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Original article

Impact of diabetic retinopathy on late cardiac events after percutaneous coronary intervention

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ABSTRACT

Background: Diabetic retinopathy has been identified as a predictor of cardiovascular events and heart failure in patients with diabetes mellitus (DM). This study aimed to assess the impact of diabetic retinopathy on the incidence of late cardiac events following percutaneous coronary intervention.
Methods: We enrolled 88 consecutive DM patients who underwent elective percutaneous coronary intervention and whose ophthalmologic records were available. Patients were divided into 2 groups: those with diabetic retinopathy (DR+ group; $n=47$), and those without diabetic retinopathy (DR− group; $n=41$). We examined the incidence of major adverse cardiac events (MACE) including cardiac death, myocardial infarction, and acute heart failure requiring emergency admission over a period of up to 5 years.
Results: Patients in the DR+ group were likely to have a lower estimated glomerular filtration rate. Kaplan–Meier analysis showed that the event-free survival rates for all MACE, myocardial infarction, and heart failure were significantly lower in the DR+ group than in the DR− group ($p=0.002$, $p=0.025$, and $p=0.022$, respectively). Multivariate Cox proportional hazards analysis indicated that the presence of DR was a significant predictor of MACE (hazard ratio: 8.7; 95% CI: 1.1–69.8, $p=0.042$).
Conclusion: The presence of DR might be a useful predictor of late cardiac events following percutaneous coronary intervention.

Introduction

Diabetic retinopathy (DR) is a common microvascular diabetic complication. Previous epidemiologic studies have demonstrated that the presence of DR is associated with an increased risk of cardiovascular events in patients with diabetes mellitus (DM) [1,2]. Reports have shown that the presence of DR confers an excess risk of heart failure, independent of known risk factors [3,4].

Furthermore, some observational studies have shown that the presence of DR in coronary artery disease patients is related to cardiovascular events following coronary revascularization [5–7]. However, the availability of data on an association between DR and late cardiac events following percutaneous coronary intervention (PCI) is limited.

Therefore, the aim of this study was to examine the association between the presence of DR and late cardiac events following PCI in Japanese DM patients.

Methods

Patients

We identified 187 consecutive DM patients who underwent elective PCI at our institution between January 2006 and December 2011. Criteria for DM were met if patients had hemoglobin A1c levels (National Glycohemoglobin Standardization Program) ≥6.5%, a fasting plasma glucose concentration >126 mg/dL, and/or a history of anti-hyperglycemic medication or previous diagnosis of diabetes. Ophthalmologic records were obtained for 88 of the patients, and these comprised the study cohort. The 88 patients were divided into the following 2 groups: those with DR (DR+ group; $n=47$), and those without diabetic retinopathy (DR− group; $n=41$). DR was defined as the presence of typical eye changes, including hemorrhages, microaneurysms, exudates, and fibrous proliferation, laser marks, a previous history of vitreous hemorrhage, and retinal surgery. The patient database was developed prospectively and

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clinical data were analyzed retrospectively. This study was performed according to the guidelines of the Declaration of Helsinki, and all subjects gave their informed consent to participate in this study, which was approved by the local Ethics Committee.

Clinical outcomes

The primary endpoint was the occurrence of a major adverse cardiac event (MACE), defined as a composite of cardiac death, myocardial infarction, and acute heart failure requiring emergency admission. Myocardial infarction was defined as an event with a new elevation in serum creatine kinase and/or evolutionary ST elevation, the development of new Q waves, or the presence of left bundle branch block. Patients were followed for up to 5 years.

Other definitions

Estimated glomerular filtration rate (eGFR) was calculated using the revised Japanese equation: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (in females) [8]. Left ventricular ejection fraction (LVEF) was assessed using echocardiography. Hypertension was defined as systolic/diastolic blood pressure (SBP/DBP) >140/90 mmHg, or as having received treatment for hypertension. Duration of diabetes was defined as the period from first diagnosis of DM to PCI procedure. The residual SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, determined as the SYNTAX score remaining after PCI, was assessed in patients without coronary artery bypass graft history [9].

Statistical analysis

Data are presented as mean ± SD. Categorical variables are expressed as counts and percentages. Continuous data were compared by using unpaired *t*-tests. Categorical data were compared using the χ^2 test. Cumulative survival rates in each group were analyzed using the Kaplan–Meier method, and the survival rate differences between the groups were estimated using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated for each factor using Cox univariate analysis. Cox multivariate regression analysis was performed to determine independent predictors of MACE. Factors with $p < 0.2$ on univariate analysis were entered into the multivariate Cox regression analysis. A p-value < 0.05 was considered statistically significant. All analyses were performed using the SPSS 18.0 software package (SPSS, Chicago, IL, USA).

Table 1
Baseline patient characteristics.

	DR+ (n = 47)	DR− (n = 41)	p-Value
Age (years)	66 ± 11	69 ± 8	0.196
Male, n (%)	42 (89%)	28 (68%)	0.015
Hypertension, n (%)	39 (83%)	27 (66%)	0.064
Dyslipidemia, n (%)	39 (83%)	32 (78%)	0.559
Diabetes mellitus, n (%)	47 (100%)	41 (100%)	–
Hemoglobin A1c, %	7.6 ± 1.2	7.2 ± 1.1	0.103
Status of diabetic retinopathy, n			
Mild to moderate non proliferative	23	–	
Severe non proliferative	7	–	
Proliferative	17	–	
Duration of diabetes mellitus, (years)	20 ± 9	11 ± 9	<0.001
Current smoking, n (%)	12 (26%)	12 (29%)	0.678
eGFR (mL/min/1.73 m^2)	50.1 ± 26.5	68.3 ± 23.3	0.001
eGFR <60, n (%)	26 (55%)	15 (37%)	0.079
Prior myocardial infarction, n (%)	9 (19%)	3 (7%)	0.129
Prior CABG, n (%)	9 (19%)	2 (5%)	0.056
LVEF, %	60.5 ± 13.7	67.0 ± 7.4	<0.01
E/e'	15.6 ± 5.7	13.5 ± 5.0	0.123
Target lesion, n (%)			
Left main trunk	0 (0%)	0 (0%)	0.205
Left anterior descending artery	22 (47%)	23 (56%)	
Left circumflex artery	4 (9%)	7 (17%)	
Right coronary artery	19 (40%)	11 (27%)	
Graft	2 (4%)	0 (0%)	
DES use, n (%)	21 (45%)	18 (44%)	0.942
Residual SYNTAX score, n			
0–8	28	26	0.501
9+	10	13	
Medication, n (%)			
Aspirin	46 (98%)	41 (100%)	1
Thienopyridine	39 (83%)	33 (80%)	0.762
Statin	29 (62%)	23 (56%)	0.594
ACEI/ARB	33 (70%)	24 (59%)	0.253
β-Blocker	14 (30%)	7 (17%)	0.163
Ca-antagonist	26 (55%)	20 (49%)	0.54
Insulin	25 (53%)	16 (39%)	0.184
Sulfonylurea	13 (28%)	12 (29%)	0.867
Alpha-glucosidase inhibitor	13 (28%)	16 (39%)	0.258
DPP-4 inhibitor	3 (6%)	4 (10%)	0.423
Biganide	11 (23%)	6 (15%)	0.299
Glitazone	5 (11%)	3 (7%)	0.436
Glinide	1 (2%)	4 (10%)	0.141

eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; DES, drug-eluting stent; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker; DPP, dipeptidyl peptidase.

Results

The baseline characteristics of all patients are shown in Table 1. There were significantly more males in the DR+ group than in the DR− group. No significant differences were observed between the groups with regard to age, the presence of hypertension or dyslipidemia, and smoking status. The patients in DR+ group had longer duration of DM. Insulin use and hemoglobin A1c levels tended to be higher in the DR+ group than in the DR− group, but the differences were not significant. The mean eGFR level in the DR+ group was significantly lower than that in the DR− group. Rates of medication use did not significantly differ between the groups. LVEF, determined using echocardiography, was lower in the DR+ group than in the DR− group.

The 88 eligible patients were followed for a mean of 1057 ± 583 days. The cumulative MACE-free survival rate was calculated for both groups using the Kaplan–Meier method (Fig. 1a). The MACE-free survival rate was significantly lower in the DR+ group than in the DR− group (p = 0.002). The cumulative event-free survival curves for cardiac death, myocardial infarction, and acute heart failure requiring emergency admission are shown in Fig. 1b–d, respectively. Event-free survival for cardiac death tended to be lower in the DR+ group than in the DR− group (p = 0.056). Event-free survival rates for both myocardial infarction and heart failure were significantly lower in the DR+ group than in the DR− group (p = 0.025 and p = 0.022, respectively). Table 2 shows the details of events during follow-up.

Multivariate Cox proportional hazard analysis indicated that the presence of DR was a significant and independent predictor of MACE (HR: 8.7; 95% CI: 1.1–69.8, p = 0.042; Table 3).

Discussion

DR is a common microvascular diabetic complication. In this study, we showed that the presence of DR was a significant predictor of late cardiac events following PCI.

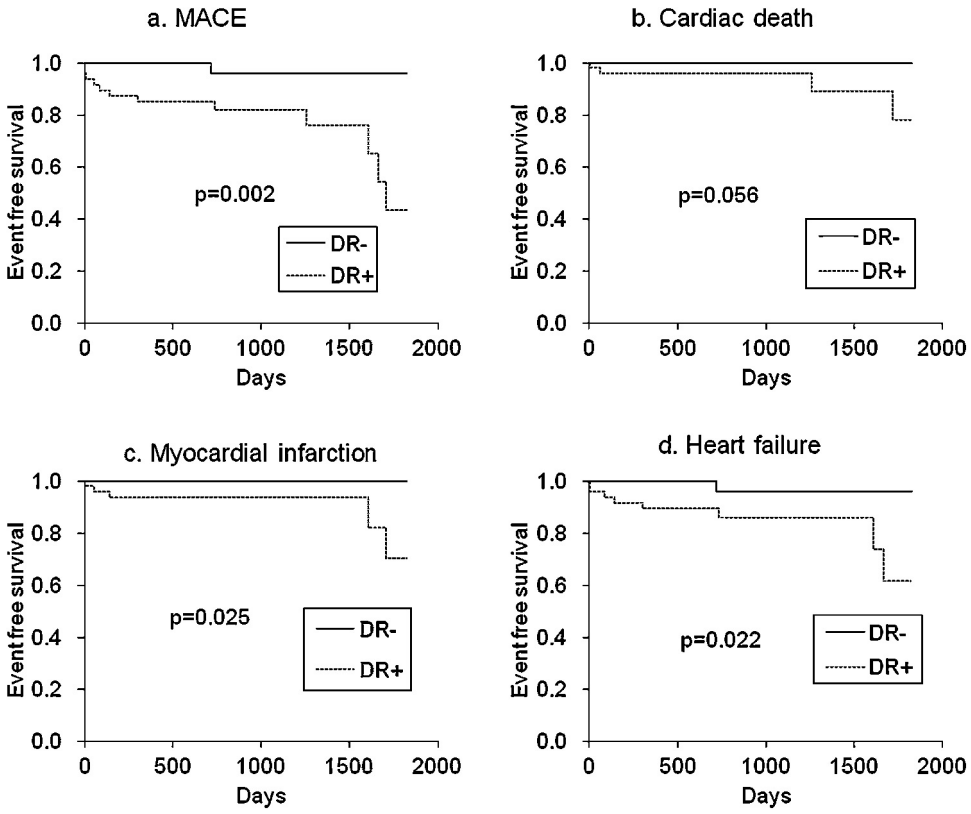

Fig. 1. (a) The cumulative MACE-free survival rate was calculated for both groups using the Kaplan–Meier method. The MACE-free survival rate was significantly lower in the DR+ group than in the DR− group ($p = 0.002$). (b) Event-free survival rate for cardiac death tended to be lower in the DR+ group than in the DR− group ($p = 0.056$). (c) Event-free rate for myocardial infarction was significantly lower in the DR+ group than in the DR− group ($p = 0.025$). (d) Event-free rate for heart failure was significantly lower in the DR+ group than in the DR− group ($p = 0.022$). DR, diabetic retinopathy; MACE, major adverse cardiac events.

Table 2
Incidence of MACE during follow-up.

	DR+ ($n = 47$)	DR− ($n = 41$)
MACE, *n*	12	1
Cardiac death	4	0
Myocardial infarction	5	0
Acute heart failure requiring emergency admission	8	1

MACE, major adverse cardiac events; DR, diabetic retinopathy.

Several epidemiologic studies have shown that the presence of DR is associated with increased all-cause and cardiovascular mortality risk in diabetic patients [1,2,10]. According to a recently reported meta-analysis of 20 observational studies, the presence of any degree of DR in patients with type 2 diabetes increases the chance of all-cause mortality and/or cardiovascular events by 2.34 times as compared with diabetic patients without DR [1].

The presence of DR has also been shown to be a predictor of heart failure, independent of preexisting coronary heart disease [3,4]. Cheung et al. demonstrated that the presence of DR was associated with concentric remodeling independent of traditional

Table 3
Predictors for MACE: Cox proportional hazards analysis.

	Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Male	1.379 (0.305–6.230)	0.676		
Age	1.001 (0.945–1.061)	0.966		
Hypertension	1.883 (0.417–8.501)	0.410		
Dyslipidemia	1.190 (0.263–5.378)	0.821		
Current smoking	1.781 (0.519–6.108)	0.359		
Prior myocardial infarction	1.737 (0.474–6.371)	0.405		
Prior CABG	1.715 (0.376–7.810)	0.486		
Body mass index	1.084 (0.945–1.243)	0.249		
eGFR	0.979 (0.959–0.998)	0.033	0.986 (0.966–1.008)	0.207
LVEF	0.963 (0.925–1.003)	0.070	0.977 (0.938–1.018)	0.265
E/e'	1.027 (0.899–1.173)	0.693		
HbA1c	0.999 (0.647–1.544)	0.998		
The presence of DR	11.966 (1.550–92.357)	0.017	8.705 (1.086–69.76)	0.042

HR, hazard ratio; CI, confidence interval; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; Hb, hemoglobin; DR, diabetic retinopathy.

risk factors and coronary atherosclerosis, by measuring LV mass and volume with cardiac magnetic resonance imaging [11]. Takeda et al. have shown an association between DR and LV diastolic dysfunction by assessing the diastolic index of echocardiographic color kinesis [12]. DR is a microvascular complication, and its presence appears to reflect the dysfunctioning of the coronary microcirculation to some extent. The above reports may in part explain the increased incidence of heart failure in DM patients with DR.

As described above, the presence of DR predicts long-term cardiovascular events and heart failure in diabetic patients. Furthermore, some studies have reported an association between cardiac events and DR in DM patients with coronary artery disease receiving coronary revascularization [5–7,13]. However, the number of such reports is limited and further data on this issue are needed. In this Japanese cohort study, we showed that the presence of DR was an independent predictor of late adverse cardiac events, including cardiac death, myocardial infarction, and acute heart failure requiring emergency admission following PCI. Furthermore, patients with DR had significantly higher incidence rates of both myocardial infarction and heart failure when each event was analyzed separately. The occurrence of cardiac death tended to be higher in patients with DR than in those without DR. We consider the absence of a statistically significant difference between the groups in the case of cardiac death to be a consequence of our small patient sample. According to our results, the presence of DR could predict late cardiac events following elective PCI. DR is still not widely used as a common predictive marker. However, we should assess the presence of DR in diabetic patients receiving PCI and consider the DR patients as subjects who require more careful follow-up.

The presence of even mild chronic kidney disease (CKD) is an established predictor of adverse prognosis after PCI [14–18]. In this study, patients with DR had lower eGFR levels and tended to have a higher prevalence of CKD than those without DR. However, the presence of DR remained a significant predictor of late cardiac events following PCI after adjustment for eGFR.

Our study has several limitations. First, this was a single center study with a relatively small population. Second, we excluded patients for whom we could not obtain the results of ophthalmologic examination. Large multicenter prospective clinical investigations are required to further explore this issue.

In conclusion, we showed that the presence of DR was a significant predictor of late cardiac events following PCI. This result can be of benefit in daily clinical practice, and ophthalmologic examination for the detection of DR might be required as routine practice in diabetic patients undergoing PCI.

References

[1] Kramer CK, Rodrigues TC, Canani LH, Gross JL, Azevedo MJ. Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: meta-analysis of observational studies. Diabetes Care 2011;34:1238–44.
[2] Kawasaki R, Tanaka S, Abe S, Sone H, Yokote K, Ishibashi S, Katayama S, Ohashi Y, Akanuma Y, Yamada N, Yamashita H. Risk of cardiovascular diseases is increased even with mild diabetic retinopathy: The Japan Diabetes Complications Study. Ophthalmology 2013;120:574–82.
[3] Cheung N, Wang JJ, Rogers SL, Brancati F, Klein R, Sharrett AR, Wong TY. Diabetic retinopathy and risk of heart failure. J Am Coll Cardiol 2008;51:1573–8.
[4] Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, Folsom AR, Klein R. Retinopathy and risk of congestive heart failure. JAMA 2005;293:63–9.
[5] Briguori C, Condorelli G, Airoldi F, Manganelli F, Violante A, Focaccio A, Ricciardelli B, Colombo A. Impact of microvascular complications on outcome after coronary stent implantations in patients with diabetes. J Am Coll Cardiol 2005;45:464–6.
[6] Ono T, Kobayashi J, Sasako Y, Bando K, Tagusari O, Niwaya K, Imanaka H, Nakatani T, Kitamura S. The impact of diabetic retinopathy on long-term outcome following coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:428–36.
[7] Ono T, Ohashi T, Asakura T, Ono N, Ono M, Motomura N, Takamoto S. Impact of diabetic retinopathy on cardiac outcome after coronary artery bypass graft surgery: prospective observational study. Ann Thorac Surg 2006;81:608–12.
[8] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.
[9] Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012;59:2165–74.
[10] Sasaki A, Uehara M, Horiuchi N, Hasegawa K, Shimizu T. A 15-year follow-up study of patients with non-insulin-dependent diabetes mellitus (NIDDM) in Osaka, Japan. Factors predictive of the prognosis of diabetic patients. Diabetes Res Clin Pract 1997;36:41–7.
[11] Cheung N, Bluemke DA, Klein R, Sharrett AR, Islam FM, Cotch MF, Klein BE, Criqui MH, Wong TY. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol 2007;50:48–55.
[12] Takeda Y, Sakata Y, Mano T, Ohtani T, Tamaki S, Omori Y, Tsukamoto Y, Aizawa Y, Komuro I, Yamamoto K. Diabetic retinopathy is associated with impaired left ventricular relaxation. J Card Fail 2011;17:556–60.
[13] Kim YH, Hong MK, Song JM, Han KH, Kang DH, Song JK, Kim JJ, Park SW, Park SJ. Diabetic retinopathy as a predictor of late clinical events following percutaneous coronary intervention. J Invasive Cardiol 2002;14:599–602.
[14] Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, Berger PB. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–9.
[15] Reinecke H, Trey T, Matzkies F, Fobker M, Breithardt G, Schaefer RM. Grade of chronic renal failure, and acute and long-term outcome after percutaneous coronary interventions. Kidney Int 2003;63:696–701.
[16] Ix JH, Mercado N, Shlipak MG, Lemos PA, Boersma E, Lindeboom W, O'Neill WW, Wijns W, Serruys PW. Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). Am Heart J 2005;149:512–9.
[17] Kumagai S, Ishii H, Amano T, Uetani T, Kato B, Harada K, Yoshida T, Ando H, Kunimura A, Shimbo Y, Kitagawa K, Hayashi M, Yoshikawa D, Matsubara T, Murohara T. Impact of chronic kidney disease on the incidence of peri-procedural myocardial injury in patients undergoing elective stent implantation. Nephrol Dial Transplant 2012;27:1059–63.
[18] Yoda S, Nakanishi K, Tano A, Kasamaki Y, Kunimoto S, Matsumoto N, Sato Y, Hirayama A. Risk stratification of cardiovascular events in patients at all stages of chronic kidney disease using myocardial perfusion SPECT. J Cardiol 2012;60:377–82.