# ORIGINAL ARTICLE

# Endovascular or open surgical treatment of high-risk patients with infrainguinal peripheral arterial disease and critical limb ischemia

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## ABSTRACT

**Aim** To determine preferable type of treatment in our clinical circumstances by following two groups of patients with critical limb ischemia (CLI), who were treated endovascularly and surgically.

**Methods** Research was carried out in the form of a prospective study of 80 patients with CLI and Trans-Atlantic Inter-Society Consensus (TASC) C or D type of arterial disease, with American Society of Anesthesiology (ASA) class III risk, who were randomly divided in two groups as per the treatment they received, surgical and endovascular. Patients were followed during 28 months using clinical examination and Duplex Ultrasound (DUS) in accordance with prescheduled control visits.

**Results** There was a statistical difference between surgical and endovascular group in two years patency (82.5% vs. 55%; p=0.022) but it did not result in the difference in amputation free survival (AFS) (95% vs. 85%; p=0.171) or two-year freedom from major adverse limb events (MALE) (87.5 vs. 77.5; p=0.254). Also, there was no difference in the overall survival of patients (100% vs. 97.5%; p=0.317).

**Conclusion** Initial endovascular treatment is a preferred form of the treatment for selected patient population.

**Key words:** amputation-free survival, endovascular procedure, infrainguinal bypass, patient survival critical limb ischemia, endovascular, peripheral arterial disease, surgical

## INTRODUCTION

Currently, the treatment of critical limb ischemia is complicated by the development of endovascular procedures (1-4). While in the recent past the main problem was presence of conditions suitable for open surgery or ability of the patient to withstand that treatment, today the main problem is how to treat the patient – by endovascular procedure or by open surgery (5-7). Endovascular procedures involve lesser invasiveness for decreased patency (6-8). On the other side, bypass procedures involve greater invasiveness and risk to the patient for prolonged patency (7-9).

The dilemma is particularly pronounced in subpopulation of patients with critical limb ischemia (CLI) and serious comorbidities that make these patients poor candidates for open surgical procedures (1, 6-9). Endovascular treatment that losses its effect after a couple of months, puts a patient in even more risk without the resolution of ischemia (10,11). Repeat endovascular procedures often do not produce wanted results (with the assumption that health care system could afford it) and, if we exclude amputation as a form of preferred treatment, the patient is left with surgical intervention as the only option after a lot of wasted time (11,12).

The patients with CLI are not good candidates for both treatments at the same time, as shown in the BASIL study (1). However, there were attempts to standardize the treatment such as the one in a study by Goodney et al. (2) on a validation of the society for vascular surgery's objective performance goals (OPGs) for critical limb ischemia, or in a study by Conte et al. (3) on suggested objective performance goals in catheter-based treatment of critical limb ischemia (2,3).

Anyway, at the time we designed and started this study, literature review did not show without doubt a preferred treatment for high risk patients with CLI, having ischemic ulceration that needed more than 6 months for healing (1-15). Additionally, there is another very important dilemma. Is it correct for centres with low annual number of operations and with limited resources to base their decision making on guidelines developed in centres with high annual number of operations (e. g. referral centres)? Also, gaining sufficient endovascular skills is complicated by progressive development of technology – the problem encountered by most developed countries (5,7,12,13).

The aim of this study was to investigate for a preferred treatment, endovascular or surgical, of high-risk patients with CLI and infrainguinal peripheral arterial disease (PAD) and limited life expectancy, as well as to validate our endovascular/surgical skills.

## PATIENTS AND METHODS

### Patients and study design

This prospective clinical study was conducted from 2012 until 2016 on 80 consecutive patients admitted to the Clinic for Vascular Surgery of Clinical Centre of the University of Sarajevo (CCUS) that suffered from CLI.

Inclusion criteria were: patients with critical limb ischemia, Trans-Atlantic Inter-Society Consensus (TASC) II B or C disease, and American Society of Anesthesiology Class III surgical risk (4,16). During the study period, precisely in 2014, there was a revision of TASC II classification but we remained adhered to 2007 TASC II classification as per the original design of the study (17).

Exclusion criteria were: lost to follow-up, pathology of the extremity not related to the intervention or occlusion of the bypass (trauma, infection or deep vein thrombosis), disease of the patient that could cause disturbance of the coagulation system (malignancy).

The patients were divided into two groups of 40: patients with infrainguinal revascularization by endovascular intervention (ET group), and patients with infrainguinal revascularization by vein bypass (BX group).

The sample was calculated based on knowledge of the population related to the Clinic for Vascular Surgery Sarajevo (600,000 inhabitants), prevalence of CLI in the local population (6%), confidence interval (95%) and 5% of margin of error. We tried to randomize patients to different groups by the time of their admission to hospital. Consecutive and eligible patients were intermittently assigned to endovascular intervention or to surgical bypass and that schedule was followed as long as technical and personal resources allowed us doing so. In cases of insufficient equipment for endovascular intervention, or lack of staff, we performed surgical revascularization and vice versa – number of patients treated in this manner was reimbursed once the equipment and staff were sufficient.

All participants signed a written consent upon admission to the study. The study was approved by the Ethics Committee of the CCUS based on its compliance with the Helsinki Declaration.

## Methods

Endovascular intervention considered angioplasty with or without stenting. Stenting was reserved for cases with complications such as dissection or rupture of blood vessel or when international guidelines recommended usage of stents (superficial femoral artery). Usage of popliteal stents was limited by lack of specialized stents for that delicate region. Access artery was most frequently common femoral artery. Immediately upon access we administered 100 IU/kg of heparin with the aim of Activated Partial Thromboplastin Time (APTT) of 250 seconds. A desirable result was absence of residual stenosis or persistent stenosis of less than 30% on control angiography and continuity of patency to the foot. Before the intervention, patients received low-molecular-weight heparin (LMWH) administered according to the body weight. From the moment of the intervention, patients were kept on conventional heparin infusion for 24 h with ttt aim of maintaining APTT two to three times of the normal. After 24 h, during the first postintervention month, patients were kept on dual antiplatelet therapy, acetyl salicylic acid (ASA) 100 mg 1x1 and Clopidogrel 75 mg 1x1. Starting with the second postintervention month all patients received lifelong ASA 150 mg 1x1.

Great saphenous vein (GSV) was checked and mapped by duplex ultrasound (DUS) to all surgical patients the day before surgery. Bypass was performed using the technique of reversed great saphenous month (GSV). Only veins greater than 3 mm in diameter, perfused without resistance and without fibrotic segments were used. We preferred tunelization within vascular bed. Only in reoperations we performed subcutaneous tunnels. Surgery was performed with the aim to bypass all occluded segments to achieve continuous patency until the foot.

The most frequent inflow site was the common femoral artery (CFA). Only in cases dictated by specific anatomic distribution of the disease or insufficient GSV length, superficial femoral artery (SFA) or popliteal artery (PA) was used as the inflow site.

Patients were given LMWH preoperatively and that regime was held by the time of discharge from the hospital. A few days before the discharge, patents were given aspirin (100 mg/day) as well, and they remained on aspirin for lifetime (150 mg/day).

Patients were controlled on prescheduled visits which were: thirty days post discharge, three months post discharge, six months post discharge for three consecutive visits, and then yearly. We examined patency of bypass or intervention using clinical examination and DUS. The study was designed to follow up patients for at least two years. Patients that did not show up on control visits were contacted by phone and those that could not be reached in that way were considered lost to follow up.

The recommendation of the Society for Vascular Surgery (SVS) is to incorporate all adverse limb events into survival analysis. That includes recurrence of ischemic suffering due to the graft occlusion or intervention failure and the need for additional bypass or endovascular reinterventions, so called MALE (Major Adverse Limb Event) (2,3).

## Statistical analysis

Demographic data and other characteristic of the patients were expressed as nominal or categorical variables. Student T test was used for comparison of groups where applicable or adequate nonparametric test. In case of skewed distribution, Mann-Whitney test was used. Pearson $\chi2$ test with Yates correction for small samples was used for categorical variables.

Patency, amputation free survival and overall survival were calculated using Kaplan-Meier analysis and were graphically expressed by Kaplan-Meier curve. Log rank, Breslow (generalized Wilcoxon) or Tarone-Ware analysis were used for measuring statistical significance. Binary logistic regression was used to show influence of different input variables on likelihood of negative outcome (occlusion or amputation). In all tests p<0.05 was used as statistically significant.

## RESULTS

A total of 80 patients were enrolled in the study from during the period 2012 to 2014 (plus two years of follow up). The average age was 66 years; 58 (73%) patients were males; 43 (53%) patients were diabetics and 30 (38%) were treated for tissue loss (Table 1). The ET and BX groups

were a good match. Significant differences were found in gender distribution e.g. more females in the ET group, 16 (40%) (p=0.012), and in TASC II classification, e.g. TASC II B was more prevalent in the ET group, 24 (60%) and TASC II C in the surgical group, 28 (70%) (p=0.007). Fibular artery was a more prevalent target artery in the ET group, 4 (10%) (p=0.002) (Table 1).

**Table 1. Characteristics of the patients with critical limb ischemia (CLI) treated endovascularly and surgically**

| Characteristic | No (%) of patients in the group | | p |
|---|---|---|---|
| | Endovascular | Surgical | |
| Age mean (SD) (years) | 67 (8.8) | 65 (7.1) | 0.267 |
| Male | 24 (60) | 34 (85) | 0.012 |
| Diabetes | 23 (57.5) | 20 (50) | 0.501 |
| **Elevated cardiac risk** | 38 (95) | 32 (80) | 0.043 |
| HTA | 34 (85) | 29 (72.5) | 0.076 |
| Atrial fibrillation | 8 (20) | 5 (12.5) | 0.152 |
| IM in history (CAD) | 6 (15) | 5 (12.5) | 0.632 |
| Episodes of heart failure | 3 (7.5) | 2 (5) | 0.468 |
| **Elevated pulmo risk (COPD)** | 16 (40) | 20 (50) | 0.369 |
| Low (FEV ≥80%) | 11 (27.5) | 17 (42.5) | 0.073 |
| Mild (FEV1 50-79%) | 3 (7.5) | 2 (5) | 0.468 |
| High (FEV1 3 -49%) | 2 (5) | 1 (2.5) | 0.312 |
| **Elevated renal risk (kidney failure)** | 19 (47.5) | 18 (45) | 0823 |
| Low (creatinine 110 – 160 mmol/L) | 16 (40) | 16 (40%) | 1 |
| Mild (creatinine 161 – 240 mmol/ L) | 3 (7.5) | 2 (10%) | 0.468 |
| High (creatinine > 241 mmol/ L) | 0 | 0 | |
| Smoking | 34 (85) | 36 (90%) | 0.499 |
| **Diagnosis** | | | |
| Pain / gangrene | 26 (65) / 14 (35) | 24 (60) / 16 (40) | 0.501 |
| **TASC** | | | |
| B/C | 24 (60/ 16 (40) | 12 (30%) / 28 (70) | 0.007 |
| **Target artery of revascularization** | | | |
| SFA | 18(45) | 35 (87.5) | 0.001 |
| PA | 25 (62.5) | 28 (70) | 0.306 |
| PTA | 9 (22.5) | 12 (30) | 0.320 |
| ATA | 1 (2.5) | 3 (7.5) | 0.223 |
| FA | 4 (10) | 1 (2.5) | 0.002 |

FA, fibular artery; superficial femoral artery; PA, popliteal artery; ATA, anterior tibial artery; PTA, posterior ttibial artery; CAD, coronary artery disease; FEV1, forced expiratory volume at 1st sec.; HTA, arterial hypertension; SD, standard deviation; TASC, transatlantic inter-society consensus;

Technical success was achieved in 100% of patients. Patency of bypass was 82.5% and patency of endovascular intervention was 55% (p=0.013); the difference was not statistically significant until the 240th day of the study (or in the first 8 months). Seven patients in BX group experienced bypass failure and intervention failure affected 18 patients in the ET group. Most of the failures in theET group happened in he second half of the study period (Figure 1).
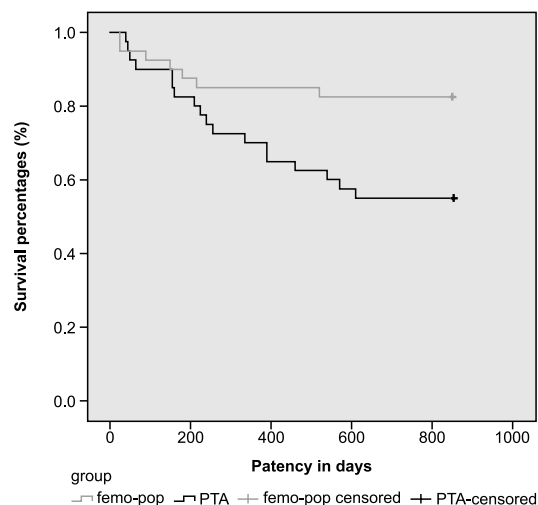


**Figure 1. Patency of surgical grafts and edovascular intervention;** Fem-pop, all infraingvinal bypasses; PTA, percutanous transluminal angioplasty;

Two patients in the BX group had major amputation (above knee) in early stages of the study. In the ET group six patients were amputated; four had below knee amputation and two above knee amputation (p=0.150) (Figure 2).
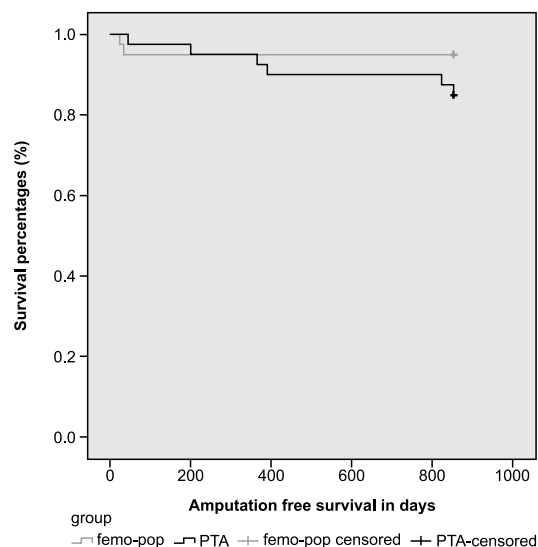


**Figure 2. Amputation free survival of the patients treated by surgical bypass and by endovascular intervention;** Fem-pop, all infraingvinal bypasses; PTA, percutanous transluminal angioplasty;

In relation to the patency analysis, not all occlusions resulted in the recurrence of CLI, especially in ET. Recurred CLI after failed bypass or endovascular intervention was always considered for revascularization. In the BX group occlusion of grafts in two patients resulted in recurrence of CLI and both patients got additional bypass with contralateral great saphenous vein. Remaining two patients with graft occlusion did not

develop CLI and did not need reintervention. Additionally, one patient had stenosis of the graft close to proximal anastomosis that was resolved by endovascular intervention (crossover patient). There was also one crossover patient in ET and two patients with recurrence of ischemia resolved by endovascular reintervention. Nine patients did not experience recurrent CLI upon the intervention failure. In six patients reintervention was not possible and they eventually ended up with amputation.

Survival without MALE in BX and ET group was 87.5% and 77.5% respectfully (p=0.243) (Figure 3).
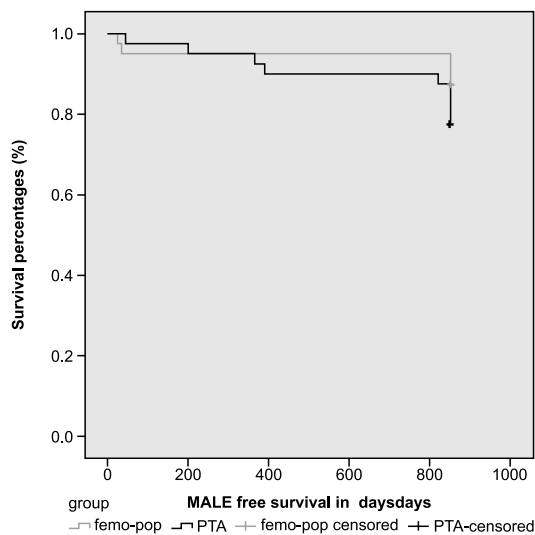


**Figure 3. Survival analysis of the patients without major adverse limb events (MALE) treated by surgical bypass and by endovascular intervention;** Fem-pop, all infraingvinal bypasses; PTA, percutanous transluminal angioplasty;

One patient from the ET group died due to massive myocardial infarction at the start of the second half of the study period. However, overall survival of patients between groups was not different.

Binary logistic regression model showed statistical significance as a whole [$\chi^2$ (5, N=80) = 48.242] (p=0.0001). Three independent variables had unique, significant contribution to model. The strongest predictor of the failure was renal insufficiency (QP=0.044; p=0.0001), followed by diabetes (QP=0.09; p=0.0009), and pulmonary insufficiency (QP=0.177; p=0.020). When similar was applied for other independent variables such as diagnosis, age and gender, we also got a statistically significant model [$\chi^2$ (3, N=80) = 10.569] (p=0.014). The strongest predictor of failure was gender (QP=2.896) followed by age (QP=1.079).

Binary logistic regression model showed significance for amputation free survival [$\chi^2$ (3, N=80) = 14.510] (p=0.002). Age had significant influence on amputation free survival (AFS) (QP=1.175; p=0.008). Gender had a trend toward significance (QP=4.8; p=0.068).

The most frequent systemic complication in the BX group was respiratory failure, in two (5%) patients, followed by myocardial infarction (1%) and heart failure (1%). The most frequent local complication in the BX group was lymphedema, in 8 (20%) patients, followed by superficial wound infection (10%), deep wound infection (5%) and bleeding (2.5%).

The most frequent systemic complication in the ET group was renal failure, in two (5%) patients, followed by myocardial infarction (1%). The most frequent local complication in the ET group was access site hematoma, in three (7.5%) patients, followed by pseudoaneurysm, dissection and embolization – each occurred in 2.5% of patients.

Median of postoperative hospitalization in the BX group was 10 days and 2 days in the ET group (p=0.0001).

## DISCUSSION

After 28 months of follow up, patency of bypass was 82.5% and patency of endovascular intervention was 55%. Results of our study are in accordance with recommended range of OPG (Objective Performance Guidelines) (2,3). Also, when compared with patency of endovascular intervention in similar studies, significant difference was not detected (1,2,3, 6-13).

Venous bypasses patency in our study was better or equal to that reported in the literature. In some cases, results were significantly better, but detailed analysis showed that these studies with inferior results dealt predominantly with especially vulnerable patient subpopulations, such as diabetics, or patients treated exclusively for tissue loss (3,5,14). Again, patency of venous bypasses in this study was within the recommended range of OPG (2,3).

The results of our study found three risk factors with significant influence on patency. The best predictor of occlusion was renal insufficiency (95% greater chances for occlusion than those without renal pathology), followed by diabetes mellitus (91% greater chances for occlusion than nondiabetics), and pulmonary insufficiency (82%

greater chances for occlusion). Negative effects of renal failure and diabetes were well recognized in numerous studies (3,15,20,21). Some of them also found renal insufficiency to be a better predictor of occlusion than diabetes (3,15).

Regarding demography, best predictor of occlusion found in our study was female gender – women had nearly three times greater chances to experience occlusion than men, followed by age – each year above the average increased chances for occlusion by factor 1.1. There are numerous studies showing gender related disparity in the treatment and outcome of CLI (9,15,18,19). Although other factors could confound inference, we can consider female gender as a risk factor per se, probably because women were older at presentation and with more advanced PAD (18,19).

Amputation free survival (AFS) and limb salvage (LS) are the most frequent outcome measures in literature (1,2,3,8,10). The AFS is a more realistic indicator of outcome than LS since the latter censors from analysis patients who died with intact extremity (1), and it is the reason why we used AFS and MALE free survival as measures of outcome.

Two-year MALE free survival in this study was better or equal compared to the results of other similar studies (2,3,5-9), which also means that our result was within the range recommended by OPG (2,3).

Four variables were statistically significant predictors of AFS as found in our study: age, gender (with tendency toward significance), TASC "C" class of PAD and superficial femoral artery as a target artery of revascularization. Also, it is understandable that more advanced PAD predicts worse outcome and numerous studies justified that (2,3,15,20). An effect of advanced PAD is well recognized with special recommendation by OPG for patients with high risk anatomy of the disease in the form of TASC C or D lesions (2,3). Also, there are special OPG recommendations for patients older than 80, recognizing age as an influential factor on outcome (2,3).

Influence of superficial femoral artery on outcome is interesting and not easy to explain. Superficial femoral artery is most frequently affected by PAD and its isolated occlusion rarely produces a limb threatening condition (6,7,8,14). However, its affection in CLI is usually combined with extensive infrapopliteal lesions, resulting in high TASC score (4,17). Accordingly, we could assume that affection of superficial femoral artery in CLI is just a marker but not a cause of bad outcome. Our study is not alone in this finding. Similar influence of superficial femoral artery on outcome is reported by Belvins and Beard in their review of forms of revascularization of lower extremity (6,14).

Two-year survival of patients in this study was 97.5% and 100% in the ET and the BX group, respectfully; one patient in the ET group died from massive myocardial infarction at the start of the second half of the study period after suffering from occlusion of treated segment and consequent irreparable recurrent ischemia resulting in major amputation one month later. Of course, there is a cause and effect of relationship between failure of treatment and patients' demise. It looks counterintuitive that it happened in the group exposed to lesser invasive treatment. However, a lot of studies with similar design did not find mortality increase in the surgical group. For instance, BASIL study did not find significant difference in survival of patients in surgical and endovascular group (68% vs. 71%, respectively) (1). The results of two-year survival of other studies show similar findings (7,9, 13-17). None of the studies reported better survival in endovascular group. Even more, Masaki et al. reported significantly better survival in the surgical group with constant hazard ratio throughout five years of follow up (9). We could relate this to the fact that higher risk patients were treated in the endovascular group.

Systemic complications in infrainguinal bypass surgery on 7% were frequently reported, of which, 4.5% was myocardial infarction and heart failure and 1.5% cerebrovascular insult (20,21); the remaining 1% were other systemic complication, such as renal and respiratory failure (20,21). In our study 5% of patients suffered from heart complications (2.5% MI and 2.5% CHF), and 5% from respiratory complications, latter being significantly different from reports in theworld literature (21). The most frequently reported systemic complications related to the endovascular treatment were myocardial infarction (1.2%), heart failure (1.5%), cerebrovascular insult (1.4%) and renal failure (2%), of which 1% needed haemodialysis treatment) (3, 22-25). Seven percent is also frequently reported percentage of systemic complications in endovascular interventions (3, 22-25). In our study we found myocardial infarc-

tion in one patient (2.5%), and renal impairment in two (5%), latter being significantly different from reference literature (22-25).

The most frequent local postoperative complication in the BX group was superficial wound infection, found in 10% of patients, what was exactly the percentage reported in the literature (20), followed by deep wound infection (5%), also in accordance with reports in the literature – (4.8%) (16). Bleeding requiring intervention was found in one patient (2.5%), significantly different than literature reports (0.4%), probably due to small sample size in our study. Lymphoedema was present in 20% of patients as reported in the literature (2,16,20,21).

The most frequent local complication in postintervention period in the ET group was access site hematoma (7.5%), which was significantly different from the data in the literature (3.5%) (2,16,20,21). Postintervention dissection happened in 2.5% of patients also different from the literature (0.5%) (2,16,20,21). Access site pseudoaneurysm was found in 2.5% of patients,,,,,, while average from the literature was 0.4% (2,16,20,21). Prevalence of patients who suffered from distal embolization was not different from the literature (2.2%) (2,16,20,21).

Ambiguity related to best therapeutic approach to patients with CLI has lasted for years. Despite marked advancement in pharmacologic therapy, it remains insufficient in the treatment of CLI (26-28). However, pharmacologic modification of risk factors is indisputable and is highly recommended (28). With rapid development of minimally invasive percutaneous technologies, discussion on best treatment of patients with CLI, surgical or endovascular, became more complicated (1,6-10,13). Powerful technological progress and improvements in the equipment on a daily basis complicate the creation of a study with reliable results that could serve as durable guidelines on the treatment

to wider population (7,10,13). That could be the reason for serious insufficiency of valid evidence related to this issue; probably, the most important limiting factor is human. In that context we could consider this study as an attempt to offer guidelines for preferred treatment with local technical and human resources.

This study has several limitations. Most importantly, the process of randomization was improvised due to technical issues. It is very hard to accomplish true randomization in surgical studies performed by several surgeons. Also, it is very difficult to adhere to strict randomization protocol in the situation of unpredictable equipment provision and lack of staff.

Additionally, if we were in a position to recruit more patients we could expect significant difference in the outcome between treatment groups (insufficient randomization affects this as well). The sample size was actually small, possibly in accordance with sample size calculation. We were forced to this because of slow accrual of patients into the study, which might be related to the small target population and narrow inclusion criteria.

In conclusion, there was statistically significant difference in two-year patency of bypass and endovascular intervention. However, difference in patency did not affect amputation free survival. The difference remained insignificant even with MALE included. Also, overall survival of patients, crossover percentage and morbidity were the same in the groups. Therefore, endovascular treatment could be considered as preferred initial treatment in selected patients that match our study population.

## FUNDING

## TRANSPARENCY DECLARATION

Conflict of interest: None to declare

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