Peripheral arterial disease (PAD) affects 8 to 12 million Americans and carries an increased risk of cardiovascular morbidity and mortality and limb loss [1]. Patients presenting with PAD have traditionally been treated with surgical bypasses; however, development in lower extremity endovascular techniques has changed the therapeutic approach to this disease [2-5]. Advances in catheter-based technology have made endovascular interventions increasingly popular and they are commonly used as an alternative to open surgical procedures. Several studies have documented that although the number of bypass surgeries has remained stable, the number of endovascular interventions performed globally for PAD is consistently increasing [6,7].

Critical limb ischemia (CLI) represents the most severe form of PAD, and includes ischemic rest pain, non-healing wounds, and tissue gangrene. The role of endovascular therapy in CLI for femoropopliteal disease has been studied and consensus treatment guidelines have been published [8]. However, its role in atherosclerotic disease affecting the infrapopliteal (IP) arteries, is less defined.

Below-the-knee (BTK) endovascular interventions present a different challenge to the interventionist when compared to arteries above the knee. Tibial arteries are smaller in diameter, are frequently severely calcified and can be diffusely diseased with long segments of stenosis or occlusion. In addition, patients presenting with diabetes or dialysis typically show occlusive disease of the pedal arteries. All of these factors contribute to the complexity of BTK interventions.

The last decade has seen an exponential increase in technology and devices aimed at treating BTK arteries. Such devices include dedicated bare metal stents, drug coated balloons (DCB), drug eluding stents (DES), and atherectomy devices. In addition, other modalities of treatment are being performed, such as pedal angioplasty, tibial and pedal access, and multiple target vessel revascularization. Despite this, it is not clear whether these measures translate into improvement in limb preservation and decreased rate of amputation. The purpose of this study was to report our experience with changing trends in BTK interventions and to evaluate whether these changes resulted in improvement in limb salvage.

**ABSTRACT**

**Background:** Patients with critical limb ischemia (CLI) involving the below-the-knee (BTK) arteries are at increased risk of limb loss. Despite improvement in endovascular modalities, it is still unclear whether an aggressive approach results in improved limb salvage.

**Objectives:** To assess whether an aggressive approach to BTK arterial disease results in improved limb salvage.

**Methods:** A comparative study of two groups was conducted. Group 1 included patients treated between 2012 and 2014, primarily with transfersenlar angioplasty of the tibial arteries. Group 2 included patients treated between 2015–2019 with a wide array of endovascular modalities (stents, multiple tibial artery and pedal angioplasty, retrograde access). Primary endpoint was freedom from amputation at 4 years.

**Results:** A total of 529 BTK interventions were performed. Mean age was 71 ± 10.6 years, 382 (79%) were male. Patients in group 1 were less likely to be taking clopidogrel (66% vs. 83%, P < 0.01) and statins (72 % vs. 87%, P < 0.01). Several therapeutic modalities were used more often in group 2 than in group 1, including pedal angioplasty (24 % vs. 43 %, P = 0.01), tibial and pedal retrograde access (0 vs. 10%, P = 0.01), and tibial stenting (3% vs. 25%, P = 0.01). Revascularization of two or more tibial arteries was performed at a higher rate in group 2 (54% vs. 50%, P = 0.45). Estimated freedom from amputation at 40 months follow-up was higher in group 2 (53% vs. 63%, P = 0.05).

**Conclusions:** An aggressive, multimodality approach in treating BTK arteries results in improved limb salvage.

**KEY WORDS:** balloon angioplasty, critical limb ischemia (CLI), endovascular revascularization, peripheral arterial disease (PAD), tibial angioplasty

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**PATIENTS AND METHODS**

We performed a retrospective study of all patients who underwent BTK interventions at our institution between 2012 and 2019. Treated patients were identified from an electronic, prospectively maintained data base containing all patients who
underwent any angiographic procedure. From that database we identified those who underwent BTK interventions.

The data of each patient was retrieved from an institutional electronic medical records system (Chameleon, Elad Group, Israel). Data collected included patients demographics, clinical indication for intervention, freedom from any major amputation (below or above the knee), and mortality.

Procedural data were obtained from the hospital's Radiology Information and Picture Archiving and Communication System (PACS). Each patient's angiographic images were studied individually. Data collected included access site, number of tibial arteries revascularized, and technique used to treat the target vessel.

**INCLUSION CRITERIA**
Patients diagnosed with CLI were defined as presenting with ischemic rest pain, non-healing ulcers and gangrene (Rutherford category 4, 5, 6). All patients had a tibial artery intervention with or without a more proximal intervention.

**EXCLUSION CRITERIA**
Exclusion criteria included patients with PAD and intermittent claudication (Rutherford category 1-3) and patients who underwent unsuccessful revascularization of at least 1 tibial artery. Primary endpoint included freedom from major amputation at 4 years. Secondary endpoints included all-cause mortality and freedom from reintervention at 4 years.

**PRE-PROCEDURAL EVALUATION**
All patients were evaluated by a senior vascular surgeon, and all underwent non-invasive vascular testing in our vascular lab, which included ankle-brachial indexes (ABIs), segmental pressures, and pulse volume recordings (PVRs). A computer tomography angiogram (CTA) of the abdomen and lower extremities was routinely performed in patients who had a normal renal function in order to plan the intervention. The procedure was performed through the contralateral femoral artery with an up-and-over access or through an antegrade puncture of the ipsilateral superficial femoral artery.

**DECISION ON TYPE OF INTERVENTION**
The majority of the procedures (> 90%) were performed by a single interventional radiologist who exclusively performs endovascular procedures. In the earlier years of the study, our common practice was to perform BTK interventions through a femoral artery. A simple balloon angioplasty of a single tibial artery was the most common intervention performed.

With our increasing skills and experience, starting from 2015 we implemented several changes into our practice. These included attempting to revascularize more than one tibial artery, performing pedal interventions, and selective stenting of the treated tibial artery with designated bare metal stents. In addition, when antegrade recanalization of a tibial artery was unsuccessful, an attempt to perform retrograde recanalization via...
a pedal artery was performed. Atherectomy devices and DCB/DES were rarely used.

**FOLLOW-UP TREATMENT**
Following the index procedure, patients were evaluated at 1, 3, 6 and 12 months and every 6 months thereafter. Evaluation included a physical exam and a full non-invasive vascular evaluation in our vascular lab, including duplex of the treated artery. In addition, patients were followed in a parallel wound clinic at our institution.

Indication for reinterventions included a decrease in in ABIs > 0.15 from the previous exam, increase in velocity within the treated segments, and worsening in the clinical features of the wound.

**STUDY GROUPS**
We performed an initial query of all patients to determine at what point in time we saw a striking change in treatment paradigm of these patients [Figure 1]. Based on the data presented in Figure 1, we determined that from the year 2015, we adopted a more aggressive approach to BTK interventions. This approach included increasing attempts to revascularize more than one tibial artery when possible and performing selective stenting, pedal interventions, and tibial and pedal access. Based on these findings, we performed a comparative study between the two groups: those who underwent interventions from 2012–2014 (group 1) and 2015–2019 (group 2).

**STATISTICAL ANALYSIS**
Continuous and categorical variables were analyzed using Student’s t-test, and chi-square test as appropriate. The Kaplan-Meier curves were used to estimate freedom from amputations and reinterventions as well as mortality. Comparison between survival curves was performed with the Mantel-Cox log-rank test. Multivariate Cox regression models were used to assess factors associated with amputations. Statistical significance was estimated at $P < 0.05$

This study was approved by our institutional review board. Patient consent was waived due to the retrospective nature of the study.

**RESULTS**
During the study period we performed 529 BTK interventions in 495 patients. Mean age of the entire cohort was 71±10.6 years, and 382 (79%) were male. Mean follow-up of the entire cohort was 19 ± 18 months. The demographics of the two groups are presented in Table 1. There were no significant differences between the age, gender, and co-morbidities in the two groups. Patients in group 1 were less likely to be taking clopidogrel (66% vs. 83%, $P < 0.01$) and statins (72% vs. 87%, $P < 0.01$). The percentage of patients treated for rest pain and gangrene was equal in both groups; however, there was a higher percentage of patients treated for non-healing wounds in group 2 (56% vs. 64%, $P = 0.09$). The mean ABIs prior and after interventions were similar between the 2 groups.

**INTERVENTIONS**
The distribution of the procedures performed is presented in Table 2.
Several interventions were used at a greater capacity in group 2 compared to group 1. These included pedal interventions (24% vs. 43%, \( P < 0.01 \)), tibial and pedal retrograde access (0% vs. 10%, \( P < 0.01 \)), and pedal stenting (3% vs. 25%, \( P < 0.01 \)). Revascularization of more than one tibial artery was performed at a higher rate in group 2 (54% vs. 50%); however, this difference did not reach statistical significance.

After a follow-up of 40 months, estimated freedom from amputations was higher in group 2 compared to group 1. Based on Kaplan–Meyer estimation, freedom from amputation in group 1 and group 2 was 53% vs. 63% (\( P = 0.05 \)), respectively [Figure 2].

No significant difference was seen in overall survival between group 1 and group 2 (76% and 79%, respectively, \( P = 0.5 \)), and freedom from reintervention was equal between group 1 and group 2 (70% and 65%, respectively, \( P = 0.15 \)).

Using a Cox regression model to determine factors associated with improved rates of amputation, only the use of clopidogrel, tibial and pedal access, and pedal angioplasty were associated with improved limb salvage.

<table>
<thead>
<tr>
<th>Table 2. Procedural data</th>
<th>2012–2014</th>
<th>2015–2019</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 tibial treated</td>
<td>55 (50%)</td>
<td>227 (54%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Pedal angioplasty</td>
<td>27 (24%)</td>
<td>179 (43%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stent</td>
<td>4 (3%)</td>
<td>103 (25%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Retrograde access</td>
<td>0 (0%)</td>
<td>43 (10%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Reinterventions</td>
<td>21 (19%)</td>
<td>78 (19%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

The utilization of endovascular techniques for the treatment of CLI is gradually increasing. These procedures are particularly attractive compared to bypass surgery as they are less invasive and are associated with less periprocedural morbidity and mortality, while resulting in similar limb salvage rates [9,10]. The number of BTK interventions, and with them the utilization of different techniques, is also increasing. Devices such as bare metal stents, atherectomy catheters, DCBs and DESs, and pedal artery angioplasty have all been reported as modalities for managing BTK arterial disease. In addition, recanalization of tibial arteries from a retrograde approach through the dorsalis pedis artery or posterior tibial artery, and revascularization of several tibial arteries simultaneously are becoming increasingly common [11]. None of these modalities have been shown to be conclusively superior to others in BTK interventions and the literature does not currently support the preferential use of one device over the other.

Percutaneous transluminal angioplasty (PTA) has been considered the most common endovascular treatment modality employed for BTK CLI, and has shown comparable outcomes at 2 years in patients treated with endovascular therapy compared to open surgery [9]. Based on this data, all patients in this series were treated initially with PTA.

Each of the other modalities used for BTK intervention has been evaluated with inconclusive results. To the best of our knowledge, there have not been any multi-center randomized trials that compare bare-metal self-expanding stents with traditional PTA for BTK interventions, and there is no evidence that stenting itself results in superior limb salvage over PTA. DCBs and DESs have shown favorable results in terms of patency [12] but some studies have raised concern regarding association with higher rates of amputation and long-term mortality in patients treated with these modalities [13,14].

In this study we presented two groups of patients. Those who underwent BTK interventions prior to 2015 were treated for the most part with PTA alone, performed through femoral access. From the year 2015, we adopted a more aggressive approach for treating tibial disease with the hope of improving our limb salvage results. Our study confirms that between the two periods we achieved a 10% improvement in limb salvage, increasing from 53% to 63% at 4 years. The difference in limb salvage rate does not seem to be related to the selection of patients as the demographics and co-morbidities, particularly diabetes, and severity of disease was similar in the two groups. There were,
however, several differences between the two groups. Patients in group 2 were more likely to be treated with statins and dual antiplatelet therapy (DAPT). Treatment with statins for patients with PAD has been shown to be associated with a significant reduction in limb loss and mortality [15,16], a fact that partially explains the difference in the results between the two groups. The role of DAPT vs. monotherapy for PAD is debatable; however, there is evidence that administration of aspirin with clopidogrel following interventions results in improved patency of the treated vessel [17].

Retrograde pedal and tibial access is a relatively new concept, and data is lacking regarding its long-term benefit in terms of limb salvage. It does, however, offer additional options for recanalization of tibial vessels, particularly when a femoral approach was unsuccessful. In our study, retrograde pedal or tibial access was more common in group 2, presumably due to increasing familiarity and experience obtained with the procedure.

Pedal angioplasty was more commonly performed in group 2. It is reasonable to assume that this treatment would result in an improvement in limb salvage as patients with tibial disease commonly have involvement of the small vessels of the pedal arch.

As part of our aggressive approach in treating tibial disease, we have attempted to revascularize more than one tibial artery when possible. This approach, although intuitively logical, has not been adopted as common practice and there is no clear evidence that it resulted in superior limb salvage rates compared to single vessel revascularization. In fact, data have shown that multiple synchronous tibial interventions were predictive of limb loss compared to single vessel revascularization [18].

Our results showed that in the group treated from 2015 onward with a more aggressive approach, an improvement in limb salvage was achieved. Despite several procedural differences between the two groups, none of these changes by themselves could account for the difference as a sole entity. Therefore, we assume that the decrease in amputation rates is a combination of factors (medical, procedural) and not a single factor that results in the decrease in amputation rate.

CONCLUSIONS

An aggressive, multimodality approach to treating BTK arteries resulted in improved limb salvage. This approach included changes in medical therapy, technical procedures, and access. Despite these findings, it is unclear which of the changes had the greatest impact on the improved outcome. Further studies are needed to determine the best combination of therapies that will provide the optimal results.

References