Comparison of Long-Term Mortality in Patients With Single Coronary Narrowing and Diabetes Mellitus to That of Patients With Multivessel Coronary Narrowing Without Diabetes Mellitus

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It is well recognized that patients with diabetes mellitus (DM) and multivessel coronary artery disease (MVD) undergoing percutaneous coronary intervention (PCI) have poorer long-term outcomes compared with those undergoing coronary artery bypass grafting. However, the relative impact of DM status and extent of coronary artery disease on long term mortality in patients undergoing PCI is unknown. We sought to compare patients with DM undergoing PCI for single and multivessel disease to their non-DM counterparts. Overall, 34,690 consecutive patients undergoing PCI from the Melbourne Interventional Group registry (2005 to 2017) were included (mean age 64.5 ± 12 years, 76.6% male). Our cohort was stratified by the presence of DM and extent of CAD (DM-SVD [single-vessel disease] [n = 2,669], DM-MVD [n = 6,118], no-DM-SVD [n = 10,993], no-DM-MVD [n = 14,910]). DM-SVD and no-DM-MVD cohorts demonstrated comparable baseline cardiovascular risk profiles, although the no-DM-MVD cohort had higher rates of prior myocardial infarction, while the DM-SVD cohort had a higher proportion of patients with renal impairment. Over a median follow-up of 4.8 (IQR 2.0 to 8.2) years, 6,031 (17.5%) patients died. Using the no-DM-SVD group as the reference category, adjusted risk of mortality was highest in the MVD-DM cohort (HR 1.90; 95% CI 1.71 to 2.09). Similar adjusted risk of long-term mortality was observed in the DM-SVD (HR 1.32, 95%CI 1.15 to 1.51) and no-DM-MVD (HR 1.30, 95%CI 1.20 to 1.40) groups. In conclusion, we found that the long-term mortality of patients with DM and SVD undergoing PCI was the risk equivalent of non-DM patients with MVD. **(Am J Cardiol 2021;142:1−4)**

It is well recognized that patients with diabetes mellitus (DM) and multivessel coronary artery disease (MVD) undergoing percutaneous coronary intervention (PCI) have poorer long-term outcomes compared with those undergoing coronary artery bypass grafting (CABG).[1] However, the relative impact of DM status and extent of coronary artery disease (CAD) on long term mortality in patients undergoing PCI is unknown. While the widespread use of new generation drug-eluting stents (DES) has reduced the risk of target lesion revascularization, the heightened risk of recurrent cardiovascular events including, stent thrombosis, myocardial infarction (MI) and death in patients with DM has not been alleviated.[2−4] We compared patients with DM undergoing PCI for single and multivessel disease to their non-DM counterparts. Our aim was to assess long-term mortality following revascularization stratified by DM and extent of disease.

Methods

The study included prospectively collected data from consecutive patients between 2005 and 2017 undergoing PCI from the Melbourne Interventional Group (MIG) registry. The MIG registry is a collaboration of 6 Australian tertiary referral hospitals in the state of Victoria, Australia, that prospectively collects detailed demographic, clinical, procedural and outcome data from all PCI procedures.[5] The registry is coordinated by the independent Center of Cardiovascular Research and Education in Therapeutics at Monash University with periodic quality control audits that demonstrate a data accuracy of 98%.[6,7] The ethics committee in each participating hospital has approved the MIG registry, including the use of "opt-out" consent. Data for each patient was recorded the time of the index PCI.

Patients undergoing PCI for both stable CAD and acute coronary syndromes were included. Those with prior

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CABG were excluded. MVD was defined as ≥50% stenosis in ≥2 separate epicardial coronary arteries. Left main coronary artery stenosis ≥50% was classified as MVD. The primary outcome was long-term mortality obtained by linkage to the Australian National Death Index which records all deaths in Australia.

Categorical data have been expressed as numbers and/or percentages and continuous variables as mean ± standard deviation. Comparison of the baseline clinical and procedural characteristics of the 4 groups was performed. Categorical variables were compared using Fisher's exact or chi-square tests as appropriate. Continuous variables were compared using Kruskal-Wallis equality-of-populations rank test. Cox-regression modelling was performed to obtain adjusted hazard ratios (HR) and 95% confidence intervals (CI). The demographic and clinical variables considered included DM status stratified by extent of CAD, age, gender, hypertension, smoking status, dyslipidemia, family history of CAD, previous ACS, heart failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, renal failure and left ventricular ejection fraction. Procedural characteristics including DES use, lesion length, lesion location (ostial, bifurcation) and glycoprotein IIb/IIIa use were also assessed. Univariate variables yielding p <0.10 were included in the final multivariate model. The data analysis was carried out using Stata 14.1 (StataCorp LP, College Station, Texas). A p value of <0.05 was considered to be statistically significant.

Results

Overall, 34,690 consecutive patients undergoing PCI were included (mean age 64.5 ± 12 years, 76.6% male). Our cohort was stratified by the presence of DM and extent of CAD (DM-SVD [single-vessel disease] [n = 2,669], DM-MVD [n = 6,118], no DM-SVD [n = 10,993], no DM-MVD [n = 14,910]). The patients with DM-MVD were the highest cardiovascular risk cohort as evidenced by their older age and higher prevalence of hypertension, dyslipidemia, renal impairment, peripheral vascular disease, prior MI and heart failure (Table 1). DM-SVD and no-DM-MVD cohorts demonstrated comparable baseline cardiovascular risk profiles, although the no-DM-MVD cohort had higher rates of prior MI, ST segment elevation MI, and cardiogenic shock while the DM-SVD cohort had a higher proportion of patients

Table 1
Baseline characteristics

	Overall (n=34,690)	No-diabetes mellitus-single vessel disease (n = 10,993)	Diabetes mellitus-single vessel disease (n = 2,669)	No-diabetes mellitus-multivessel disease (n = 14,910)	Diabetes mellitus-multivessel disease (n = 6,118)	p value
Clinical Characteristics						
Age (years)	64.5 ±12	61.9 ±12	64.3 ±11	65.2 ±12	67.4 ±11	<0.001
Men	26579 (76.6%)	8329 (75.8%)	1849 (69.3%)	11882 (79.7%)	4519 (73.9%)	<0.001
Body Mass Index (kg/m2)	28.5 ±5	28.0 ±5	30.7 ±6	27.9 ±5	30.0 ±6	<0.001
Hypertension	23064 (66.5%)	5989 (54.5%)	2106 (78.9%)	9775 (65.6%)	5194 (84.9%)	<0.001
Dyslipidemia	23292 (67.2%)	6353 (57.9%)	2017 (75.6%)	9892 (66.4%)	5030 (82.3%)	<0.001
Current Smoker	8572 (25.1%)	3338 (30.8%)	553 (21.1%)	3692 (25.1%)	989 (16.5%)	<0.001
Family History of Coronary Artery Disease	12463 (37.6%)	4166 (39.2%)	849 (33.5%)	5580 (39.0%)	1868 (32.7%)	<0.001
Prior Myocardial Infarction	9317 (26.9%)	1511 (13.8%)	546 (20.5%)	4644 (31.2%)	2616 (42.8%)	<0.001
Heart failure	1375 (4.0%)	176 (1.6%)	103 (3.9%)	572 (3.8%)	524 (8.6%)	<0.001
Left Ventricular Ejection Fraction						<0.001
type="Other">46%	23128 (76.2%)	7797 (79.9%)	1853 (81.0%)	9835 (75.1%)	3643 (70.3%)	
36%-45%	6950 (21.7%)	1843 (18.9%)	403 (17.6%)	2985 (22.8%)	1359 (26.2%)	
≤35%	612 (2.0%)	116 (1.2%)	31 (1.4%)	283 (2.2%)	182 (3.5%)	
Peripheral Vascular Disease	2110 (6.1%)	308 (2.8%)	162 (6.1%)	840 (5.6%)	800 (13.1%)	<0.001
Stroke	2076 (6.0%)	450 (4.1%)	163 (6.1%)	847 (5.7%)	616 (10.1%)	<0.001
Estimated Glomerular Filtration Rate, ml/min/1.73 m2						<0.001
≥60	25487 (76.3%)	8772 (83.4%)	1901 (73.7%)	11086 (77.3%)	3728 (62.7%)	
30-59	6845 (20.5%)	1636 (15.6%)	567 (22.0%)	2916 (20.3%)	1726 (29.0%)	
<30	1050 (3.1%)	108 (1.0%)	112 (4.3%)	341 (2.4%)	489 (8.2%)	
Presentation & Procedural Characteristics						
Presentation						<0.001
Stable Coronary Artery Disease	11720 (33.8%)	3012 (27.4%)	1028 (38.5%)	5161 (34.6%)	2519 (41.2%)	
Unstable angina pectoris	2918 (8.4%)	874 (7.9%)	250 (9.4%)	1196 (8.0%)	598 (9.8%)	
Non ST-elevation myocardial infarction	9542 (27.5%)	3096 (28.2%)	750 (28.1%)	3892 (26.1%)	1804 (29.5%)	
ST-elevation myocardial infarction	10510 (30.3%)	4011 (36.5%)	641 (24.0%)	4661 (31.3%)	1197 (19.6%)	
Cardiogenic shock	1252 (3.6%)	291 (2.6%)	47 (1.8%)	629 (4.2%)	285 (4.7%)	<0.001
Femoral access	26595 (76.9%)	8246 (75.2%)	2015 (75.6%)	11453 (77.1%)	4881 (80.2%)	<0.001
Glycoprotein iib/iiia use	9757 (28.1%)	3605 (32.8%)	619 (23.2%)	4264 (28.6%)	1269 (20.8%)	<0.001
Mean stent length (mm)	20.1 ±9	19.9 ±9	19.6 ±9	20.4 ±10	20.0 ±9	0.02
Drug eluting stent use	18281 (52.7%)	5240 (47.7%)	1629 (61.0%)	7654 (51.3%)	3758 (61.4%)	<0.001

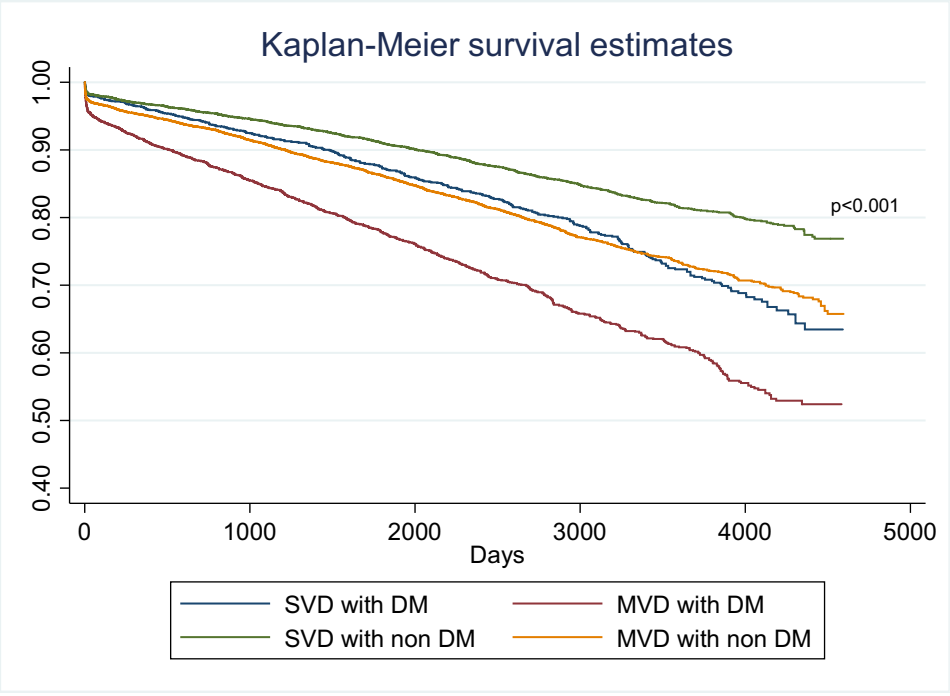

Figure 1. Kaplan-Meier survival estimates of long-term survival stratified by diabetes status and extent of coronary artery disease.

with renal impairment. Rates of DES use was significantly higher in patients with DM.

Over a median follow-up of 4.8 (IQR 2.0 to 8.2) years, 6031 (17.5%) patients died. The Kaplan Meier survival curves illustrating long-term mortality following PCI for the 4 groups is shown in Figure 1. The crude unadjusted mortality rates were highest in the DM-MVD cohort (27.9%) and lowest in the no-DM-SVD cohort (11.5%). Cox regression was performed adjusting for variables significant on univariate analysis including cardiovascular risk factors, presentation type (ACS vs stable CAD), DES use, left ventricular ejection fraction, heart failure and renal impairment (Table 2). Using the no-DM-SVD group as the reference category, adjusted risk of mortality was highest in the MVD-DM cohort (HR 1.90; 95% CI 1.71 to 2.09). Similar adjusted risk of long-term mortality was observed in the DM-SVD (HR 1.32, 95% CI 1.15 to 1.51) and no-DM-MVD (HR 1.30, 95% CI 1.20 to 1.40) groups (Figure 1).

Discussion

Consistent with prior reports, our study highlights the significant hazard associated with the presence of DM and extent of CAD.[1] This was most pronounced in patients with DM and MVD, who had a 2-fold higher risk of death when compared to patients without DM with SVD. The most striking finding was the near identical adjusted risk of long-term mortality observed in DM patients with SVD and non-DM with MVD. To our knowledge, this has not been previously reported.

DM is associated with marked vascular perturbation that is known to increase risk of cardiovascular and all-cause mortality.[1,8] In particular, increased vascular disease burden, accelerated atherosclerosis and multisystem involvement in DM can impair long-term outcomes following revascularization.[9] Although target-lesion-failure has fallen with contemporary DES,[3] the presence of DM increases propensity towards both target and nontarget vessel ischemic events and may offer a potential mechanism for the observed findings.[10,11]

Given these findings, the importance of aggressive risk factor modification and medical therapy in patients with

Table 2
Predictors of long-term mortality on cox regression

	Adjusted hazard ratio	95% confidence interval	p value
Age	1.06	1.05-1.07	<0.001
Sex (female)	0.95	0.87-1.02	0.10
Hypertension	1.14	1.06-1.25	0.01
Current smoker	1.32	1.20-1.45	<0.001
Drug Eluting Stent	0.81	0.76-0.87	<0.001
Estimated Glomerular Filtration Rate <30	3.69	3.27-4.16	<0.001
Ejection Fraction<35%	2.25	1.95-2.61	<0.001
Out of Hospital Cardiac Arrest	1.62	1.37-1.91	<0.001
Cardiogenic Shock	2.58	2.26-2.96	<0.001
Cerebrovascular Disease	1.42	1.29-1.58	<0.001
Peripheral Vascular Disease	1.46	1.32-1.61	<0.001
Chronic lung disease	1.62	1.49-1.76	<0.001
No-Diabetes Mellitus- Single Vessel Disease	Reference category	-	-
Diabetes Mellitus-Single Vessel Disease	1.32	1.15-1.51	<0.001
No-Diabetes Mellitus-Multi-Vessel Disease	1.30	1.30-1.40	<0.001
Diabetes Mellitus-Multi-Vessel Disease	1.90	1.71-2.09	<0.001

DM undergoing PCI requires careful consideration. Although intensive glycemic control has consistently been reported to reduce microvascular complications, there is limited data supporting its role in reduction of cardiovascular events. Some,[12] but not all studies,[13] have reported a reduction in adverse cardiovascular events in contemporary populations of patients undergoing PCI with HbA1c <7.0%. In addition, importance of strict adherence to secondary preventative medical therapies including antiplatelets, beta-blockers, statins and ACE inhibitors may be of even greater significance among patients with DM.[8] With the advent of sodium-glucose cotransporter 2 inhibitors, it is plausible that the difference in outcomes between DM and non-DM undergoing PCI may decrease further.[14] The comparable long-term mortality in DM-SVD and no-DM-MVD raises the question of the most appropriate mode of revascularization in diabetic patients with SVD. This could only truly be answered by a randomized study comparing medical therapy, PCI and CABG in patients with DM-SVD.

Strengths of this real-world registry is the inclusion of consecutive patients undergoing PCI, duration of follow-up, prospective data collection and validation of data accuracy. However, the study has a number of inherent limitations due to the observational study design. First, there are likely unmeasured factors including the duration of DM, glycemic control and therapy for DM, that have not been accounted for in our analysis. Further, the generalizability of these findings may not apply to patients with DM who receive CABG or medical therapy without revascularization.

In conclusion, our findings strongly suggest that the long-term mortality of patients with DM and SVD undergoing PCI is the risk equivalent of non-DM patients with MVD. Although guidelines recommend CABG for patients with DM and MVD,[8] PCI remains the standard of care for most patients with SVD, irrespective of their DM status.

Authors' Contributions

Mohammad Omair: Conceptualization, Methodology, Writing - Original Draft; Anoop N Koshy: Conceptualization, Methodology, Writing - Original Draft; Diem T Dinh: Formal analysis, Data Curation; Angela L Brennan: Formal analysis, Data Curation, Project administration Christopher M Reid: Supervision; Andrew E Ajani: Supervision; Stephen J Duffy: Supervision; Matias B Yudi: Supervision, Writing- Reviewing and Editing; David J Clark: Supervision, Writing- Reviewing and Editing.

Disclosures

The authors have no conflicts of interest to disclose.

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