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# Impact of diabetes on long term follow-up of elderly patients with chronic total occlusion post percutaneous coronary intervention

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**Abstract**

**Background** The prognosis of elderly patients with chronic total occlusion (CTO) and diabetes mellitus (DM) treated with percutaneous coronary intervention (PCI) is not known. **Objective** To investigate the effect of diabetes on long-term follow-up of CTO after PCI in elderly patients. **Methods** A total of 153 elderly patients (age > 65 years old) with CTO lesions which were successfully treated with PCI were enrolled. Fifty one patients with diabetes and 102 without diabetes were compared for long-term outcomes (mean follow up: 36 ± 12 months). Major adverse cardiac events (MACE) which include death, myocardial infarction or target lesion revascularization (TLR) were considered as a combined endpoint. **Results** The combined endpoint occurred in 29.4% of diabetes patients, and 11.3% of the patients without diabetes ($P < 0.05$). The Cox proportional hazards model identified: drug eluting stent (DES) or bare metal stent (BMS) (HR: 0.13, 95% confidence interval (95% CI): 0.03–0.62, $P = 0.004$), DM (HR: 6.69, 95% CI: 1.62–15.81, $P = 0.01$) and final minimal lumen diameter (MLD) (HR: 0.37, 95% CI: 0.13–0.90, $P = 0.03$ ) as independent predictors of MACE, DM with renal impairment (HR: 6.64, 95% CI: 1.32–33.36, $P = 0.02$), HBA1C on admission (HR: 1.79, 95% CI: 1.09–2.94, $P = 0.02$), as independent predictors of MACE at long term follow-up. **Conclusions** The study demonstrates that DM is a predictive factor for MACE in elderly CTO patients treated with PCI, type of stent, final minimal lumen diameter and DM with renal impairment, and HBA1C level on admission are predictors of MACE.

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**Keywords:** Diabetes; Chronic total occlusion; Percutaneous coronary intervention; Elderly patient; Drug eluting stent

## 1 Introduction

Percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) has aroused increased interest because of the improved success rate and clinical benefit after revascularization.[1–3] The introduction of drug eluting stents (DES) further contributed to a reduction of restenosis in CTO lesions.[4–7] A recent study also showed that DES use in elderly patients undergoing CTO-PCI was associated with lower mortality.[8] A previous report showed diabetes mellitus (DM) had a deleterious effect on the outcome of PCI.[9] Successful CTO-PCI in patients with DM was associated with a reduction in mortality and the need for coronary artery bypass grafting. Compared to non-insulin-dependent DM, patients with insulin-dependent DM had an increased risk for long-term mortality.[10] However, the effect of diabetes on the long-term outcome of percutanous treatment for CTO in elderly patient is not well understood.

In this article, we sought to investigate the effect of diabetes on the long-term follow-up of CTO after PCI in elderly patients.

## 2 Method

### 2.1 Patients

From January 2005 to April 2009, 186 patients ≥ 65 years old underwent PCI for CTO lesions in cardiovascular center, Toho University. One hundred and fifty three patients (82.2%) who underwent successful PCI for CTO lesions were included. One hundred and fifty eight CTO lesions were treated by PCI and successful implanted with either a bare metal stent (BMS), or a drug eluting stent (DES) which included sirolimus-eluting stents (SES, Cypher, Cordis, Johnson & Johnson, Miami Lakes, FL, USA) and paclitaxel-eluting stents (PES, Taxus, Boston Scientific Corp., Natick, MA, USA). The choice of stent was at the

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operator's discretion. Most patients without any contraindication for dual antiplatelet therapy were implanted with DES. The patients were divided into two groups, DM group, or the non-DM group. Diabetes was considered to be present if patients were receiving a prescribed treatment (insulin or an oral hypoglycemic drug) before coronary angioplasty, or on the basis of elevated levels (> 126 mg/dL) of fasting and non-stressed blood glucose on at least two separate occasions, during the hospital stay corresponding to the procedure.[11]

Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or use of blood pressure-lowering agents. Hypercholesteremia was defined as total cholesterol > 230 mg/dL, or use of a lipid-lowering agent.

Serum creatinine level was determined 24 h before PCI procedures, and renal function was assessed by the estimated creatinine clearance (CrCl) derived from Cockroft–Gault formula, where CrCl (mL/min) = (140-age) × weight (kg)/serum creatinine (mg/dL) × 72, corrected in women by a factor of 0.85. A calculated CrCl cutoff of 60 mL/min at the time of presentation was chosen to define at least moderate renal insufficiency (RI) according to guidelines established by the National Kidney Foundation.[12] The patients with acute complications during or after PCI, such as perforation, significant bleeding, or temponade, were excluded from this study.

### 2.2 Procedures

We inserted a 6–7 Fr catheter, either by the femoral or transradial approach, followed by 5000 IU heparin administrated through the sheath and isosorbide dintrate administered intracoronary via the guiding catheter. Patients were pretreated by oral antiplatelet medication consisting of aspirin 100 mg daily and either Ticlodipine 200 mg (recommended by Japanese Society of Cardiology before May 2006), or Clopidogrel 75mg (currently the standard therapy after approval in Japan since 2006) daily for at least two weeks, followed by aspirin 100 mg/d indefinitely, and ticlodipine 200 mg/d, or clopidogrel 75 mg/d, for two months with the BMS, or at least one year with the DES after a successful procedure.

CTO was defined as lesion exhibiting Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 in a native coronary artery, with duration of occlusion over three months.

Procedure success was defined as the ability to cross the occluded segment with both wire and balloon and successfully open the artery with < 70% residual stenosis.

Angiographic data were studied and Quantitative coronary angiography (QCA) was analyzed by CCIP 310 (CATHEX Co., Japan). The narrowing of the diseased vessel before and post treatment was compared at the same angiographic view. Reference vessel diameter (RD) and minimal lumen diameter (MLD) were measured. Percent diameter stenosis (DS) was calculated. Left ventricular ejection fraction was measured by left ventriculogram. Follow-up angiography was performed six months later. Restenosis was defined as more than 50% DS of the treated CTO vessels.

Patients were followed clinically for at least one year after PCI. Major adverse cardiac events (MACE) were defined as cardiac death, acute myocardial infarction or target lesion revascularization (TLR).

### 2.3 Statistical analysis:

Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± SD and compared with Student *t* test. Survival-free of adverse events was calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the two groups. Independent predictors of MACE at long-term follow-up were analyzed using the Cox proportional hazards regression model. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

## 3 Results

Baseline clinical and angiographic characteristics are shown in Table 1 & 2. Mean age was 76 ± 8.6 years old (range 65–86 years); 93 (87.7%) patients were men. Among patients with DM, six had insulin-requiring diabetes. Angiotensin receptor blocker and angiotensin-converting enzyme inhibitors were also more commonly used in the DM group. The DM group had a statistically significant lower final MLD in comparison with the non-DM group (2.47 ± 0.2 *vs*. 2.79 ± 0.48, $P = 0.007$). A DES was used in 62.9% of the CTO patients and a bare metal stent was used in 31.4% of the patients.

One hundred and fifty three patients were followed clinically for 36 ± 12 months. Ninety percent of patients completed angiographic follow-up. Clinical events are described in Table 3. MACE occurred in 18 patients (12.2%); 10 patients in the DM group (29.4%) and 13 in the non-DM group (12.7%), (log rank $P = 0.01$, Figure 1). During the follow-up period, five patients in the DM group and four patients in the non-DM group underwent a TLR procedure. Three patients from the DM group and three patients from the non-DM group died from a cardiac etiology, whereas two patients from the DM and one patient from the non-DM group suffered myocardial infarction.

**Table 1. Basic and clinical characteristics.**

| | DM ($n$ = 51) | Non DM ($n$ = 102) | $P$ value |
|---|---|---|---|
| Age | 76.58 ± 8.95 | 74.48 ± 8.1 | 0.35 |
| Sex /Male | 34 (66.7%) | 86 (84.5%) | 0.21 |
| Hypertension | 40 (78.4%) | 68 (67%) | 0.35 |
| Hyperlipidemia | 25 (49%) | 50 (49.3%) | 1 |
| Smoking | 25 (49%) | 69 (67.6%) | 0.50 |
| Ejection fraction (%) | 55.31 ± 16.23 | 57.35 ± 14.5 | 0.61 |
| Renal Impairment | 20 (39.2%) | 31 (30.7%) | 0.50 |
| Creatinine clearance (mL/min) | 64.09 ± 25.66 | 69.90 ± 21.2 | 0.40 |
| Beta-blocker | 11 (21.6%) | 14 (14.1%) | 0.41 |
| Statin | 30 (58.8%) | 52 (50.7%) | 0.53 |
| ARB or ACEI | 36 (70.6%) | 51 (50%) | 0.04 |
| Fasting glucose (mg/dL) | 144 ± 50.7 | 112.41 ± 22.26 | 0.0002 |
| Total cholesterol (mg/dL) | 192.85 ± 61.94 | 181.51 ± 41.74 | 0.43 |
| Triglyceride (mg/dL) | 136.52 ± 52.57 | 132.14 ± 60.71 | 0.77 |
| High-density lipoprotein (mg/dL) | 42.59 ± 13.44 | 46.25 ± 18.53 | 0.19 |

Data are reported as mean ± SD or *n* (%). ARB: Angiotensin receptor blockers; ACEI: Angiotensin-converting enzyme inhibitors.

**Table 2. Angiographic lesion characteristics and quantitative coronary angiography analysis.**

| | DM ($n$ = 53) | Non DM ($n$ = 105) | $P$ value |
|---|---|---|---|
| CTO > 20 mm | 25 (47.1%) | 49 (46.1%) | 0.84 |
| Blunt | 31 (58%) | 47 (45.7%) | 0.32 |
| Tortuosity | 12 (35.3%) | 27 (25.7%) | 0.89 |
| Calcification | 15 (29.2%) | 13 (12.3%) | 0.06 |
| LAD | 14 | 19 | |
| LCX | 9 | 19 | |
| RCA | 7 | 26 | |
| SVG | 1 | 1 | |
| TVD | 24 (45.1%) | 38 (36.1%) | 0.5 |
| Reference vessel | 2.74 ± 0.49 mm | 2.88 ± 0.43 mm | 0.17 |
| Post stent MLD | 2.47 ± 0.20 mm | 2.79 ± 0.48 mm | 0.007 |
| Stent length | 45.91 ± 25.15 mm | 43.71 ± 19.00 mm | 0.69 |
| DES | 37 (70.5%) | 63 (60%) | 0.3 |

CTO: chronic Total Occlusion; DES: drug eluting stent; DM: diabetes mellitus; LAD: left anterior descending artery; LCX: circumflex artery; RCA: right coronary artery, SVG: saphenous vein graft; TVD: triple vessel disease; MLD: Minimal lumen diameter.

The following variables were entered into the Cox proportional hazards model to determine the independent predictors of MACE: DM, moderate to severe renal impairment, lesion length, stent length, reference vessel diameter and final MLD (Table 4). The Cox proportional hazards model identified: the type of stent, DES *vs*. BMS, [Hazard ratio (HR): 0.13, 95% confidence interval (95% CI): 0.03–0.62,

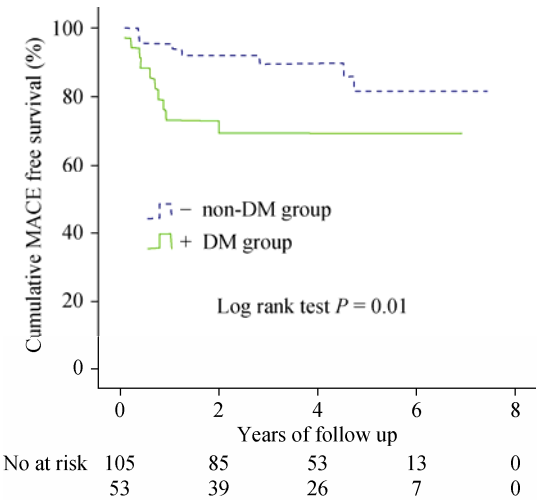


**Figure 1. Major Adverse Cardiac Event (MACE) free survival in relation to Diabetes Mellitus (DM) in Percutaneous coronary intervention ( PCI ) of elderly chronic total occlusion (CTO) patient during follow up.**

**Table 3. Clinical outcomes at long term follow up.**

| | DM ($n$ = 51) | Non DM ($n$ = 102) | $P$ value |
|---|---|---|---|
| MACE | 15 (29.4%) | 13 (12.7%) | 0.01 |
| Death | 3 (5.9%) | 3 (2.9%) | 0.65 |
| TLR | 10 (19.6%) | 9 (8.8%) | 0.17 |
| AMI | 2 (3.9%) | 1 (1.0%) | 0.53 |

AMI: acute myocardial infarction; DM: diabetes mellitus; MACE: major adverse cardiac event; TLR: target lesion revascularization.

**Table 4. Predictors of major adverse cardiac event at long term follow up.**

| | Hazard ratio | $P$ | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| DM | 6.69 | 0.01 | 1.62 | 15.81 |
| DES | 0.13 | 0.002 | 0.01 | 0.35 |
| Length of occlusion | 1.05 | 0.15 | 0.98 | 1.12 |
| Reference vessel diameter | 3.68 | 0.08 | 0.89 | 15.2 |
| Final MLD | 0.37 | 0.03 | 0.13 | 0.90 |
| Stent length | 1.03 | 0.06 | 0.99 | 1.19 |
| Renal impairment | 2.73 | 0.10 | 0.82 | 9. 05 |

DES: Drug eluting stent; DM: diabetes mellitus; MLD: Minimal lumen diameter.

*P* = 0.004]; DM (HR: 6.69, 95% CI: 1.62–15.81, *P* = 0.01); and final MLD (HR: 0.37, 95% CI: 0.13–0.90, *P* = 0.03) as independent predictors of MACE. That is, the risk of MACE was decreased by 37% per one millimeter increase of final MLD.

To determine severity of DM as predictors for MACE, the following variables in replace of DM were entered into the previous Cox proportional hazards model individually: fasting glucose, HBA1C, insulin usage, DM with renal impairment. Multivariate analysis only identified: DM with renal impairment (HR: 6.64, 95% CI: 1.32–33.36, *P* = 0.02); and HBA1C on admission (HR: 1.79, 95% CI: 1.09–2.94, *P* = 0.02) as independent predictors of MACE at long term follow-up.

## 4 Discussion

The present study demonstrated that DM was a predictive factor for MACE in elderly patients with CTO treated with PCI. We also identified that the type of stent, final MLD, DM with renal impairment, and HBA1C level on admission were predictive of worse prognosis.

The DES has dramatically changed the outcomes of complicated PCI. Recently, some studies have confirmed that the DES is superior to the BMS in CTO patients.[4–6] A three years follow-up study by De Felice F, *et al*.[5] showed DES reducing TLR by 60%, suggesting that the DES should be considered as the preferred treatment strategy for CTO. A mean two years of follow-up also showed that CTO lesions treated with SES showed better angiographic and long-term clinical outcomes than those treated with PES.[13] This study suggested that DM and chronic kidney disease are predictors for target lesion revascularization.

Several other previous studies have pointed out DM has a deleterious effect on the clinical outcomes of CTO post PCI.[6] In this study, we observed a relatively high incidence of MACE in diabetic patients, however, in some other studies, the difference was not found.[14] In this study, we found that diabetic patients with worse renal function, or the higher HbA1c level on admission, had a worse prognosis. A recent published study showed that Hemoglobin A1c is associated with an increased risk of MACE after successful DES implantation in patients with DM.[15] In our study, we included more elderly patients with poor renal function, more calcified lesion and uncontrolled diabetes on admission. This may partially explain why the results were different from other studies in which the differences of clinical outcomes after PCI between patients with DM and without DM were not found.

We also found that the elderly patients in the DM group had relative smaller minimal lumen diameters after stent deployment. This may correlate well with the finding that small minimal lumen diameters carried poor prognosis and higher risk for further restenosis, which was also suggested from previous studies.[16] These findings seem to suggest that: (1) one must try to obtain the best minimal lumen diameter after stent deployment; and (2) DES should be preferred when the expected final minimal lumen diameter is small.

The relative poor prognosis and response to revascularization maybe attributed to a few factors: elderly patients with diabetes had more diffuse coronary atherosclerosis, a greater prevalence of mild, moderate, and severe stenosis and a two-fold higher occlusion rate than patients without diabetes.[17]

### 4.1 Study Limitations

Our report presents some limitations. First, the study was not randomized, operator selection, and inclusion criteria may have influenced the final results. Moreover, the sample size was relatively small.

Despite these limitations, our study has a high angiographic follow-up rate and describes a real-world cohort of elderly patients who had never been analyzed before and merits further investigation.

### 4.2 Conclusions

The present study demonstrates that DM is a predictive factor for MACE in elderly patients with CTO treated with PCI, that the DES, and a final MLD are independent predictors for MACE during long term follow-up. DM with renal impairment and high HbA1C on admission showed worse prognosis.

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