

# Long Term Outcome of Type 2 Diabetic Patients With Critical Limb Ischemia

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## Abstract

**Introduction:** Diabetes Mellitus is associated with vascular disease. One of its macrovascular complications is peripheral arterial disease (PAD), which can present as critical limb ischemia (CLI) that can eventually lead to amputation and death.

**Objective:** Determine the long-term outcome of Type 2 diabetic patients with critical limb ischemia in National Kidney and Transplant Institute (NKTi).

**Methods:** Computerized search of NKTi Medical Records Section was done using the Docuview. Type 2 diabetic patients with critical limb ischemia of the lower extremities were included in the study. Patients were grouped according to the intervention received (No intervention, Bypass Graft or Peripheral Angioplasty). Endpoints such as amputation and mortality were ascertained on readmissions and on outpatient records. Data processing and analyses were performed using SPSS v20. Kaplan-Meier Survival Analysis was used to examine days to amputation

and days to mortality between groups.

**Results:** Twenty-three (23) patients were included in the study. There was no significant difference on the baseline characteristics of those who received revascularization and those who did not have revascularization. Amputation rate was 31% while mortality rate was 30% for the whole population. Patients who had revascularization seemed to have greater probability of amputation and lesser probability of dying, but these were not statistically significant based on Kaplan - Meier Survival Curves p values of 0.918 and 0.433, respectively.

**Conclusion:** Diabetic patients with CLI still carries a high risk of amputation and mortality even with revascularization but the time to amputation is longer for those who were revascularized.

**Keywords:** critical limb ischemia, bypass graft, angioplasty, amputation, mortality

## Introduction

Diabetes Mellitus (DM) is a condition wherein there is insulin deficiency or progressive insulin secretory defect on the background of insulin resistance.<sup>1</sup> One of its macrovascular complications is peripheral arterial disease (PAD) which can present as critical limb ischemia (CLI) that can eventually lead to amputation.<sup>2</sup> Because of these the Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of PAD put emphasis on revascularization to improve the quality of life and decrease the mortality of patients with CLI. Revascularization can either be surgical which is bypass grafting or endovascular, which consists of balloon angioplasty, stents, stent-grafts and plaque debulking procedures.

## Review of Related Literature

Peripheral arterial disease (PAD) is hemodynamically defined as ankle-brachial systolic pressure index (ABI) of 0.90 and below. It is a spectrum<sup>3</sup> wherein a patient can be asymptomatic, a claudicant or present as chronic ischemic rest pain with or without ulcer or gangrene, the latter defines CLI.<sup>4</sup>

Several risk factors are associated with PAD such as diabetes mellitus<sup>5-12</sup>, hypertension (HPN)<sup>5,10-16</sup>, smoking<sup>5-8,11,12,17</sup>, increased age<sup>6,9,10,14-16</sup>, chronic kidney disease (CKD)<sup>14</sup>, decreased glomerular filtration rate<sup>9,15</sup>, coronary artery disease (CAD)<sup>10,15</sup>, cerebrovascular disease,<sup>9,15,17</sup> as well as a family history of premature cardiovascular disease<sup>7</sup>. The following laboratory parameters are associated with the development of PAD: increased Hemoglobin A1c (HgbA1c),<sup>9,16,18,19</sup> dyslipidemia,<sup>6,7,14,17</sup> albuminuria<sup>14</sup>, microalbuminuria,<sup>8,9</sup> HS-CRP<sup>14</sup>, CRP,<sup>8,20</sup> vWF, D-Dimer, thrombin-antithrombin complex,<sup>20</sup> fibrinogen<sup>9,11</sup> and high level of small platelet aggregates<sup>21</sup> Insulin use independent of HbA1c and status of diabetes also showed increased risk of PAD.<sup>14</sup>

Approximately 1.0-2.0% of patients with PAD presents as critical limb ischemia,<sup>3</sup> but factors that

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predispose a patient with PAD to the development of CLI is not yet well defined. The Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of PAD objectively defines CLI as ankle pressure of <50-70 mmHg or toe pressure <30-50 mmHg or transcutaneous oxygen tension <30-50 mmHg. Lesions are classified type A to D, type A having minimal lesion while D having the worst. TASC recommends the following goals: relieve ischemic pain, heal neuro-ischemic ulcers, prevent limb loss, improve function and quality of life and prolong survival. With these goals, it seems logical that reperfusion of the said limb is essential. There are currently two modalities to manage critical limb ischemia depending on the severity of the lesion: bypass grafting for type C and D lesions and endovascular intervention commonly known as peripheral angioplasty for type A and B lesions.<sup>4</sup>

Because of CLI's morbidity as well as BPG's high financial cost and morbidity, several advances in care and technology are being done to improve the quality of life of these patients. The update from TASC I to TASC II leans toward the use of angioplasty in more extensive lesions. It was followed by a recent study done by Bradbury making a recommendation that for patients who are predicted to be alive for less than two years, angioplasty is preferred because BPG has significant morbidity and higher cost within the first two years.<sup>22</sup> With all these advances, care for CLI patients has been better throughout the years. A recent study shows amputation rates of 8.2% and 21.1% for those who were managed with PA and BPG, respectively compared with a high amputation rate of 59.2% without revascularization. The annual death incidence was likewise improved, 11.9% for those who had revascularization versus 52.9% who did not.<sup>2</sup>

### Significance of the Study

As of the present time there is sparse data describing the outcome of critical limb ischemia in the Philippines and there is no data in National Kidney and Transplant Institute (NKTi) that describes the outcome of type 2 diabetic patients with CLI. Hence, this will be the initial study that will describe the long-term outcome of these patients.

## Objectives

### General:

Determine the long-term outcome of type 2 DM patients with CLI in NKTi.

### Specific:

Determine the mortality and amputation rate of type 2 DM patients with CLI in NKTi.

## Methodology

This is a retrospective cohort study done in NKTi, a government-owned and controlled corporate tertiary specialty center with a mandate to specialize in the prevention, diagnosis, rehabilitation and treatment of kidney and allied diseases. Since diabetes mellitus is one of the most common causes of chronic kidney disease, we have a great number of this patient population and its complications.

Computerized search of the NKTi Medical Records Database was done using Docuview with ICD 10 Code I73.9 (Peripheral vascular disease, unspecified), inclusive dates were January 1, 2002 to December 31, 2006 with the intent of at least a five-year follow up. Follow up was ascertained on readmission and on outpatient records from the primary physician's offices for private patients and out-patient department medical records for service patients.

Patients included were those who had PAD based on ABI or doppler ultrasound of the lower extremities with chronic ischemic rest pain or chronic foot ulcer and those who were revascularized because of chronic ischemic rest pain or foot ulcer with poor pulses. Ankle, toe and transcutaneous oxygen pressure were not available hence not included in the study. All patients were previously diagnosed as diabetics.

Data gathered were age, sex, diabetes duration, presence of hypertension, CAD, ESRD, glycosylated hemoglobin, smoking, status, lipid profile, date of CLI diagnosis, intervention, amputation and death. The last two were the primary endpoints of the study.

### Statistical Methods

Data processing and analyses were performed using SPSS v20. Missing values were not replaced or estimated. Descriptive statistics (count, mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum) were computed for quantitative variables (e.g. age, diabetes duration, glycosylated hemoglobin, lipid profile, days until amputation and days until mortality). Count and percentage of patients on qualitative variables were also generated (e.g. sex, comorbidities, smoking status and procedure: no revascularization, bypass graft or angioplasty).

Variables were presented in tables or graphs as percent (count) or mean  $\pm$  SD or median (IQR) where appropriate. Test for normality for quantitative variables was performed. T-test was used to compare difference in means between procedures. Chi-square test or Fisher's exact test was used to compare proportions. Follow-up rate, rate of amputation and mortality rates were computed. Kaplan-Meier Survival Analysis was used to examine days to amputation and days to mortality between groups. Two-sided 95%

confidence intervals were also estimated. Conclusions were based on a 5.0% level of significance.

## Results

There were 57 patients with PAD, however only 26 satisfied the criteria for CLI, three of them were not diabetic hence excluded from the study. No revascularization procedure was done in 14 patients, while seven had bypass graft and two had angioplasty (Figure 1).

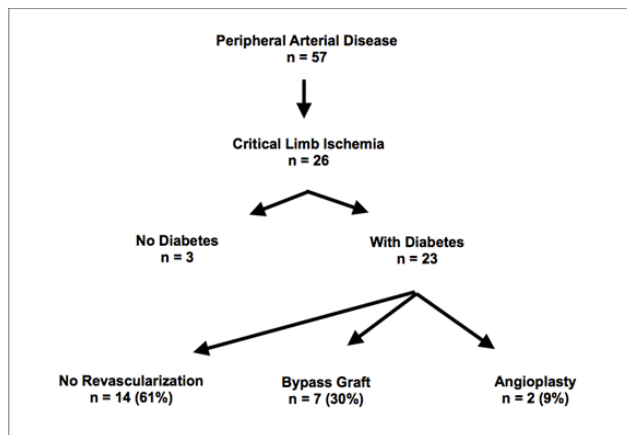


**Figure 1: Critical Limb Ischemia groups based on treatment received**

**Table II: Demographic and clinical characteristics of revascularization group**

|                                          | Bypass Graft    | Angioplasty |
|------------------------------------------|-----------------|-------------|
| n*                                       | 78% (7)         | 22% (2)     |
| Age (years)**                            | 52.1 ± 15.3     | 60.0 ± 1.4  |
| Sex (male) *                             | 71% (5)         | 100% (2)    |
| Diabetes duration (years) **             | 21.2 ± 3.9 (4)  | 10 (1)      |
| Hypertension*                            | 86% (6)         | 100% (2)    |
| End stage renal disease*                 | 57% (4)         | 100% (2)    |
| Coronary Artery Disease*                 | 43% (3)         | 100% (2)    |
| Total Cholesterol (mg/dL) **             | 133 ± 28.3 (2)  | 98.0 (1)    |
| Triglyceride (mg/dL) **                  | 78.0 ± 39.6 (2) | 156.0 (1)   |
| Low Density Lipoprotein (mg/dL) **       | 80.0 ± 18.4 (2) | 52.8 (1)    |
| High Density Lipoprotein (mg/dL) **      | 37.5 ± 2.1 (2)  | 14.0 (1)    |
| Hgba1C (%)**                             | 6.0 ± 0.6 (2)   | 5.9 (1)     |
| Ankle-brachial pressure systolic index** | -               | 0.6 (1)     |
| Smoking*                                 | 57% (4)         | 100% (2)    |

Note: Data presented as \* percent (count), \*\* mean ± SD

There is no significant difference between groups (Bypass graft group vs. Peripheral Angioplasty group)

Of the twenty-three patients, thirteen followed up ranging to 346 days. Four had major amputations at 270 days, while four patients died ranging 240 days (see Table III).

Among the group with no revascularization, eight followed up at range of 234 days, two had major amputation at 148 days and 3 died with range of 319 days. While by pass graft patients had a follow up rate of 57%, two had major amputation with range of 1473 days and one died at 20 days of

**Table I: Demographic and clinical characteristics of study population**

|                                          | All Patients      | No Revascularization | Revascularization |
|------------------------------------------|-------------------|----------------------|-------------------|
| n*                                       | 23                | 61% (14)             | 39% (9)           |
| Age (years)**                            | 59.4 ± 12.3       | 62.9 ± 10.4          | 53.9 ± 13.7       |
| Sex (male) *                             | 65% (15)          | 57% (8)              | 78% (7)           |
| Diabetes duration (years) **             | 16.6 ± 7.2 (16)   | 15.5 ± 7.7 (11)      | 19.0 ± 6.1 (5)    |
| Hypertension*                            | 78% (18)          | 71% (10)             | 89% (8)           |
| End stage renal disease*                 | 52% (12)          | 43% (6)              | 67% (6)           |
| Coronary Artery Disease*                 | 57% (13)          | 57% (8)              | 56% (5)           |
| Total Cholesterol (mg/dL) **             | 146.3 ± 39.9 (12) | 154.7 ± 40.9 (9)     | 121.3 ± 28.4 (3)  |
| Triglyceride (mg/dL) **                  | 108.9 ± 54.7 (12) | 110.6 ± 58.3 (9)     | 104.0 ± 53.0 (3)  |
| Low Density Lipoprotein (mg/dL) **       | 94.1 ± 39.7 (12)  | 101.8 ± 42.3 (9)     | 70.9 ± 20.4 (3)   |
| High Density Lipoprotein (mg/dL) **      | 31.6 ± 11.7 (12)  | 32.2 ± 11.8 (9)      | 29.7 ± 13.6 (3)   |
| Hgba1C (%)**                             | 8.0 ± 2.6 (11)    | 8.8 ± 2.7 (8)        | 6.0 ± 0.5 (3)     |
| Ankle-brachial pressure systolic index** | 0.5 ± 0.1 (7)     | 0.5 ± 0.1 (6)        | 0.6 (1)           |
| Smoking*                                 | 56% (13)          | 50% (7)              | 67% (6)           |

Note: Data presented as \* percent (count), \*\* mean ± SD

There is no significant difference between groups (Revascularization group vs No Revascularization group)

Patients' ages varied from 33 to 73 years with average of 59.4 years. Majority of the patients were male, hypertensive, smoker, had a history of coronary artery disease and end stage renal disease. Duration of diabetes ranged from two to 30 years with mean 16.6 years. Mean glycosylated hemoglobin was 8.0% while lipid profile was within normal limits. Average ABI was 0.5. No significant differences between the revascularization and no revascularization groups (Table I) or between bypass graft and angioplasty groups were observed at 5.0% level (Table II).

CLI diagnosis. One of the two angioplasty patients followed up after 379 days, neither amputation nor death was reported.

Kaplan-Meier survival analysis (Figure 2) showed that revascularization group seemed to have a greater probability of amputation but the average days to amputation was longer, however there was no statistically significant difference between groups ( $p < 0.918$ ).

Patients who had revascularization seemed to have lesser probability of dying and average days to mortality were longer however it was not significant

between groups ( $p < 0.433$ ). (Figure 3)

**Table III: Follow up, amputation and mortality**

|                              | Follow up* | Days of Follow-up** | Major Amputation* | Days to Amputation** | Mortality* | Days to Mortality** |
|------------------------------|------------|---------------------|-------------------|----------------------|------------|---------------------|
| All Patients (n=23)          | 57% (13)   | 71 (346)            | 31% (4)           | 159.5 (270)          | 31% (4)    | 21.5 (240)          |
| No Revascularization (n=14)  | 57% (8)    | 63.5 (234)          | 25% (2)           | 118.0 (148)          | 38% (3)    | 23 (319)            |
| With Revascularization (n=9) | 56% (5)    | 379 (1086)          | 40% (2)           | 254.5 (255)          | 20% (1)    | 20                  |
| Bypass Graft (n=7)           | 57% (4)    | 226.5 (1473)        | 50% (2)           | 254.5 (255)          | 25% (1)    | 20                  |
| Angioplasty (n=2)            | 50% (1)    | 379.0               | 0                 | -                    | 0          | -                   |

Note: Data presented as \* percent (count), \*\* median (IQR)

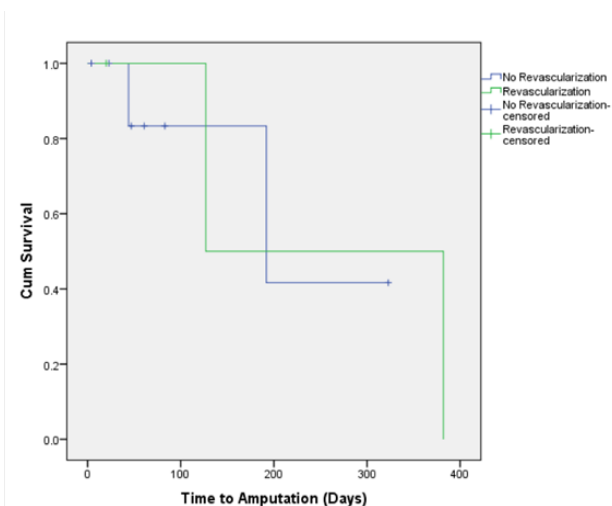


**Figure 2: Kaplan-Meier Survival Curves (time to amputation)**

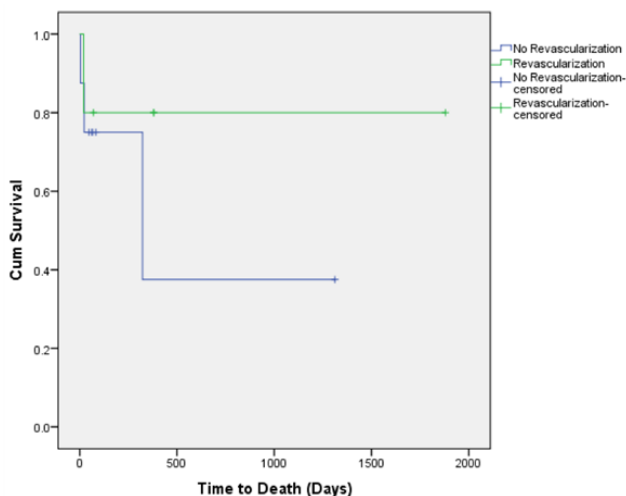


**Figure 3: Kaplan-Meier Survival Curves (time to death)**

## Discussion

Amputation rate of CLI patients in NKTl was 31% compared with 13.4% from an international study done

by Faglia, et al.<sup>2</sup> This study likewise showed that more patients who had revascularization had major amputation (above the ankle amputation) compared to those who did not have revascularization, however this can be explained by their longer follow-up allowing us to observe this endpoint more frequently in this group. The mean time to amputation was longer for those who had bypass grafting, since the leg was able to heal with adequate blood flow after the revascularization procedure.

Mortality rate was 30% compared to 49.8% from an international study done by Faglia, et al.,<sup>2</sup> however our mean follow up was only 346 days instead of a five-year follow up which this study initially intended to do.

## Conclusion

Diabetic patients with CLI still carries a high risk of amputation (31%) and mortality (30%) even with revascularization but the time to amputation is longer for those who were revascularized. However due to the small number of our sample our conclusion may not be accurate.

## Recommendation

This is the first study to describe the outcome of CLI patients in NKTl. However due to the nature of the study design i.e. retrospective cohort, gathering of pertinent data and follow-up of patients can not be done adequately. Hence, I recommend that a multicenter, prospective study be done in this subject.

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