 4 to 5 chronic kidney disease, when compared with the non-ITDM group. However, similar to other studies, there were no significant differences between the two groups in terms of other traditional cardiovascular risk factors such as hypertension, hypercholesterolemia and current smoking.[7, 16] It has been suggested that the increased risk of adverse cardiovascular outcomes following PCI in ITDM patients compared with non-ITDM patients is due to the more severe cardiovascular risk profile in the ITDM group. Indeed, in several studies, the increased risk of adverse clinical outcomes following PCI in the ITDM group is mitigated by adjustment for baseline risk factors.[8, 17] In our study, after adjustment for other factors in a multivariable regression analysis model, ITDM continued to be an independent, though modest predictor of 12-month MACCE. This suggests that while some of the effect of ITDM on 12-month MACCE may be due to the associated risk factors in an ITDM population, they do not explain the full association of ITDM on 12-month MACCE after PCI.

One possible explanation for the independent association between ITDM and 12-month MACCE is that insulin may have direct effects that promote worsening of coronary artery disease. One of the earliest suggestions of this came from Janka *et al* in 1987 who demonstrated a positive

association between required dose of exogenous insulin and presence of atherosclerotic coronary artery disease (CAD) in patients with type 2 DM.[18] Insulin is thought to increase atherogenesis and therefore cardiovascular risk by promoting pro-inflammatory macrophage response and enhancing fibrinogen production.[19, 20] In a large study of patients post MI, patients with ITDM were found to have the highest risk of mortality followed by diabetics treated by OHG and then diabetics on diet control treatment only.[21] The present study also demonstrated increasing long-term mortality with escalating treatment intensity for diabetes mellitus. Several other studies have found that patients with ITDM have significantly more cardiovascular events compared with patients with non-ITDM, even after controlling for baseline risk factors suggesting that insulin may have an independent deleterious effect.[5, 16, 22] One possible reason may be that patients treated with insulin tend to have more fluctuations in blood glucose level, which has been shown to be independently associated with the development of thin-cap fibroatheromas, which themselves are associated with spontaneous plaque rupture and increased ischemic clinical events.[23, 24]

However, interestingly in our study, no differences in rates of TVR were seen with escalating treatment intensity for diabetes mellitus. Our results were comparable to previous studies by Bangalore et al and Pi et al who only included patients with second generation DES.[8, 22] Bangalore et al showed higher rates of both mortality and MACE at 1-year follow-up in patients with ITDM compared with patients with non-ITDM, while Pi et al reported similar results at 3-year follow-up. Similar to our study, both studies showed that there were no significant differences in rates of TVR between patients with ITDM and non-ITDM, suggesting that greater co-morbidities in the ITDM group, rather than the atherogenic effects of insulin, may be more responsible for the difference in MACCE between the groups in our study.

Somewhat surprisingly in our study of diabetic patients, 30.9% of patients received a bare-metal stent (BMS), while 61.8% of patients received a DES. There is robust evidence from several studies, including a pooled analysis of 7 randomized controlled trials, favoring the use of DES over BMS in diabetic patients.[25, 26, 27, 28] Additionally, in our study, DES use was independently associated with lower 12-month MACCE. The relatively high use of BMS in our diabetic population is likely due to the time period of this study and local funding restrictions at that time for the use of DES. In a sensitivity analysis of outcomes in patients who received a DES, we found that there was no difference in outcomes between the non-ITDM and ITDM groups in patients receiving a first generation DES, unlike the results seen among patients receiving a second generation DES. A potential reason for this may be that the advent of more deliverable second generation DES greatly expanded the scope of lesions amenable to treatment by PCI and consequently increased the number of patients with more complex disease being treated, a group associated with an increased risk of mortality and complications, and thus, more likely to demonstrate outcome differences between patients with other high-risk characteristics such as ITDM.[29] Our results in first generation DES are also different to those from Akin et al of the German DES.DE registry, who showed that among patients receiving a first generation DES, ITDM patients had higher 12-month mortality and TVR rates.[7] Overall rates of TVR were also higher in the German registry data. The reasons for this discrepancy are unclear and would require closer exploration of the data especially as our study included more patients presenting with acute coronary syndromes, which may be expected to lead to worse outcomes. In addition, the number of patients treated with first compared with second generation DES was much smaller, making it statistically much more difficult to detect any difference in outcomes between ITDM and non-ITDM patients treated with first generation DES.

Our study had some limitations. Firstly, while our data are collected prospectively, this was a retrospective analysis, and is therefore subject to inherent limitations that exist in this study design. Secondly, the proportion of type 1 and type 2 diabetes, duration of time patients had had diabetes or glycosylated hemoglobin values to assess glycemic control were not recorded which may have had an impact on clinical outcomes. However, given there was only a 2-year difference in mean age between the ITDM and non-ITDM groups, the ITDM group is likely to have mostly included patients with type 2 diabetes. Thirdly, data regarding the type of OHG or the amount of insulin therapy used were not available. Fourthly, due to the time period of our study, approximately a third of the patients received a BMS despite being diabetic, possibly due to concerns regarding a potentially increased risk of late stent thrombosis with first generation DES compared with BMS.[30] This may limit the applicability of our results to contemporary practice. However, even in the subgroup of patients who received contemporary, second generation DES, those in the ITDM group continued to have a higher rate of mortality and MACCE compared with the non-ITDM group. Finally, patients were only followed up for a maximum of 12 months for MACCE, and longer-term follow up may have altered the findings, particularly given the chronic nature of the diabetic atherosclerotic process. However, the long-term mortality data are consistent with the 12-month data reported herein.

In conclusion, among patients with diabetes mellitus in a contemporary Australian multicenter registry, those on insulin treatment had significantly worse cardiovascular outcomes compared with their non-insulin treated counterparts. There was a clear gradient of risk of adverse outcomes with escalation of therapy from diet control only to OHG and finally to insulin therapy.

Credit Author Statement

Sinjini Biswas: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Review and Editing, **Diem Dinh**: Methodology, Formal analysis, **Nick Andrianopoulos**: Methodology, Formal analysis, **Jeffrey Lefkovits**: Writing – Review & Editing, **Andrew Ajani**: Writing – Review & Editing, **Stephen J. Duffy**: Writing – Review & Editing, **William Chan**: Writing – Review & Editing, **Antony Walton**: Writing – Review & Editing, **Angela Brennan**: Project administration, Writing –

Review & Editing, **David J Clark**: Writing − Review & Editing, **Chin Hiew**: Writing − Review & Editing, **Ernesto Oqueli**: Writing − Review & Editing, **Christopher M. Reid**: Writing − Review & Editing, **Dion Stub**: Writing − Review & Editing, **David Eccleston**: Conceptualization, Writing − Review & Editing, Supervision

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Disclosures

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Supplementary materials

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