The Influence of Glycemic Control on the Prognosis of Japanese Patients Undergoing Percutaneous Transluminal Angioplasty for Critical Limb Ischemia

MITSUYOSHI TAKAHARA, MD1
HIDEAKI KANETO, MD, PHD1
OSAMU IDA, MD2
SHIN-ICHI GOROGAWA, MD, PHD2
NAOTO KATAKAMI, MD, PHD1
TAKA-AKI MATSUOKA, MD, PHD1
MASAHIKO IKEDA, MD, PHD2
ICHIRO SHIMOMURA, MD, PHD1

OBJECTIVE — To reveal the influence of preoperative factors on the prognosis of patients undergoing percutaneous transluminal angioplasty (PTA) for critical limb ischemia (CLI).

RESEARCH DESIGN AND METHODS — We recruited 278 Japanese patients who underwent PTA for CLI between 2003 and 2009. The outcome measures were mortality and major amputation. Cox proportional hazards regression analyses were performed.

RESULTS — The prevalence of diabetes was 71%, and A1C was 7.0 ± 1.4%. The follow-up period was 90 ± 72 weeks, and 48 patients underwent major amputations and 89 died. The presence of diabetes in the whole population and A1C level in the diabetic population had no influence on mortality; rather, mortality was associated with age (P = 0.007), impaired activities of daily living (P < 0.001), hemodialysis (P < 0.001), and albumin level (P = 0.010). In contrast, the presence of diabetes and A1C level had significant association with major amputation (P = 0.012 and P = 0.007, respectively). The quartile analysis showed that diabetic subjects with an A1C ≥ 6.8% but not < 6.8%, had a significantly higher risk of major amputation than nondiabetic subjects. The adjusted hazard ratio of diabetes with A1C ≥ 6.8% was 2.907 (95% CI 1.606–5.264) (P < 0.001).

CONCLUSIONS — Diabetes with poor glycemic control is associated with major amputation, but not mortality, in CLI patients undergoing PTA. Prognostic indicators seem somewhat different between survival and limb salvage in the population.

Critical limb ischemia (CLI) is a manifestation of peripheral arterial disease (PAD) that describes patients with chronic ischemic rest pain or with ischemic skin lesions, either ulcers, or gangrene. CLI is associated with an extremely poor prognosis for both survival and limb salvage; amputation-free survival after 1 year is as low as 50%, and most of the patients ultimately need a revascularization procedure (1).

Recent studies have confirmed the effectiveness of revascularization with percutaneous transluminal angioplasty (PTA) for patients with CLI; its outcomes seem similar to surgical revascularization even in infrapopliteal segments (2,3). Because of its minimal invasiveness, PTA is ideally suited even to those at high risk for bypass surgery, including patients with diabetes. The increasingly wide application of PTA now calls for established preoperative risk assessment.

It is well known that CLI has a high prevalence of diabetes. The presence of diabetes in the general population and poor glycemic control in diabetic patients are associated with infection and delayed wound healing as well as micro- and macroangiopathy (4–8). Therefore, we thought that glycemic control may influence the prognosis of CLI patients.

Few studies have, however, examined the association of preoperative factors, including diabetic condition, with mortality and limb loss in CLI patients, especially those undergoing PTA (9). The aim of this study was to reveal the influence of a variety of preoperative factors including diabetic condition on their outcome.

RESEARCH DESIGN AND METHODS — We recruited Japanese patients who underwent PTA for CLI in Kansai Rosai Hospital, Hyogo, Japan, between 2003 and 2009.

All patients with chronic ischemic rest pain and/or foot ulcer or gangrene were evaluated for limb ischemia by angiography. The diagnosis and management of CLI were compliant with the Transatlantic Inter-Society Consensus (TASC) (10) or its revised consensus, TASC II (1). Once they were diagnosed as having CLI, we utilized PTA as the first-choice procedure for revascularization, within the recommendations in TASC II. The indication of PTA was judged by consensus among vascular specialists, including vascular surgeons. PTA was not considered to be feasible when lesions were heavily calcified and/or with diffuse occlusions, whereas poor-risk patients, having relative contraindications for bypass surgery, those with advanced age, expected high mortality under general anesthesia, and morbidity setting, for instance, would not necessarily be contraindications for PTA.

Major amputation, namely, above-the-ankle amputation, was indicated when revascularization failed to relieve patients from rest pain or control their foot lesions. The indication for amputation was judged by consensus among plastic surgeons as well as vascular specialists. Insufficient blood flow even after revascularization and uncontrollable limb infection were considered to be indications for amputation.
In the current study, we analyzed all of the recruited patients as well as those with diabetes. The outcome measures were limb loss by major amputation and mortality. The preoperative variables considered in the analyses were sex, age, activities of daily living (ADLs), Fontaine stage, the presence of infection, diabetic condition, hypertension, dyslipidemia, smoking, receiving regular hemodialysis, and serum albumin level as a nutritional marker. Diabetic condition was determined as the presence of diabetes in the whole population and as a glycemic control in the diabetic population. The diagnosis of diabetes was based on World Health Organization criteria, whereas glycemic control of diabetic patients was evaluated by A1C. Hypertension was diagnosed as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg or having been treated for hypertension. Dyslipidemia was defined as serum LDL cholesterol ≥100 mg/dl or HDL cholesterol <40 mg/dl or triglycerides ≥150 mg/dl or having been treated for dyslipidemia. Partial or total dependence in transferring (requiring some help in moving in and out of bed/chair or a complete transfer) were regarded as impaired ADLs.

**Statistical analysis**

Data are given as means and SDs for continuous variables or as percentages for dichotomous variables. Limb salvage and survival were plotted using the Kaplan-Meier method, and, if necessary, the differences between the two groups were assessed by a log-rank test. Cox proportional hazards regression model was used to determine the unadjusted association of each variable with the outcome. The statistically significant variables in the univariate analyses, as well as sex and age, were entered into multivariate models to reveal the independent impact on the outcome. Hazard ratios (HRs) and 95% CIs are reported. P < 0.05 was considered significant. Statistical analyses were performed using SPSS version 15.0J (SPSS, Chicago, IL).

**RESULTS** — A total of 278 CLI patients undergoing primary PTA procedures were recruited; aorto-iliac lesions were revascularized in 23% of the population, femoro-popliteal in 63%, and infrapopliteal in 68%. Baseline characteristics are shown in Table 1. The prevalence of diabetes was 71%, and their mean A1C level was 7.0%. Diabetic patients had a significantly higher prevalence of Fontaine stage IV and hemodialysis than those without diabetes (P = 0.006 and P = 0.001, respectively).

Follow-up period was 90 ± 72 weeks (1.7 ± 1.4 years), and 48 patients underwent major amputations and 89 died. Figure 1 shows the cause of death and Kaplan-Meier estimates of major amputation and mortality. The leading cause of death was cardiac and vascular disease (n = 40); followed by infection (n = 31), including pneumonia (n = 16), sepsis secondary to infective gangrene of the foot (n = 8), bed sore infection (n = 1), and catheter-related infection (n = 1); and unspecified causes (n = 5). Diabetic patients had a higher rate of major amputation compared with nondiabetic patients (P = 0.008, log-rank test), whereas they had a similar life prognosis (P = 0.717).

**Prognostic factors in the whole population**

Table 2 shows the influence of preoperative variables on the prognosis in the whole population. The presence of diabetes was independently associated with major amputation, and the adjusted HR was 3.101 (95% CI 1.262–7.621) (P = 0.014). The variable had, however, no statistically significant influence on mortality. Rather, mortality was associated with age, impaired ADLs, hemodialysis, and serum albumin level; the adjusted HRs were 1.036 (1.010–1.063) in the 1-year increment (P = 0.007) and 2.302 (1.407–3.605) (P < 0.001), 2.699 (1.682–4.332) (P < 0.001), and 1.788 (1.150–2.782) in the 1-g/dl decrement (P = 0.010), respectively.

**Prognostic factors in the diabetic population**

We also performed analyses with a focus on the patients with diabetes (Table 3). Here again, mortality was associated with age, impaired ADLs, hemodialysis, and serum albumin level. No significant association was found between mortality and A1C level. A1C level was, however, independently associated with major amputation, whose adjusted HR was 1.349 (95% CI 1.032–1.730) in the 1% increment (P = 0.004). Its association was still significant in the multivariate models in which every other peripheral vascular factor available in our dataset was substituted for Fontaine stage IV (online appendix Table A, available at http://care.diabetesjournals.org/cgi/content/full/dc10-0939/DC1).

Next, we divided the A1C dataset into quartiles to analyze the relationship between the increment of A1C level and the risk for major amputation in the diabetic patients. A1C ≤5.9% was categorized into the first quartile (Q1), 6.0–6.7% into the second quartile (Q2), 6.8–7.6% into the third quartile (Q3), and ≥7.7% into the fourth quartile (Q4). In a stepwise multivariate model, the categorized A1C level was independently associated with major amputation, with adjustment for Fontaine stage IV, hemodialysis, and infection. The adjusted HRs of Q2, Q3, and Q4 relative to Q1 were 2.030 (95% CI 0.657–6.266) (P = 0.218), 3.398 (1.227–9.412) (P = 0.019), and 3.983 (1.398–11.35) (P = 0.010), respectively.

We further analyzed the influence of the presence of diabetes on major ampu-
tation according to their A1C level; each A1C quartile of the diabetic group, defined above, was compared with the non-diabetic group in a stepwise multivariate model. As shown in Fig. 2A, the two higher A1C quartiles of the diabetic group (that is, A1C ≥6.8%) had a significantly higher risk than the nondiabetic group, whereas the two lower A1C quartiles (that is, A1C <6.8%) did not. Based on these findings, we reanalyzed with substitution of diabetes with A1C ≥6.8% for the presence of diabetes in the original multivariate model shown in Table 2. The result was that diabetes with A1C ≥6.8%, infection, and hemodialysis were significantly associated with major amputation; their adjusted HRs were 2.907 (95% CI 1.606–5.264) (P = 0.001), 2.375 (1.198–4.711) (P = 0.014), and 3.530 (1.772–7.029) (P < 0.001), respectively (online appendix Table B). Note that these three variables were independent of one another and therefore were expected to have additive influences on major amputation. In fact, a Kaplan-Meier model showed that those with the accumulation of these prognostic factors had an increased risk of major amputation (Fig. 2B). When they had all of these three

| Table 2—Association of preoperative variables with the prognosis of CLI patients undergoing PTA |
| --- |
| **Outcome measures** | **Univariate model** | **Multivariate model** |
| **Major amputation** Preoperative variables Male | 1.030 (0.565–1.877) | 0.746 (0.400–1.391) |
| Age (in 1-year increments) | 0.983 (0.958–1.009) | 0.989 (0.959–1.020) |
| Impaired ADLs | 2.102 (1.191–3.711)* | 1.777 (0.972–3.250) |
| Fontaine stage IV | 6.607 (1.603–27.24)† | 4.326 (1.028–18.20)* |
| Infection | 2.663 (1.480–4.791)† | 2.298 (1.177–4.486)* |
| Diabetes | 2.992 (1.272–7.039)* | 3.101 (1.262–7.621)* |
| Hypertension | 0.561 (0.292–1.078) | — |
| Dyslipidemia | 0.678 (0.364–1.265) | — |
| Smoking | 0.995 (0.540–1.832) | — |
| Receiving hemodialysis | 2.778 (1.508–5.117)† | 2.875 (1.481–5.582)* |
| Albumin (in 1-g/dl increase) | 0.577 (0.365–0.914)* | 0.659 (0.361–1.202) |
| **Mortality** Preoperative variables Male | 1.567 (0.974–2.521) | 1.481 (0.902–2.429) |
| Age (in 1-year increments) | 1.027 (1.005–1.049)* | 1.036 (1.010–1.063)* |
| Impaired ADLs | 3.272 (2.135–5.103)† | 2.302 (1.470–3.605)† |
| Fontaine stage IV | 1.772 (0.975–3.221) | — |
| Infection | 2.106 (1.365–3.250)† | 1.206 (0.710–2.050) |
| Diabetes | 1.090 (0.683–1.742) | — |
| Hypertension | 0.736 (0.447–1.211) | — |
| Dyslipidemia | 0.847 (0.359–1.983) | — |
| Smoking | 1.100 (0.700–1.729) | — |
| Receiving hemodialysis | 2.290 (1.486–3.527)† | 2.699 (1.682–4.332)† |
| Albumin (in 1-g/dl increase) | 0.496 (0.357–0.688)* | 0.559 (0.359–0.870)† |

Data are HR (95% CI). *P value ≤0.05; †P value ≤0.01.
risk factors, their prognosis was extremely poor. Their estimated median time to limb loss was only 23 weeks, which would be rarely different from the natural course of nonrevascularized CLI patients (1).

CONCLUSIONS — As is mentioned in the TASC II (1), a primary outcome in the TASC II (1), a primary outcome in the TASC II (1), a primary outcome in the TASC II (1), a primary outcome in the TASC II (1), a primary outcome in mortality care.diabetesjournals.org DIABETES CARE, VOLUME 33, NUMBER 12, DECEMBER 2010

Table 3—Association of preoperative variables for the prognosis with CLI patients with diabetes undergoing PTA

| Outcome measures | Univariate model | Multivariate model |
|------------------|------------------|--------------------|
| Major amputation  |                  |                    |
| Preoperative variables |        |                    |
| Male             | 1.328 (0.769–2.293) | 1.376 (0.784–2.414) |
| Age (in 1-year increments) | 1.032 (1.005–1.061) | 1.045 (1.012–1.080) |
| Impaired ADL      | 3.124 (1.890–5.163) | 2.514 (1.506–4.197) |
| Fontaine stage IV | 2.120 (0.952–4.722) |                |
| Hypertension      | 1.618 (0.960–2.727) |                |
| Dyslipidemia      | 0.874 (0.475–1.607) |                |
| Smoking           | 0.975 (0.520–1.828) |                |
| A1C (in 1% increment) | 1.093 (0.650–1.839) |                |
| Receiving hemodialysis | 2.082 (1.242–3.247) | 3.046 (1.976–8.825) |
| Albumin (in 1-g/dl increment) | 0.624 (0.366–1.064) |                |
| Mortality         |                  |                    |
| Preoperative variables |        |                    |
| Male             | 1.328 (0.769–2.293) | 1.376 (0.784–2.414) |
| Age (in 1-year increment) | 1.032 (1.005–1.061) | 1.045 (1.012–1.080) |
| Impaired ADL      | 3.124 (1.890–5.163) | 2.514 (1.506–4.197) |
| Fontaine stage IV | 2.120 (0.952–4.722) |                |
| Hypertension      | 1.618 (0.960–2.727) |                |
| Dyslipidemia      | 0.874 (0.475–1.607) |                |
| Smoking           | 0.975 (0.520–1.828) |                |
| A1C (in 1% increment) | 1.093 (0.650–1.839) |                |
| Receiving hemodialysis | 2.082 (1.242–3.247) | 3.046 (1.976–8.825) |
| Albumin (in 1-g/dl increment) | 0.624 (0.366–1.064) |                |

Data are HR (95% CI). *P value <0.05; †P value <0.01.

In the TASC II (1), a primary outcome in mortality care.diabetesjournals.org DIABETES CARE, VOLUME 33, NUMBER 12, DECEMBER 2010

Figure 2—The association of poor glycemic control and other variables with major amputation. A: The adjusted HRs for major amputation according to glycemic control. Data are the adjusted HRs and 95% CIs of each A1C quartile of the diabetic group relative to the nondiabetic group in the stepwise multivariate model. They were adjusted for impaired activity of daily living, Fontaine stage IV, infection, and receiving hemodialysis. The quartiles of A1C were as follows: Q1: 5.9%, Q2: 6.0–6.7%, Q3: 6.8–7.6%, and Q4: 7.7%. B: Kaplan-Meier estimates of major amputation according to the number of risk factors (P < 0.001, log-rank test). Risk factors considered here are the following three variables: diabetes with A1C ≥6.8%, the presence of infection, and receiving hemodialysis, all of which have independent associations in the stepwise multivariate Cox proportional hazards regression model. DM, diabetes.

care.diabetesjournals.org DIABETES CARE, VOLUME 33, NUMBER 12, DECEMBER 2010

Takahara and Associates
Successful revascularizations would improve peripheral blood flow and could lead to avoidance of limb loss, even if the preoperative peripheral flow is severely impaired. The severity of preoperative peripheral flow would not always mean the similar severity of postoperative peripheral flow. Given that peripheral blood flow can be changed by revascularization procedures, it is not surprising that limb prognosis after PTA is associated with postoperative, rather than preoperative, peripheral arterial factors.

We also surveyed the influence of preoperative variables on survival, which confirmed that diabetes failed to have a significant association with mortality. Some recent trials (11,12,16–18) likely supported the absence of this association. Yet, most studies surveyed CLI patients undergoing PTA together with those undergoing bypass surgery and/or nonrevascularized patients, whereas we limited our study population to those undergoing PTA. In addition, we revealed that A1C level in diabetic patients had no significant association with mortality. The prognostic factors for mortality were, rather, age, impaired ADLs, hemodialysis, and serum albumin level. These significant associations were affirmed even with additional adjustment for cardiac function or ejection fraction evaluated with echocardiography (online appendix Table C). Previous reports (9,18,19) investigated some of these prognostic variables, but they did not mention nutritional status in the population. As is well known, malnutrition affects life prognosis in various clinical situations (20,21). We adopted serum albumin level as a nutritional marker in the current study because of its great advantages in ease and cost and its wide use in clinical practice. It is possible that serum albumin level is affected by clinical factors other than malnutrition. But we confirmed the relationship between malnutrition and mortality by the analyses with other nutrition-related markers, such as lymphocyte count and serum cholesterinase level (online appendix Table D).

In conclusion, we investigated the association of preoperative variables with the prognosis of CLI patients undergoing PTA, which suggests that prognostic indicators are somewhat different between survival and limb salvage. Diabetes and poor glycemic control, for instance, was significantly associated with limb loss but not mortality. Diabetes with poor glycemic control, infection, and hemodialysis was independently associated with limb loss, and the accumulation of these prognostic factors increased the amputation risk. Especially, those with all of the three risk factors had such poor limb prognosis that they might fail to receive a prognostic benefit of PTA. It is possible, however, that correction of poor glycemic control by adequate interventions leads to prognostic improvement. A further prospective investigation is required to determine whether the intervention on glycemic control subsequently improves their prognosis.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

M.T. and H.K. researched data and wrote the manuscript. O.I., S.G., N.K., T.M., and M.I. contributed to the discussion. I.S. reviewed/edited the manuscript.

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. International consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(Suppl J):S5–S67
2. Faglia E, Mantero M, Caminetti M, Caravaggi C, De Giglio R, Pritelli C, Clerici G, Fratino P, De Cater P, Dalla Paola L, Maiani G, Poli M, Settembrini PG, Sciangula L, Morabito A, Graziani L. Extensive use of peripheral angioplasty, particularly infrainguinal, in the treatment of ischemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Intern Med 2002;252:225–232
3. Fowkes F, Leng GC. Bypass surgery for chronic lower limb ischemia. Cochrane Database Syst Rev 2008;CD002000
4. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet 2005;366:1736–1743
5. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003;26:510–513
6. Benfield T, Jensen JS, Nordregaard BG. Influence of diabetes and hyperglycemia on infectious disease hospitalization and outcome. Diabetologia 2007;50:549–554
7. Markussen M, Hanson D, Anderson J, Langemo D, Hunter S, Thompson P, Paulson R, Rustvang D. The relationship between hemoglobin (A1c) values and healing time for lower extremity ulcers in individuals with diabetes. Adv Skin Wound Care 2009;22:365–372
8. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–1847
9. Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, Caminitti M, Curci V, Quantiello A, Lupattelli T, Morabito A. Long-term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. Diabetes Care 2009;32:822–827
10. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD): TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000;31(Suppl 1):S1–S296
11. Virkkanen J, Heikkinen M, Lepantalo M, Metsaoman J, Salenius JP. Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia. J Vasc Surg 2004;40:761–767
12. Bailey CM, Saha S, Magee TR, Galland RB. A 1 year prospective study of management and outcome of patients presenting with critical lower limb ischemia. Eur J Vasc Endovasc Surg 2003;25:131–134
13. Turina M, Fry DE, Polk HC Jr. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. Crit Care Med 2005;33:1624–1633
14. Peppa M, Stavroulakis P, Raptis SA. Advanced glycoxidation products and impaired diabetic wound healing. Wound Repair Regen 2009;17:461–472
15. Gary Sibbald R, Woo KY. The biology of chronic foot ulcers in persons with diabetes. Diabetes Metab Res Rev 2008;24(Suppl 1):S25–S30
16. Barani J, Nilsson A, Mattiasson I, Lindblad B, Gotsater A. Inflammatory mediators are associated with 1-year mortality in critical limb ischemia. J Vasc Surg 2005;42:75–80
17. da Silva AF, Desgranges P, Holdsworth J, Harris PL, McCollum P, Jones SM, Beard J, Callam M. The management and outcome of critical limb ischemia in diabetic patients: results of a national survey. Audit Committee of the Vascular Surgical Society of Great Britain and Ireland. Diabet Med 1996;13:726–728
18. Dick F, Diehm N, Galimain A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg 2007;45:751–761
19. Flu HC, Lardenoye JH, Veen EJ, Van Berge Henegouwen DP, Zwinderman HF. Functional status as a prognostic factor for primary revascularization for critical limb ischemia. J Vasc Surg 2010;51:360–371
20. Herselman M, Esau N, Kruger JM, Labadarios D, Moosa MR. Relationship between serum protein and mortality in adults on long-term hemodialysis: exhaustive review and meta-analysis. Nutrition 2010;26:10–32
21. O’Daly BJ, Walsh JC, Quinnan JF, Falk GA, Stapleton R, Quinnan WR, O’Rourke SK. Serum albumin and total lymphocyte count as predictors of outcome in hip fractures. Clin Nutr 2010;29:89–93