Impact of Guideline-Directed Medical Therapy on 10-Year Mortality after Revascularization for Patients with Chronic Limb-Threatening Ischemia

Yosuke Hata¹, Osamu Iida¹, Shin Okamoto¹, Takayuki Ishihara¹, Kiyonori Nanto¹, Takuya Tsujimura¹, Naoko Higashino¹, Taku Toyoshima¹, Ikurou Kitano², Yoshihiko Tsujit², Mitsuyoshi Takahara³ and Toshiaki Mano¹

¹Kansai Rosai Hospital Cardiovascular Center, Inabaso, Hyogo, Japan
²Department of Surgery, Shinsuma General Hospital, Hyogo, Japan
³Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Aims: This study aimed to investigate the long-term impact of guideline-directed medical therapy (GDMT) on 10-year mortality in patients with chronic limb-threatening ischaemia (CLTI) after revascularization.

Methods: We performed a retrospective multicentre study enrolling 459 patients with CLTI who underwent revascularization (396 endovascular therapy [EVT] and 63 bypass surgery [BSX] cases) between January 2007 and December 2011. The primary outcome measure was all-cause mortality. We additionally explored the predictors for all-cause mortality using Cox regression hazard models; the influence of GDMT, defined as prescription of antiplatelet agents, statins, and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in aggregate, on all-cause mortality, and the association between baseline characteristics using interaction effects.

Results: During the 10-year follow-up after revascularization, 234 patients died. In Kaplan-Meier analysis, 10-year mortality was significantly lower in patients who received statins ($p<.001$) and ACE inhibitors or ARBs ($p=.010$) than those who did not. However, there were no differences in 10-year mortality between patients who received anti-platelet agents and those who did not ($p=.62$). Interaction analysis revealed that GDMT had a significantly different hazard ratio in patients who were and were not on hemodialysis and in those treated with EVT or BSX ($p$ for interaction =.002 and .044, respectively). In the multivariate analysis, age $\geq$ 75 years, non-ambulatory status, hemodialysis, congestive heart failure, left ventricular ejection fraction $\leq$ 50%, and GDMT were significantly associated with all-cause mortality.

Conclusions: Appropriate GDMT use was independently associated with 10-year mortality in patients with CLTI after revascularization.

Key words: Chronic limb-threatening ischemia, Endovascular therapy, Bypass surgery, Guideline-directed medical therapy, Long-term mortality

Introduction

Chronic limb-threatening ischaemia (CLTI) is a presentation of advanced lower-extremity atherosclerotic disease with threatened limb loss with an increased risk of cardiovascular mortality. Although advancement in surgical experience and development of endovascular devices for revascularization attribute to improved limb-based outcomes, mortality of patients with CLTI remains poor, ranging from 14 to 56% at 1-year. Therefore, comprehensive management is important in achieving optimal patient-based outcomes. The
current guidelines for the management of lower extremity arterial disease (LEAD) suggest that antiplatelet agents and hydroxymethylglutaryl coenzyme A reductase agents (statins) are Class I and Level A recommendations for all symptomatic LEAD patients, while angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are Class IIa and Level B recommendations for LEAD patients with hypertension. The prescription of these agents is defined as guideline-directed medical therapy (GDMT), and they have shown a reduced risk of cardiovascular mortality following revascularization. However, the long-term impact of GDMT on mortality in patients with CLTI has not yet been systematically studied. Therefore, we investigated the long-term impact of GDMT on 10-year mortality in patients with CLTI who underwent endovascular or surgical revascularization.

Revascularization was indicated for the lesions showing angiographic stenosis of >75% of the vessel diameter, and mean pressure gradient of 10 mmHg or greater was defined as haemodynamically significant. The revascularization strategy was depend on the physician’s discretion. Genrally, in patients who underwent EVT, a primary stenting strategy was used for aortoiliac lesions and a provisional stenting strategy was used for femoropopliteal lesions. The infrapopliteal lesions were treated using plain angioplasty. Nevertheless, BSX was performed by standard bypass techniques, and autogenous vein grafts were routinely used. Expanded polytetrafluoroethylene (ePTFE) grafts were used in cases without appropriate autogenous vein grafts.

Follow-Up Assessment and Management
The follow-up intervals and modalities were largely at the discretion of the attending physician. We generally followed up patients every 2–4 weeks until the wound had healed. Reinterventions were indicated in cases of recurrent ischaemic pain or delayed wound healing accompanied by recurrent occlusion or stenosis hemodynamically indicated by ABI, DUS, and SPP.

Study Outcome Measure
The primary outcome measure was the 10-year all-cause mortality.

Definitions
Definition of CLTI was in accordance with the European Society of Cardiology (ESC)/ European Society for Vascular Surgery (ESVS) guidelines. When definition-required measurements could not be obtained because of intractable rest pain or due to a non-compressible artery with severe calcification, SPP was measured instead of toe or ankle pressure; an SPP <40 mmHg was defined as a critically ischaemic limb.

Non-ambulatory status was defined as wheelchair dependence or bedridden status, as assessed upon admission. Coronary artery and cerebrovascular diseases were defined as the presence of symptoms or a history of any intervention or infarction. Congestive heart failure was defined as the need for medical treatment or past admission for heart failure. All medical treatment data were entered at the time of discharge during the first admission. GDMT was defined as the aggregate prescription of antiplatelet agents, statins, and ACE inhibitors or ARBs, according to the current guidelines for LEAD and hypertension.

Baseline Assessment and Revascularization Strategy
The severity of limb ischemia in the index limb was routinely evaluated by ankle brachial index (ABI) and skin perfusion pressure (SPP). The severity and location of lower limb arterial lesions were generally evaluated using duplex ultrasound scanning (DUS), and the presence of significant arterial lesions was verified using angiography before revascularization.

Materials and Methods

Study Participants
This study was a retrospective observational study. In this study, we included a total of 459 patients with CLTI who underwent revascularization (396 endovascular therapy [EVT] and 63 bypass surgery [BSX] cases) between January 2007 and December 2011 at two centres (Kansai Rosai Hospital and Shinsuma General Hospital) in Japan. One limb was included for each enrolled patient. Decisions regarding revascularization strategy, EVT, or BSX were at the clinician’s discretion.

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each hospital. The current analysis involved observational research without intervention or invasiveness and did not use human biological specimens; therefore, the study was exempted from the requirement of written informed consent from patients, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information regarding the study was made available to the public, and opportunities for individuals to refuse the inclusion of their data were ensured.

Baseline Assessment and Revascularization Strategy
The severity of limb ischemia in the index limb was routinely evaluated by ankle brachial index (ABI) and skin perfusion pressure (SPP). The severity and location of lower limb arterial lesions were generally evaluated using duplex ultrasound scanning (DUS), and the presence of significant arterial lesions was verified using angiography before revascularization. The revascularization strategy was depend on the physician’s discretion. Genrally, in patients who underwent EVT, a primary stenting strategy was used for aortoiliac lesions and a provisional stenting strategy was used for femoropopliteal lesions. The infrapopliteal lesions were treated using plain angioplasty. Nevertheless, BSX was performed by standard bypass techniques, and autogenous vein grafts were routinely used. Expanded polytetrafluoroethylene (ePTFE) grafts were used in cases without appropriate autogenous vein grafts.
for continuous variables and as percentages for discrete variables, unless otherwise indicated. Intergroup differences in the baseline characteristics were assessed using unpaired t-tests for continuous variables and \( \chi^2 \) tests for discrete variables. All-cause mortality rates were estimated using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test when necessary. Cox proportional hazards regression analysis was used to determine the association between the baseline characteristics and all-cause mortality. Factors associated with all-cause death in the univariate analysis were examined using multivariate analysis. The influence of GDMT on all-cause death and the association between baseline characteristics were demonstrated using interaction effects. We also evaluated the follow-up index which indicates the follow-up completeness at a given study end date as ratio between the investigated and the potential follow-up period to avoid attrition bias\(^{11}\). The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set at \( p < .05 \). Statistical analyses were performed using SPSS version 24.0 J (SPSS Inc., Chicago, IL, USA).

### Results

#### Baseline Characteristics

The characteristics of the patients and their limbs are summarised in Table 1: 64% (\( n = 294 \)) of patients were male, and the mean age was 72 ± 10 years. The

### Table 1. Baseline patient characteristics

| No. patients | All |
|--------------|-----|
| **Patient characteristics** |     |
| Male         | 294 (64) |
| Age, years   | 72 ± 10 |
| Body mass index, kg/m\(^2\) | 21 ± 3 |
| Non-ambulatory status | 228 (50) |
| Hypertension | 771 (65) |
| Dyslipidemia | 391 (33) |
| Diabetes mellitus | 313 (68) |
| Hemodialysis | 215 (47) |
| Coronary artery disease | 189 (41) |
| Congestive heart failure | 84 (18) |
| Cerebrovascular disease | 102 (22) |
| Left ventricular ejection fraction, % | 62 ± 12 |
| Serum albumin, g/dL | 3.4 ± 0.6 |
| **Medical treatment** |     |
| Antiplatelet agents | 411 (90) |
| ACE inhibitors or ARBs | 149 (33) |
| Statins | 84 (19) |
| **Revascularization strategy** |     |
| BSX | 63 (14) |
| EVT | 396 (86) |
| Follow-up index | 0.71 ± 0.39 |
| **Limb characteristics** |     |
| Ankle-brachial index | 0.65 ± 0.27 |
| Skin perfusion pressure, mmHg |     |
| Dorsal surface | 28 ± 16 |
| Planter surface | 29 ± 17 |
| **Rutherford classification** |     |
| 4 (Only rest pain) | 182 (15) |
| 5 (Minor tissue loss) | 718 (61) |
| 6 (Major tissue loss) | 284 (24) |
| **Lesion characteristics** |     |
| Arterial lesion distribution |     |
| Multi-vessel | 278 (61) |
| Isolated below-the-knee | 181 (39) |

Data are presented as \( n \) (%) or mean ± standard deviation (SD).

BSX = bypass surgery. EVT = endovascular therapy.
The main causes of death were cardiovascular disease (35.9%) and infection (27.8%).

In the Kaplan-Meier analysis, 10-year mortality was significantly lower in patients taking statins (55.8 % vs. 77.3%, \( p < .001 \), Fig. 2A) and ACE inhibitors or ARBs (70.8% vs. 74.5%, \( p = .010 \), Fig. 2B) than in those without. There were no differences in 10-year mortality between patients taking and not taking anti-platelet agents (73.1% vs. 74.9%, \( p = .62 \), Fig. 2C).

ACE = angiotensin-converting enzyme, ARBs = angiotensin receptor blockers.
Multivariate analysis revealed that age >75 years (HR 1.96 [95% CI 1.49–2.59], p < .001), non-ambulatory status (HR 2.18 [95% CI 1.66–2.87], p < .001), hemodialysis (HR 2.18 [95% CI 1.65–2.88], p < .001), congestive heart failure (HR 1.51 [95% CI 1.05–2.17], p = .028), left ventricular ejection fraction <50% (HR 1.50 [95% CI 1.03–2.20], p = .035) and GDMT (HR 0.75 [95% CI 0.60–0.93], p = .009, per one medication increase) were significantly associated

Moreover, 10-year mortality was 78.2%, 69.2%, and 52.5% in patients taking no or one, two, and three medications of GDMT, respectively (p < .001). GDMT = guideline-directed medical therapy.

**Table 2.** Association between baseline characteristics and mortality

|                      | Unadjusted model | Adjusted model |
|----------------------|------------------|----------------|
|                      | HR [95%CI]       | p value        |
| Male                 | 1.01 [0.80-1.28] | 0.91           |
| Age >75 years        | 1.67 [1.29-2.16] | <0.001         |
| Body mass index <18.5 kg/m² | 1.85 [1.38-2.47] | <0.001         |
| Non-ambulatory status| 2.73 [2.09-3.56] | <0.001         |
| Diabetes mellitus    | 0.91 [0.70-1.20] | 0.51           |
| Hemodialysis         | 2.26 [1.74-2.94] | <0.001         |
| Coronary artery disease | 1.37 [1.06-1.77] | 0.16           |
| Congestive heart failure | 2.05 [1.50-2.80] | <0.001         |
| Cerebrovascular disease | 1.00 [0.73-1.37] | 0.98           |
| Left ventricular ejection fraction <50% | 2.43 [1.75-3.36] | <0.001         |
| Serum albumin <3.0 g/dL | 1.16 [1.17-2.24] | 0.004          |
| Tissue loss          | 1.29 [0.93-1.78] | 0.13           |
| EVT (versus BSX)     | 1.12 [0.78-1.60] | 0.55           |
| GDMT, per 1 medication increase | 0.67 [0.55-0.81] | <0.001         |

Hazard ratios (HRs) were presented together with the 95% confidence intervals (CIs). GDMT = guideline-directed medical therapy.
Interaction analysis revealed that GDMT reduced the risk of 10-year mortality in patients with CLTI on hemodialysis and undergoing EVT.

Several studies have revealed the efficacy of GDMT for patient- and limb-based outcomes in patients with LEAD undergoing revascularization. Armstrong et al., in an analysis of 739 patients, reported that in those with intermittent claudication (IC) or CLTI and combination treatment with four guideline-recommended therapies, including antiplatelet agents, statins, ACE inhibitors or ARBs, along with smoking abstinence, were significantly associated with major adverse cardiovascular events (MACE), major adverse limb events (MALE), and mortality. Although patients who were treated with four GDMTs had significantly more severe comorbidities in this study, those with lower rates of MACE and MALE demonstrated that optimal adherence of physicians and patients to guideline-recommended therapies could significantly improve long-term outcomes. The current study revealed that GDMT was significantly associated with all-cause and cardiovascular mortality which was consistent with the previous reports.

Lipid-lowering therapy using statins prevents cardiovascular events in patients with LEAD, based on their ability to reduce inflammation within

---

**Fig. 4.** Interaction analysis

Prognostic impact of GDMT on mortality in subgroups. It was revealed that GDMT had a significantly different HR in patients who were and were not undergoing hemodialysis, and were treated with EVT or BSX (interaction: \(p = .002\) and \(p = .044\), respectively).

GDMT = guideline-directed medical therapy, EVT = endovascular therapy, BSX = bypass surgery.
atherosclerotic lesions and consequently stabilise vulnerable plaques. Large cohort studies have shown that the prescription of strong statins is associated with a decreased rate of MACE, MALE, and mortality.\textsuperscript{15, 16} Postulated mechanisms of the clinical benefit would rely on the pleiotropic effect of statin therapy to stabilise atherosclerotic plaque composition or facilitate plaque regression, potentially leading to a more stable LEAD. Given the accumulating evidence, guidelines strongly recommend the administration of statins to all symptomatic patients with LEAD.\textsuperscript{7} Although, in the current study, statins had the greatest impact on mortality, only 20% of patients were on statin therapy which was somewhat discrepant with current clinical practice. This low rate of administration could be attributed to the fact that approximately 20% of study participants had malnutrition, defined as serum albumin < 3.0 g/dL, and about two-thirds had no history of dyslipidaemia. In Japan, statins were strictly recommended for patients with dyslipidaemia. In addition, clinicians might be less aware of the adverse cardiovascular risks of LEAD and, therefore, prescribe risk-reduction therapies less intensively than they do for those with coronary artery disease, as previously reported.\textsuperscript{17, 18}

ACE inhibitors and ARBs, which have antihypertensive and cardioprotective effects have reduced cardiovascular events and mortality in patients with LEAD in several trials.\textsuperscript{19, 20} In patients with LEAD and hypertension, current guidelines recommend the management of blood pressure at < 140/90 mmHg, and ACE inhibitors or ARBs should be considered first-line antihypertensive therapy.\textsuperscript{7} There are concerns that drugs that reduce blood pressure will worsen ischaemia in patients with LEAD. Although ACE inhibitors and ARBs have not been directly evaluated for CLTI, they have been shown to be effective in lowering blood pressure without worsening symptoms in IC.\textsuperscript{21} In contrast, several studies have reported that ACE inhibitors and ARBs directly inhibit the atherosclerotic process and improve vascular endothelial function.\textsuperscript{22, 23} Although optimal blood pressure control for patients with CLTI has not been established, blood pressure management may be beneficial, considering that patients with CLTI have a higher risk of MACE than patients with IC.

In this study, there were no differences in 10-year mortality between CLTI patients with and without antiplatelet agent administration. This may be due to the fact that over 90% of the population was prescribed antiplatelet agents. The current guideline recommends that single antiplatelet agents should be considered for symptomatic LEAD patients, and clopidogrel may be preferred over aspirin based on the results of a randomised trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).\textsuperscript{8} In addition, dual-antiplatelet therapy (DAPT) for over six months was associated with decreased MACE and MALE in patients with LEAD, while major bleeding events were infrequent.\textsuperscript{24} In the current study, we did not collect data regarding the duration of DAPT, and administration of DAPT for over six months in the CLTI population remains controversial because patients with LEAD itself are considered to be at high risk of bleeding. Regarding to anti-thrombotic therapy, warfarin was not associated with mortality in this study.

In the current study, the 10-year mortality was not significantly different between patients undergoing BSX and EVT. CLTI patients with poorer comorbidities were more frequently included in the EVT group, and we speculated poorer 10-year mortality in the EVT group. However, 10-year mortality was not different. It might be the lack of sufficient follow-up rate and small sample size, but the current study would suggest that the 10-year mortality of CLTI is clinically dire and GDMT plays an important role in the improvement of their mortality.

In terms of interaction analysis for clinical variables, the prescription of GDMT reduced the risk of 10-year mortality in patients on hemodialysis and undergoing EVT. Several studies have demonstrated that chronic renal failure, especially hemodialysis, has a higher risk of the potential occurrence of cardiovascular events, and GDMT would have a greater effect on risk reduction. In this study, the selection of revascularization strategy was determined by each physician’s accumulated experience, but basically by considering the general status, cognition condition, expected risk of perioperative complications, and life expectancy. Therefore, the group undergoing EVT may include patients with more comorbidities as a high-risk group for the future occurrence of cardiovascular events. Based on our results, GDMT would have a greater beneficial effect on patients with advanced LEAD, those representing hemodialysis or those unfit for surgery.

**Limitations**

The current study had several limitations. First, this was a retrospective multicentre study without a prospective or randomised design. Second, a substantial number of patients (36.6%, 168/459 patients) could not be followed-up during the study period. Therefore, the all-cause mortality would be underestimated. However, the follow-up index was applied to covariates in multivariate analysis to adjust...
the attrition bias, and the results were consistent. Third, although we did not evaluate adherence to GDMT in the follow-up periods, it was reported that a prescription of GDMT prior to discharge increases utilisation at six months in patients with symptomatic LEAD. Fourth, the scope of current guidelines is not limited to patients with CLTI and is broadly applied to those with LEAD. Although CLTI is a most advanced manifestation of LEAD, there were few reports regarding the impact of medical therapy on long-term clinical outcomes in patients with CLTI. An optimal GDMT for patients with CLTI is not definitive and further studies would be warranted to determine this issue. Finally, it may be possible that patients who are able to receive GDMT have a good prognosis because of their preferable general health and activities of daily living. However, multivariate analysis including ambulatory status and comorbidities as covariates to minimise bias demonstrated that GDMT was independently associated with mortality.

Conclusion

In conclusion, appropriate GDMT was independently associated with 10-year mortality in patients with CLTI after revascularization. GDMT had a greater beneficial effect on 10-year mortality in subgroups on hemodialysis or those receiving EVT.

Acknowledgements

The authors would like to thank the medical staff at the participating centers in performing revascularization procedures and data collection.

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval for Research

This study was approved by ethics committee of Kansai Rosai Hospital (Reference number: 20D030g).

References

1) Reinecke H, Unrath M, Freisinger E, Bunzemeier H, Meyborg M, Lüders F, Gebauer K, Roeder N, Berger K, Malyar NM. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. Eur Heart J, 2015; 36: 932-938
2) Shiraki T, Iida O, Takahara M, Okamoto S, Kitano I, Tsuji Y, Terashi H, Uematsu M. Predictive scoring model of mortality after surgical or endovascular revascularization in patients with critical limb ischemia. J Vasc Surg, 2014; 60: 383-389
3) Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, Nehler MR, Powell RJ, Sidawy AN. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg, 2009; 50: 1462-1473
4) van Reijen NS, Hensing T, Santema TKB, Ubbink DT, Koelma MW. Outcomes of Conservative Treatment in Patients with Chronic Limb Threatening Ischemia: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg, 2021; 62: 214-224
5) Iida O, Takahara M, Suga Y, Azuma N, Nanto S, Uematsu M; PRIORITY Investigators. Prognostic Impact of Revascularization in Poor-Risk Patients With Critical Limb Ischemia: The PRIORITY Registry (Poor-Risk Patients With and Without Revascularization Therapy for Critical Limb Ischemia). JACC Cardiovas Interv, 2017; 10: 1147-1157
6) Soga Y, Iida O, Takahara M, Hirano K, Suzuki K, Kawasaki D, Miyashita Y, Tsushima T. Two-year life expectancy in patients with critical limb ischemia. JACC Cardiovas Interv, 2014; 7: 1444-1449
7) Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kowannor S, Mazzolai L, Naylor AR, Roffi M, Röther J, Snyrmger M, Tepe G, Venermo M, Vlachopoulos C, Desormais I; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J, 2018; 39: 761-816
8) CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet, 1996; 348: 1329-1339
9) Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg, 2007; 45: 645-654
10) Armstrong EJ, Chen DC, Singh GD, Amsterdam EA, Laird JR. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use is associated with reduced major adverse cardiovascular events among patients with critical limb ischemia. Vasc Med, 2015; 20:
11) von Allmen RS, Weiss S, Tevaearai HT, Kuemmerli C, Tinner C, Carrel TP, Schmidli J, Dick F. Completeness of Follow-Up Determines the Validity of Study Findings: Results of a Prospective Repeated Measures Cohort Study. PLoS One, 2015; 10: e0140817

12) De Martino RR, Hoel AW, Beck AW, Eldrup-Jorgensen J, Hallett JW, Upchurch GR, Cronenwett JL, Goodney PP; Vascular Quality Initiative. Participation in the Vascular Quality Initiative is associated with improved perioperative medication use, which is associated with longer patient survival. J Vasc Surg, 2015; 61: 1010-1019

13) Ardati AK, Kaufman SR, Aronow HD, Nypaver TJ, Bove PG, Gurms HS, Grossman PM. The quality and impact of risk factor control in patients with stable claudication presenting for peripheral vascular interventions. Circ Cardiovasc Interv, 2012; 5: 850-855

14) Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, Yeo KK, Anderson D, Amsterdam EA, Laird JR. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. J Am Heart Assoc, 2014; 3: e000697

15) Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet, 2002; 360: 7-22

16) Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, Wilson PWF. Association of statin dose with amputation and survival in patients with peripheral artery disease. Circulation, 2018; 137: 1435-1446

17) Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. Circulation, 2011; 124: 17-23

18) Hess CN, Cannon CP, Beckman JA, Goodney PP, Patel MR, Hiatt WR, Mues KE, Oroth KK, Shannon E, Bonaca MP. Effectiveness of Blood Lipid Management in Patients With Peripheral Artery Disease. J Am Coll Cardiol, 2021; 77: 3016-3027

19) Feringa HH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O, Galal W, Vidakovic RV, Tangelder MJ, Poldermans D. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. J Am Coll Cardiol, 2006; 47: 1182-1187

20) Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med, 2000; 342: 145-153

21) Thomas Manapurathe D, Krishna SM, Dewdney B, Moxon JV, Biros E, Golledge J. Effect of blood pressure lowering medications on leg ischemia in peripheral artery disease patients: A meta-analysis of randomised controlled trials. PLoS One, 2017; 12: e0178713

22) Lonn EM, Yusuf S, Jha P, Montague TJ, Teo KK, Benedict CR, Pitt B. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. Circulation, 1994; 90: 2056-2069

23) Schieffer B, Schieffer E, Hilfiker-Kleiner D, Hilfiker A, Kovanen PT, Kaartinen M, Nussberger J, Harringer W, Drexler H. Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. Circulation, 2000; 101: 1372-1378

24) Cho S, Lee YJ, Ko YG, Kang TS, Lim SH, Hong SJ, Ahn CM, Kim JS, Kim BK, Choi D, Hong MK, Jang Y. Optimal Strategy for Antiplatelet Therapy After Endovascular Revascularization for Lower Extremity Peripheral Artery Disease. JACC Cardiovasc Interv, 2019; 12: 2359-2370

25) Renard BM, Seth M, Share D, Aronow HD, Laveroni EW, De Gregorio M, Hans SS, Henke PK, Gurms HS, Grossman PM. If not now, when? Prescription of evidence-based medical therapy prior to hospital discharge increases utilization at 6 months in patients with symptomatic peripheral artery disease. Vasc Med, 2015; 20: 544-550
**Supplemental Table 1.** Baseline patient characteristics regarding to revascularization strategy

|                               | BSX    | EVT    | \( p \) value |
|-------------------------------|--------|--------|---------------|
| **No. patients**              | 63     | 396    |               |
| **Patient characteristics**   |        |        |               |
| Male                          | 46 (73)| 248 (63)| 0.11          |
| Age, years                    | 70 ± 8 | 72 ± 10| 0.14          |
| Body mass index, kg/m\(^2\)   | 21 ± 3 | 21 ± 3 | 0.72          |
| Non-ambulatory status         | 23 (37)| 205 (52)| 0.02          |
| Hypertension                  | 347 (65)| 424 (65)| 0.94          |
| Dyslipidemia                  | 169 (32)| 222 (34)| 0.41          |
| Diabetes mellitus             | 45 (71)| 268 (68)| 0.55          |
| Hemodialysis                  | 21 (33)| 194 (49)| 0.02          |
| Coronary artery disease       | 28 (44)| 161 (41)| 0.57          |
| Congestive heart failure      | 14 (22)| 70 (18) | 0.39          |
| Cerebrovascular disease       | 20 (32)| 82 (21) | 0.05          |
| Left ventricular ejection fraction, % | 64 ± 12 | 61 ± 12 | 0.66          |
| Serum albumin, g/dL           | 3.3 ± 0.5 | 3.4 ± 0.6 | 0.54          |
| **Admission medications**     |        |        |               |
| Antiplatelet agents           | 48 (76)| 363 (92)| \(< 0.001\)   |
| ACE inhibitors or ARBs        | 27 (43)| 122 (31)| 0.070         |
| Statins                       | 8 (13) | 76 (19) | 0.20          |
| BSX with autogenous vein      | 49 (78)| N/A    | N/A           |
| **Limb characteristics**      |        |        |               |
| Ankle-brachial index          | 0.63 ± 0.25 | 0.66 ± 0.27 | 0.61          |
| Skin perfusion pressure, mmHg |        |        |               |
| Dorsal surface                | 30 ± 13| 27 ± 17| 0.43          |
| Planter surface               | 28 ± 15| 29 ± 17| 0.80          |
| Rutherford classification     |        |        | 0.95          |
| 4 (Only rest pain)            | 77 (14)| 105 (16)|               |
| 5 (Minor tissue loss)         | 331 (62)| 387 (59)|               |
| 6 (Major tissue loss)         | 124 (23)| 160 (25)|               |
| **Lesion characteristics**    |        |        | 0.06          |
| Arterial lesion distribution  |        |        |               |
| Multi-vessel                  | 45 (71)| 233 (59)|               |
| Isolated below-the-knee       | 18 (29)| 163 (41)|               |

Data given as \( n \) (%) or mean ± standard deviations (SD). BSX: bypass surgery. EVT: endovascular therapy. N/A: not applicable.
Supplemental Fig. 1. The 10-year mortality rate according to the revascularization strategies (BSX or EVT)
The 10-year mortality rates were not significantly different between patients treated with EVT and BSX (72.7% versus 75.7% at 10-year, log rank \( p = .55 \), respectively). EVT=endovascular therapy, BSX=bypass surgery.

Supplemental Table 2. Association between baseline characteristics and mortality adjusted by follow-up index

|                                      | Adjusted model |
|--------------------------------------|----------------|
|                                      | HR [95%CI]     | \( p \) value |
| Age >75 years                         | 1.75 [1.31-2.33]| <0.001        |
| Non-ambulatory status                 | 2.02 [1.53-2.65]| <0.001        |
| Hemodialysis                          | 1.52 [1.14-2.02]| 0.004         |
| Congestive heart failure              | 1.71 [1.19-2.26]| 0.004         |
| Left ventricular ejection fraction <50% | 1.49 [1.02-2.17]| 0.041         |
| GDMT, per 1 medication increase       | 0.71 [0.56-0.89]| 0.004         |

Hazard ratios (HR) are presented together with the 95% confidence intervals (CI). GDMT: guideline-directed medical therapy.
**Supplemental Table 3.** Association between baseline characteristics and cardiovascular mortality

| Characteristic                      | Unadjusted model | Adjusted model |
|-------------------------------------|------------------|----------------|
|                                    | HR [95%CI]       | p value        | HR [95%CI]       | p value        |
| Male                                | 1.04 [0.65-1.66] | 0.87           |                 |                |
| Age >75 years                       | 1.22 [0.77-1.93] | 0.40           |                 |                |
| Body mass index <18.5 kg/m²         | 2.04 [1.24-3.34] | 0.005          | 1.50 [0.89-2.54] | 0.13           |
| Non-ambulatory status               | 3.19 [1.98-5.13] | <0.001         | 2.13 [1.28-3.55] | 0.004          |
| Diabetes mellitus                   | 1.22 [0.74-2.02] | 0.44           |                 |                |
| Hemodialysis                        | 5.11 [3.00-8.72] | <0.001         | 3.69 [2.09-6.49] | <0.001         |
| Coronary artery disease             | 1.90 [1.21-2.98] | 0.006          | 1.06 [0.64-1.77] | 0.81           |
| Congestive heart failure            | 3.85 [2.40-6.18] | <0.001         | 2.15 [1.20-3.83] | 0.010          |
| Cerebrovascular disease             | 1.26 [0.75-2.12] | 0.38           |                 |                |
| Left ventricular ejection fraction <50% | 3.71 [2.24-6.15] | <0.001         | 1.35 [0.72-2.52] | 0.34           |
| Serum albumin <3.0 g/dL             | 1.08 [0.57-2.05] | 0.81           |                 |                |
| Tissue loss                         | 2.02 [1.04-3.95] | 0.039          | 1.44 [0.71-2.91] | 0.31           |
| EVT (versus BSX)                    | 1.15 [0.60-2.17] | 0.68           |                 |                |
| GDMT, per 1 medication increase     | 0.63 [0.44-0.88] | 0.007          | 0.65 [0.43-0.99] | 0.045          |

Hazard ratios (HRs) were presented together with the 95% confidence intervals (CIs). GDMT = guideline-directed medical therapy.