

# The Impact of Diabetic Retinopathy on Long-Term Outcome Following Coronary Artery Bypass Graft Surgery

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<b>OBJECTIVES</b>	We sought to assess the impact of diabetic retinopathy on long-term outcome among patients with diabetes and multivessel coronary artery disease (MVD) following coronary artery bypass graft surgery (CABG).
<b>BACKGROUND</b>	For diabetics, CABG is the preferred revascularization strategy. Diabetic retinopathy is a major microvascular complication of diabetes, and its severity is directly related to total glycemic exposure.
<b>METHODS</b>	We identified 223 consecutive diabetics with MVD whose retinæ were evaluated within one year prior to CABG. The most recent ophthalmologic records up until the time of CABG were used to evaluate the severity of retinopathy. The median follow-up after CABG was 11.6 years.
<b>RESULTS</b>	Diabetic retinopathy was a strong independent predictor of overall mortality (relative risk [RR], 4.0), and repeat revascularization (RR, 3.0). In separate analyses of diabetics with retinopathy and without retinopathy, predictors of mortality differed significantly between the two groups. Among diabetics with retinopathy, the presence of either preoperative renal (RR, 2.5) or ventricular (RR, 2.0) dysfunction had unfavorable effects on mortality, but the survival curves did not differ significantly according to the presence or absence of internal thoracic artery (ITA) grafting. In comparison, among diabetics without retinopathy, ITA grafting (RR, 0.34) had a beneficial effect on mortality, and the survival curves varied somewhat according to the presence or absence of renal or ventricular dysfunction.
<b>CONCLUSIONS</b>	Diabetics with retinopathy had a distinct post-CABG course with a worse long-term prognosis, as compared with diabetics without retinopathy. Retina evaluation is useful for prediction of long-term prognosis and management of diabetics who need CABG. (J Am Coll Cardiol 2002;40:428–36) © 2002 by the American College of Cardiology Foundation

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Coronary artery bypass graft surgery (CABG) is the preferred strategy for coronary revascularization in patients with diabetes mellitus and multivessel coronary artery disease (MVD) (1–6). However, even after CABG, the long-term outcome among diabetics is suboptimal as compared with among nondiabetics. This unfavorable prognosis is believed to be related to more rapid progression of atherosclerosis within native coronary arteries and grafts, a high prevalence of myocardial infarction (MI) and persistence or recurrence of congestive heart failure among diabetics who have undergone CABG (6–10). In addition, it was reported that long-term outcome among diabetics after CABG was associated with severity of diabetes at the time of surgery (11).

Diabetic retinopathy (DR) is one of the microvascular complications of diabetes, and its severity is directly related to the severity and duration of hyperglycemia (12–14). Recently, epidemiologic studies have reported that patients with severe DR have a high risk of death from coronary artery disease (CAD) (15,16). Therefore, diabetics with

retinopathy could constitute some proportion of candidates for CABG. However, little is known about the prognostic value of DR among diabetics after CABG. We conducted this study to assess the impact of DR on the long-term outcome of CABG among diabetics.

## METHODS

**Patients.** We identified 1,392 consecutive patients who underwent CABG between April 1977 and May 1993 at the National Cardiovascular Center, Osaka, Japan. Patients were eligible for inclusion in our study if: 1) they underwent first-time CABG for MVD; 2) they were considered to have diabetes mellitus if medical records review revealed that they were diagnosed as having type 2 diabetes and had received medical treatment (hypoglycemic agents or insulin injection) for diabetes at the time of CABG; and 3) they had undergone ophthalmologic examination for detection and treatment of DR within one year prior to CABG at the Department of Ophthalmology in our center. A total of 269 patients met these criteria. Furthermore, 46 patients were excluded from the study: 38 because of inadequate data concerning severity of DR, and 8 because they had nondiabetes-related retinopathy (4 had retinal branch vein occlusion, 3 had central retinal vein occlusion and 1 had

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#### Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CI	= confidence interval
DR	= diabetic retinopathy
ITA	= internal thoracic artery
MI	= myocardial infarction
MVD	= multivessel coronary artery disease
NPDR	= nonproliferative diabetic retinopathy
PDR	= proliferative diabetic retinopathy
RR	= relative risk

branch retinal artery obstruction). The remaining 223 patients' baseline characteristics concerning demographic data, medical history, coronary risk factors, preoperative and postoperative angiographic data and operative data were collected from medical and surgical records. Causes of death were determined by a review of hospital records and written questionnaires. All repeat revascularization procedures were documented for each patient during the entire follow-up period. The findings reported in this study were documented for all patients as of March 10, 2001.

**Assessment of DR.** Ophthalmologic records including ophthalmologic charts, fundus photography and fluorescein retinal angiography were reviewed to evaluate patients' retinopathy. We used the most recent ophthalmologic records up until the time of CABG to approximate the stage of DR at the time of surgery. According to a modification of the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study grading scale, the severity in the worst affected eye was used, and the patients with retinopathy were grouped into three categories of retinopathy: those with mild-to-moderate nonproliferative diabetic retinopathy (NPDR) (only microaneurysms or microaneurysms plus one or more the following: retinal hemorrhages, soft exudates, hard exudates, intraretinal microvascular abnormalities or venous beading); those with severe stage of NPDR (at least three of the following: extensive retinal hemorrhages or microaneurysms, soft exudates, intraretinal microvascular abnormalities and venous beading in two or more quadrants); those with proliferative diabetic retinopathy (PDR) (the presence of new vessels, preretinal or vitreous hemorrhages, panretinal photocoagulation scars and a history of vitrectomy) (17,18).

**Statistical analysis.** We analyzed the data using SPSS for Windows (version 10.0, SPSS Inc., Tokyo, Japan). Descriptive data for continuous variables are presented as means  $\pm$  SD. Baseline characteristics of the patient groups were compared by chi-square test or the Fisher exact test for categorical variables. The student *t* test was used for continuous variables. Overall mortality and repeat revascularization rates were estimated according to Kaplan-Meier methods and were compared using the log-rank test (19,20). We used a Cox proportional-hazards model to estimate the prognostic effect of the variables (21). The potential prognostic variables, which were significant in univariate analy-

sis, were entered into the multivariate model. The following variables were considered as potential prognostic variables: older age ( $\geq 65$  years), female gender, prior MI, unstable angina, hypertension, current smoking, treatment with insulin, hyperglycemia (blood fasting glucose  $\geq 140$  mg/dl), hypercholesterolemia (cholesterol  $\geq 200$  mg/dl), high level of low-density lipoprotein cholesterol ( $\geq 140$  mg/dl), low level of high-density lipoprotein cholesterol ( $\leq 50$  mg/dl), hypertriglyceridemia (triglyceride  $\geq 130$  mg/dl), preoperative renal dysfunction (serum creatinine  $\geq 1.4$  mg/dl), triple-vessel coronary disease, preoperative left ventricular dysfunction (ejection fraction  $< 50\%$ ), internal thoracic artery (ITA) grafting, the small number of grafts used (no.  $< 3$ ), complete revascularization and the presence of grafts with  $\geq 50\%$  luminal stenosis at discharge. Completeness of revascularization was defined as all diseased coronary systems receiving at least one graft. Two-sided *p* values of  $< 0.05$  were considered indicative of a statistically significant difference.

## RESULTS

**Fundus findings.** Fundus findings of the 223 diabetics are shown in Table 1. One hundred forty-four (64.6%) diabetics did not have retinopathy and 79 (35.4%) had DR. Among 79 diabetics with retinopathy, 39 patients were

**Table 1.** Fundus Findings of Type 2 Diabetic Patients Who Underwent CABG\*

Fundus Findings	No. of Patients (%)
No retinopathy	144 (64.6)
Mild-to-moderate NPDR	39 (17.5)
Microaneurysms only	10
Microaneurysms, retinal hemorrhages and hard exudates	17
Microaneurysms, retinal hemorrhages and soft exudates	12
Severe stage of NPDR	14 (6.3)
Extensive† microaneurysms, retinal hemorrhages and soft exudates	9
Extensive† microaneurysms, retinal hemorrhages, soft exudates and intraretinal microvascular abnormalities	5
PDR	26 (11.7)
Neovascularization‡	6
Preretinal hemorrhage	2
Vitreous hemorrhage	6
Panretinal photocoagulation scar§	6
History of vitrectomy	6
Total	223

\*Fundus findings were grouped according to severity of diabetic retinopathy prior to coronary artery bypass graft surgery (CABG). †"Extensive" means involvement of two or more quadrants of retina. ‡The patients who had both neovascularization and preretinal or vitreous hemorrhage were counted as having preretinal or vitreous hemorrhage. §The patients who had preretinal or vitreous hemorrhage after panretinal photocoagulation were counted as having preretinal or vitreous hemorrhage. ||Vitreous hemorrhage or tractional retinal detachment was included, but vitrectomy for macular edema was not. Patients who had preretinal or vitreous hemorrhage after vitrectomy were counted as having preretinal or vitreous hemorrhage.

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative retinopathy.

**Table 2.** Baseline Characteristics of Type 2 Diabetic Patients Who Underwent CABG According to the Presence or Absence of Diabetic Retinopathy\*

Characteristic	Diabetics With Retinopathy (n = 79)	Diabetics Without Retinopathy (n = 144)	p Value
Demographic profile			
Mean age (yrs)	60.8 ± 8.3	60.1 ± 9.4	0.55
Age ≥65 yrs, no. (%)	23 (29.1)	40 (27.8)	0.83
Female gender, no. (%)	19 (24.1)	32 (22.2)	0.75
Medical history			
Prior myocardial infarction, no. (%)	43 (54.4)	70 (48.6)	0.41
Unstable angina, no. (%)	11 (13.9)	22 (15.3)	0.79
Hypertension, no. (%)	45 (57.0)	62 (43.1)	0.049
Current smoking, no. (%)	39 (49.4)	74 (51.4)	0.77
Treatment with insulin, no. (%)	30 (38.0)	21 (14.6)	<0.001
Clinical profile			
Mean blood fasting glucose (mg/dl)	122.9 ± 17.9	118.2 ± 21.1	0.097
Blood fasting glucose ≥140 mg/dl, no. (%)	24 (30.4)	35 (24.3)	0.33
Mean serum total cholesterol (mg/dl)	192.8 ± 41.8	192.5 ± 39.8	0.96
Serum total cholesterol ≥200 mg/dl, no. (%)	35 (44.3)	58 (40.3)	0.56
Mean serum LDL (mg/dl)	132.8 ± 34.2	134.2 ± 32.1	0.89
Serum LDL ≥140 mg/dl	30 (38.0)	52 (36.1)	0.78
Mean serum HDL (mg/dl)	61.2 ± 13.2	63.6 ± 11.2	0.78
Serum HDL ≤50 mg/dl	25 (31.6)	33 (22.9)	0.15
Mean serum triglycerides (mg/dl)	150 ± 59.7	141 ± 56.6	0.29
Serum triglycerides ≥130 mg/dl, no. (%)	42 (53.2)	71 (49.3)	0.58
Mean serum creatinine (mg/dl)	1.2 ± 0.3	1.1 ± 0.5	0.31
Serum creatinine ≥1.4 mg/dl, no. (%)	17 (25.3)	22 (15.3)	0.24
Preoperative angiographic profile			
Triple-vessel disease, no. (%)	59 (74.5)	99 (68.8)	0.35
Mean ejection fraction (%)	52.4 ± 11.3	53.9 ± 12.8	0.39
Ejection fraction <50%, no. (%)	34 (43.0)	53 (36.8)	0.36
CABG			
ITA grafting, no. (%)	36 (45.6)	82 (56.9)	0.10
Mean number of grafts	2.7 ± 0.4	2.6 ± 1.0	0.88
Number of grafts <3, no. (%)	35 (44.3)	78 (54.2)	0.16
Complete revascularization	53 (67.1)	102 (70.1)	0.56
Postoperative angiographic profile			
Number of graft stenosis ≥50%, no. (%)	9 (4.2)	14 (3.7)	0.77
Postoperative medication			
ACE inhibitor, no. (%)	32 (40.1)	60 (41.2)	0.87
Beta-blocker, no. (%)	39 (49.3)	68 (47.2)	0.76
Calcium-channel blocker, no. (%)	48 (62.0)	83 (57.6)	0.65
Diuretics, no. (%)	35 (44.3)	61 (42.3)	0.78
Lipid-lowering drugs, no. (%)	25 (31.6)	42 (29.2)	0.70
Nitrates, no. (%)	13 (16.5)	19 (13.2)	0.51

\*Plus-minus values are mean ± SD.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; HDL = high-density lipoprotein; ITA = internal thoracic artery; LDL = low-density lipoprotein.

grouped as having mild-to-moderate NPDR, 14 as having severe NPDR and 26 patients as having PDR.

**Baseline characteristics.** The baseline characteristics of the 223 patients according to the presence or absence of retinopathy are shown in Table 2. As compared with diabetics without retinopathy, a larger proportion of diabetics with retinopathy were treated with insulin ( $p < 0.001$ ) and had hypertension ( $p = 0.049$ ).

**DR and mortality.** The average follow-up from the time of CABG was  $11.6 \pm 4.9$  years. During the entire follow-up, of 79 diabetics with retinopathy, 48 (60.8%) died and of 144 diabetics without retinopathy, 27 (18.8%) died. Table 3 shows the causes of death in both groups. Among diabetics

with retinopathy, 32 (40.5%) patients died from cardiac causes: 13 (16.5%) patients from acute MI, 18 (22.8%) from congestive heart failure and 1 (1.3%) from ventricular arrhythmia. Diabetics with retinopathy were more likely to die from acute MI ( $p = 0.008$ ) and from congestive heart failure ( $p < 0.001$ ), as compared with diabetics without retinopathy.

The 12-year overall mortality was 59.5% (95% confidence interval [CI], 47.9 to 71.2%) for diabetics with retinopathy and 18.0% (95% CI, 11.5 to 24.5%) for diabetics without retinopathy. As shown in Figure 1A, overall survival curves differed significantly according to the presence or absence of retinopathy ( $p < 0.001$ ). Multivariate analysis demonstrated

**Table 3.** Causes of Death According to the Presence or Absence of Diabetic Retinopathy During the Entire Follow-Up

Causes	Diabetics With Retinopathy (n = 79)	Diabetics Without Retinopathy (n = 144)	p Value
All causes, no. (%)	48 (60.8)	27 (18.8)	<0.001
Cardiac causes, no. (%)	32 (40.5)	10 (6.4)	<0.001
Acute myocardial infarction, no. (%)	13 (16.5)	8 (5.6)	0.008
Congestive heart failure, no. (%)	18 (22.8)	2 (1.4)	<0.001
Ventricular arrhythmia, no. (%)	1 (1.3)	0	—
Cerebrovascular accidents, no. (%)	5 (6.3)	4 (2.8)	0.20
Malignancy, no. (%)	4 (5.1)	4 (2.8)	0.38
Pneumonia, no. (%)	3 (3.8)	2 (1.4)	0.25
Mediastinitis, no. (%)	3 (3.8)	0	—
Other causes, no. (%)*	1 (1.3)	7 (4.9)	0.95

\*Other causes include gastrointestinal disease other than malignancy, aortic disease, diabetic ketoacidosis, suicide and accident.

that the presence of retinopathy was an independent predictor of all-causes death (adjusted relative risk [RR], 4.01; 95% CI, 2.41 to 6.68;  $p < 0.001$ ).

**DR and repeat revascularization.** During the entire follow-up, 72 patients (32.3%) underwent repeat revascularization: 63 patients (28.3%) underwent additional percutaneous coronary intervention and 9 patients (4.0%) underwent additional CABG. Of 79 diabetics with retinopathy, 36 patients (45.6%) underwent repeat revascularization, whereas of 144 diabetics without retinopathy 36 (16.1%) underwent repeat revascularization. Repeat revascularization rate at 12 years was 63.7% (95% CI, 49.7 to 77.6%) for diabetics with retinopathy and 23.4% (95% CI, 15.8 to 31.0%) for diabetics without retinopathy. As shown in Figure 1B, repeat revascularization rate curves differed significantly between the two groups ( $p < 0.001$ ). Multivariate analysis showed that the presence of retinopathy was an independent predictor of repeat revascularization (adjusted RR, 3.04; 95% CI, 1.89 to 4.87;  $p < 0.001$ ).

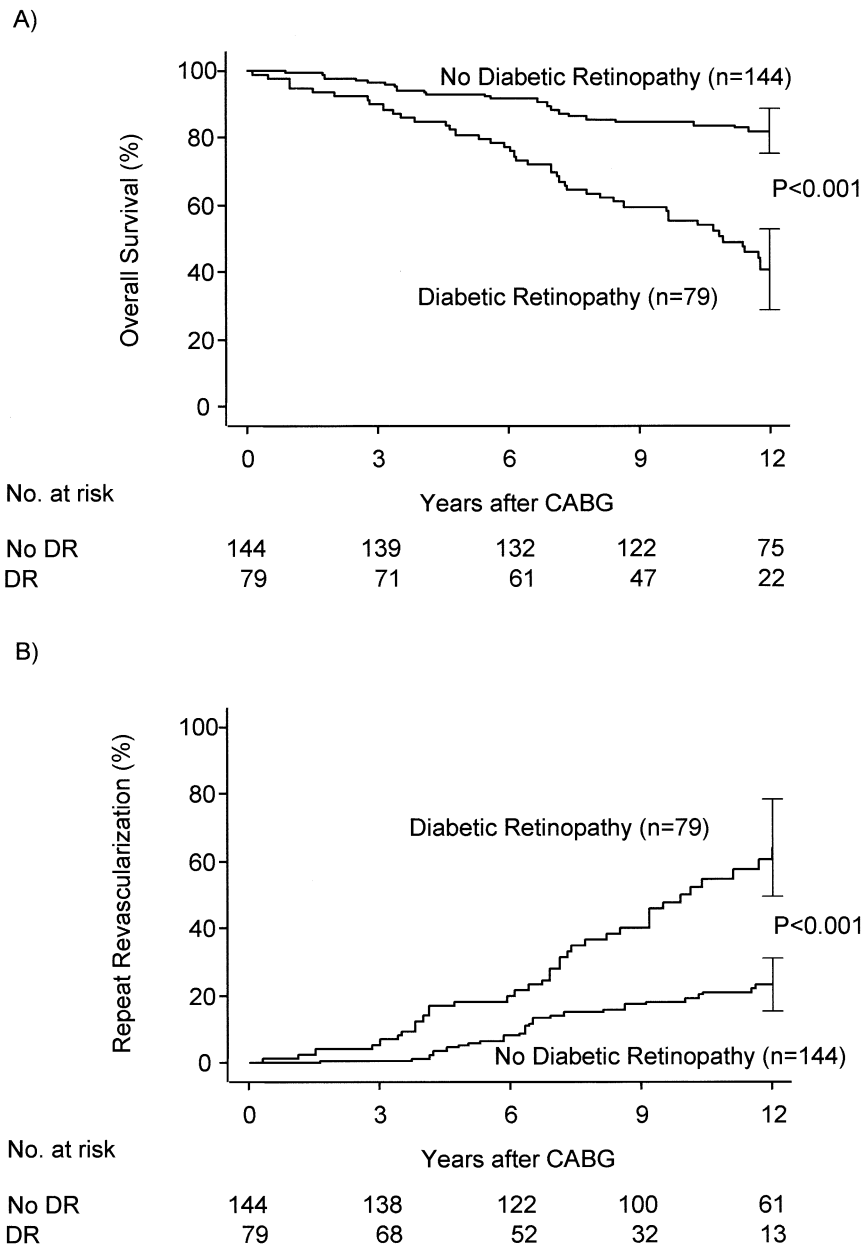
**Separate analyses of diabetics with retinopathy and without retinopathy.** Diabetics with retinopathy had a distinct post-CABG course from diabetics without retinopathy. Therefore, we studied predictors of all-causes death of the two groups separately. Predictors of overall mortality were significantly different between the two groups (Table 4). As shown in Figures 2 and 3, among diabetics with retinopathy, survival curves varied significantly according to the presence or absence of preoperative renal or left ventricular dysfunction. The presence of renal dysfunction (adjusted RR, 2.46; 95% CI, 1.33 to 4.57;  $p = 0.004$ ) and left ventricular dysfunction (adjusted RR, 2.04; 95% CI, 1.15 to 3.65;  $p = 0.016$ ) were independent predictors of all-causes death among diabetics with retinopathy. The survival curves did not differ significantly according to presence or absence of ITA graft ( $p = 0.13$ ) (Fig. 4). In comparison, among diabetics without retinopathy the survival curves were similar according to the presence or absence of preoperative renal (Fig. 2) or left ventricular dysfunction (Fig. 3). Among diabetics without retinopathy, treatment with insulin (adjusted RR, 3.01; 95% CI, 1.25 to 7.26;  $p = 0.014$ ) and ITA

grafting (adjusted RR, 0.34; 95% CI, 0.14 to 0.80;  $p = 0.011$ ) were independent predictors of overall mortality.

**Severity of DR and survival.** We estimated the degree of association between severity of retinopathy and long-term survival. Overall mortality at 12 years was 44.1% (95% CI, 27.4 to 60.8%) for patients with mild-to-moderate NPDR, 64.3% (95% CI, 39.2 to 89.4%) for patients with severe stage of NPDR and 82.1% (95% CI, 64.8 to 99.4%) for patients with PDR. We combined severe stage of NPDR and PDR into a single level of retinopathy because these two survival curves overlapped each other (survival curves not shown). As depicted in Figure 5, overall survival curves were stratified separately according to the severity of retinopathy. Patients with either severe-stage NPDR or PDR had a higher risk of all-causes mortality than patients with mild-to-moderate NPDR (RR, 2.10; 95% CI, 1.16 to 3.79;  $p = 0.012$ ). Furthermore, analysis using diabetics without retinopathy as the reference group (Table 5) demonstrated that patients with mild-to-moderate NPDR had a significantly higher risk of all-causes death (adjusted RR, 2.41; 95% CI, 1.28 to 4.53;  $p = 0.007$ ) and that patients with severe stage of NPDR or PDR had a considerably higher risk of all-causes death (adjusted RR, 5.62; 95% CI, 3.07 to 10.3;  $p < 0.001$ ).

## DISCUSSION

It has been demonstrated that diabetics with retinopathy have a distinct post-CABG course different from diabetics without retinopathy. Outcome among diabetics with retinopathy was characterized by high mortality and high repeat revascularization rate. In contrast, long-term survival among diabetics without retinopathy was excellent particularly when they underwent ITA grafting. The Bypass Angioplasty Revascularization Investigation reported a seven-year overall survival after CABG among nondiabetics of 86.4% and the Emory Angioplasty versus Surgery Trial reported 84% at eight years (2,3). In our study, overall survival rate among diabetics without retinopathy was 87.5% at seven years and 84.7% at eight years. We cannot directly compare



**Figure 1.** Kaplan-Meier estimates of the overall survival and repeat revascularization rate of type 2 diabetic patients following coronary artery bypass graft surgery (CABG), according to the presence or absence of diabetic retinopathy (DR). (A) The overall survival curves; (B) subsequent revascularization curves. DR = diabetic retinopathy. The p values were calculated by the log-rank test. I bars indicate 95% confidence intervals.

our results with previous reports because characteristics of patients and methods of studies are different. Nevertheless, in the present study long-term survival of diabetics without retinopathy seems to be as good as that of nondiabetics in other studies.

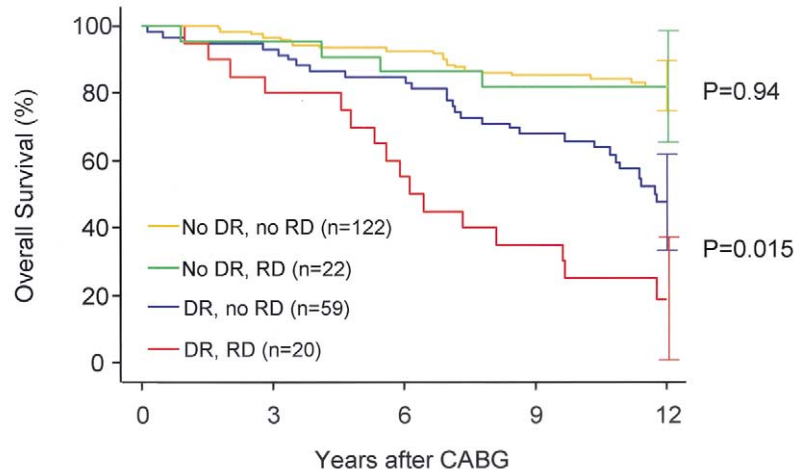
Repeat revascularization could have been due to: 1) completeness of revascularization; 2) surgical technique; 3) state of the coronary artery at initial CABG; and 4) progression of atherosclerosis within native coronary arteries and grafts following CABG. As for completeness of revascularization, we aimed at complete revascularization for all patients. However, complete revascularization was not always technically possible because of poor distal target vessel.

**Table 4.** Multivariate Analysis Among Diabetics With Retinopathy and Diabetics Without Retinopathy Who Underwent Coronary Artery Bypass Graft Surgery

Predictors of Overall Mortality	Adjusted Relative Risk* (95% CI)	p Value
Diabetics with retinopathy		
Serum creatinine $\geq 1.4$ mg/dl	2.46 (1.33-4.57)	0.004
Preoperative ejection fraction <50%	2.04 (1.15-3.65)	0.016
Diabetics without retinopathy		
Treatment with insulin	3.03 (1.25-7.30)	0.014
Internal thoracic artery grafting	0.34 (0.15-0.78)	0.010

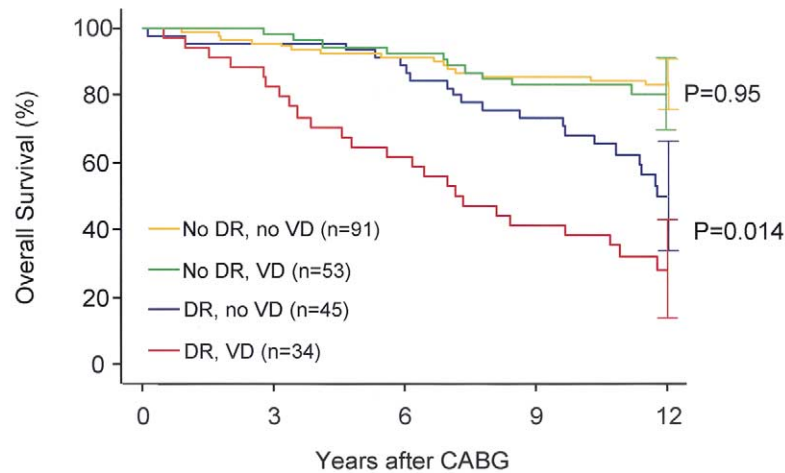
\*The analysis was adjusted for the prognostic variables, which were significant in univariate analysis.

CI = confidence interval.



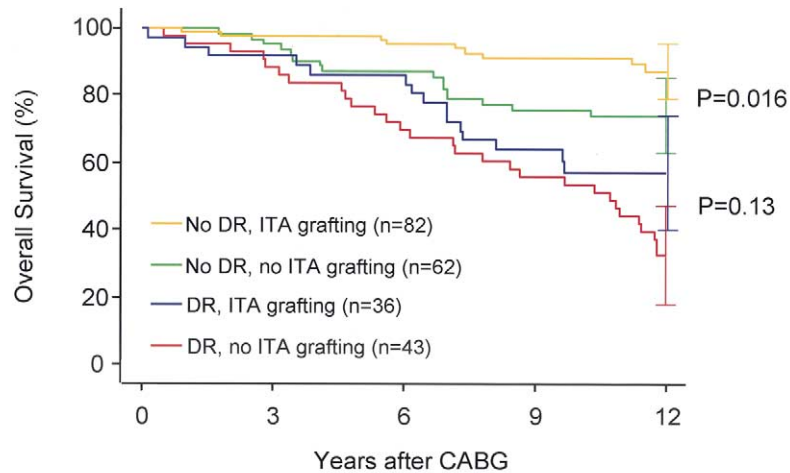
No. at risk					
No DR, no RD	122	118	113	104	67
No DR, RD	22	21	19	18	8
DR, no RD	59	55	50	40	20
DR, RD	20	16	11	7	2

**Figure 2.** Kaplan-Meier estimates of the overall survival of type 2 diabetic patients following coronary artery bypass graft surgery (CABG), according to presence or absence of renal dysfunction (RD) (serum creatinine  $\geq 1.4$  mg/dl). DR = diabetic retinopathy. The p values were calculated by the log-rank test. **I** bars indicate 95% confidence intervals.



No. at risk					
No DR, no VD	91	87	83	78	47
No DR, VD	53	52	49	44	28
DR, no VD	45	43	40	33	15
DR, VD	34	28	21	14	7

**Figure 3.** Kaplan-Meier estimates of the overall survival of type 2 diabetic patients following coronary artery bypass graft surgery (CABG), according to the presence or absence of left-ventricular dysfunction (VD) (ejection fraction  $< 50\%$ ). DR = diabetic retinopathy. The p values were calculated by the log-rank test. **I** bars indicate 95% confidence intervals.

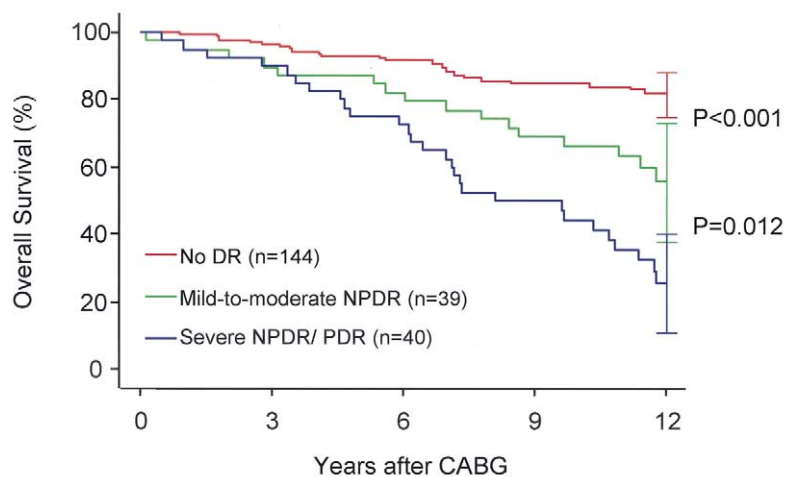


No. at risk					
No DR, ITA	82	80	78	75	34
No DR, no ITA	62	59	54	47	41
DR, ITA	36	33	31	23	8
DR, no ITA	43	38	30	25	14

**Figure 4.** Kaplan-Meier estimates of the overall survival of type 2 diabetic patients following coronary artery bypass graft surgery (CABG), according to the presence or absence of internal thoracic artery (ITA) grafting. DR = diabetic retinopathy. The p values were calculated by the log-rank test. **I bars** indicate 95% confidence intervals.

In our study, the absence of complete revascularization was a predictor of repeat revascularization (RR, 1.65; 95% CI, 1.03 to 2.65; p = 0.039) in the univariate analysis, but was not an independent predictor in the multivariate analysis. As

for surgical technique, in our hospital, cardiac catheterization was performed before discharge in all patients so as to access surgical success. The presence of grafts with luminal stenosis at discharge was not a predictor of repeat revascu-



No. at risk					
No DR	144	139	132	122	75
Mild-to-moderate	39	35	32	27	15
Severe/PDR	40	36	29	20	7

**Figure 5.** Kaplan-Meier estimates of the overall survival of type 2 diabetic patients following coronary artery bypass graft surgery (CABG), according to severity of diabetic retinopathy (DR). Overall survival curves were stratified separately according to severity of diabetic retinopathy. The p values were calculated by the log-rank test. **I bars** indicate 95% confidence intervals. NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

**Table 5.** Association Between Severity of Diabetic Retinopathy and Overall Mortality After CABG Among Type 2 Diabetic Patients

Severity of Diabetic Retinopathy	Adjusted Relative Risk* (95% CI)	p Value
No retinopathy†	1.00	
Mild-to-moderate NPDR	2.41 (1.28–4.53)	0.007
Severe stage of NPDR or PDR	5.62 (3.07–10.3)	< 0.001

\*The analysis was adjusted for treatment with insulin, high serum creatinine ( $\geq 1.4$  mg/dl), low ejection fraction (<50%) and internal thoracic artery grafting. †No retinopathy group served as the reference group.

CI = confidence interval; CABG = coronary artery bypass graft surgery; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

larization in our study. In addition, the rates of patency of the grafts did not vary according to the presence or absence of retinopathy.

Regarding the state of the coronary artery at initial CABG, our study demonstrated that the presence of triple-vessel disease was not a predictor of repeat revascularization, and the presence of DR at CABG was a strong independent predictor. We believe that diabetics with retinopathy might have more diffuse coronary disease, compared with diabetics without retinopathy, although a proportion of patients with triple-vessel disease did not differ significantly between the two groups. More diffuse coronary disease among diabetics with retinopathy might partly contribute to high repeat revascularization.

As for the progression of atherosclerosis within native coronary arteries and grafts following CABG, it is generally accepted that retinopathy does not correlate directly with macrovascular atherosclerosis within native coronary arteries and grafts. However, the association of retinopathy with microvascular dysfunction in turn probably could have a direct effect on progression of atherosclerosis. One possible explanation is that DR correlates with duration of disease, the severity of hyperglycemia and the adequacy of diabetic control. Diabetics with retinopathy, therefore, have had a longer period of poor-controlled diabetes and, therefore, are much more likely to have additional comorbidities and aggressive disease. In our study, diabetics with retinopathy were more likely to have hypertension. In addition, DR may be a marker of diabetic nephropathy. It is the hypertension and renal disease that are associated with progressive atherosclerosis.

In our study, the overall survival did not differ significantly among diabetics with and without ITA grafting in the presence of DR. This suggests that the effect of ITA grafting on the long-term survival among diabetics with retinopathy might be much smaller than among diabetes without retinopathy. The possible explanation is that among diabetics with retinopathy and advanced vascular disease, the benefit of ITA graft becomes small, because target distal coronary arteries are poor and diseased diffusely. Conversely, among diabetics without retinopathy, the caliber of the vessels may be better, which enables the superiority of the ITA on survival to become manifest.

It is interesting that in the absence of retinopathy there is

really no difference in overall survival among patients with and without renal dysfunction. The most likely explanation is that renal dysfunction in diabetics without retinopathy is not related to diabetic nephropathy. It may be that these are patients with renal dysfunction due to other factors such as hypertension. This may be why their prognosis is good.

We have shown that among diabetics with retinopathy the presence of preoperative left ventricular dysfunction had an unfavorable effect on survival. This finding might suggest that CABG conferred small improvement in survival and ventricular function among patients with these characteristics. In contrast, among diabetics without retinopathy the survival curves for patients with preoperative ventricular dysfunction were similar to those of patients without left ventricular dysfunction, suggesting that CABG conferred a significant improvement in ventricular function. Nahser et al. (22) reported that, in diabetics, coronary microvascular abnormalities may lead to myocardial ischemia in the absence of epicardial coronary atherosclerosis and contribute to ventricular dysfunction. We speculate that coronary microvascular abnormalities among diabetics with retinopathy is more profound than that among diabetics without retinopathy and that this difference may explain the unequal improvement after CABG between the two groups. Because CABG “bypasses” only the epicardial stenotic site of coronary artery, CABG alone might not be sufficient to improve ventricular function among diabetics with retinopathy.

The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study showed that tight glucose control reduced the risk of mortality after MI in diabetics (23,24). Several studies reported that poor glycemic control was associated with an increased risk of heart failure among diabetics (25,26). Considering that these adverse outcomes were more frequent among diabetics with retinopathy, it would be in this group of patients that a significant benefit could be conferred from strict glycemic control with insulin after CABG.

Nowhere is this more “visible” than in the eye, where the retinal circulation is thought to represent the cerebrovascular circulation because the retina develops from the forebrain (27). Furthermore, the retinal changes parallel the duration and severity of diabetes. We found a significant, graded association between the severity of retinopathy and overall mortality after CABG. Therefore, evaluation of retinopathy may provide a useful means of stratifying risk in the heterogeneous group of diabetics with coronary artery disease. Eye examination can be readily performed at the bedside using the direct ophthalmoscope and, therefore, is recommended for all diabetics who need coronary revascularization.

**Study limitations.** The present study has some limitations. First, our study included diabetics who had undergone eye examination at any time from one year up until CABG. Hence, the severity of retinopathy at the time of CABG may have been underestimated. Second, unrecognized biases might have led to the selection of patients referred for

eye examination. Diabetics who did not have an eye examination were not included in our study. Such patients might have severe retinopathy as a result of worse compliance with glycemic control and of less rigorous ophthalmologic care. However, the inclusion of consecutive patients minimized selection bias. Third, our patient population was small, but this could be compensated by a maximal follow-up of 22 years. Furthermore, with the high mortality among diabetics with retinopathy, power to detect differences in mortality should be sufficient. Fourth, data on the cause of death were obtained retrospectively; thus, we were unable to estimate precisely the impact of DR on cardiac survival.

**Conclusions.** Diabetic retinopathy has a profound impact on long-term outcome among diabetics with MVD after CABG. Evaluation of DR is informative for predicting long-term outcome after CABG and for developing treatment strategies for diabetics who need CABG.

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