



## Patency and Survival in Patients Undergoing Revascularization for Peripheral Arterial Disease

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### ABSTRACT

**Aim:** Peripheral arterial disease is a progressive, and chronic disease caused by atherosclerosis, and characterized by narrowing, or occlusion of the arterial structures of the lower extremities, which can lead to high morbidity and mortality. The aim of this study is to investigate the short and medium-term patency, and survival outcomes of different peripheral arterial revascularization techniques.

**Material and Methods:** Patients undergoing revascularization for lower extremity arterial disease between January 2015 and August 2019 were retrospectively analyzed. Patients were divided into three groups according to the type of revascularization: endovascular, surgical, or hybrid. Major amputation, occlusion, and death were the primary endpoints. Expected primary patency and overall survival rates were estimated using Kaplan-Meier analyses.

**Results:** The study included 285 patients and 338 revascularization procedures. There was no difference in primary outcome between treatment groups ( $p=0.080$ ). Improvement in Rutherford category was observed in 57.1% of patients after revascularization. There was no difference between the groups in terms of change in Rutherford category ( $p=0.230$ ). Expected primary patency rates were significantly lower in patients with chronic limb-threatening ischemia, and in patients with chronic renal failure (respectively;  $p<0.001$ ,  $p=0.02$ ). There was no difference in expected primary patency between the groups ( $p=0.069$ ). Overall survival rates were lower in the presence of chronic limb-threatening ischemia, chronic renal failure and atrial fibrillation (respectively;  $p=0.013$ ,  $p=0.010$ ,  $p<0.001$ ).

**Conclusion:** In our study, chronic limb-threatening ischemia and renal failure were associated with worse survival and lower primary patency rates. There was no difference in survival between revascularization groups. Atrial fibrillation was associated with worse survival.

**Keywords:** Amputation; endovascular; peripheral arterial disease; revascularization.

### Periferik Arter Hastalığı Nedeniyle Revaskülarizasyon İşlemi Yapılan Hastalarda Açıklık ve Sağkalım

#### ÖZ

**Amaç:** Periferik arter hastalığı, aterosklerozun neden olduğu, yüksek morbidite ve mortalite ile sonuçlanabilen alt ekstremitte arteriyel yapılarının daralması veya tıkanması ile karakterize, ilerleyici ve kronik bir hastalıktır. Bu çalışma, farklı periferik arteriyel revaskülarizasyon tekniklerinin, kısa ve orta dönem açıklık ve sağkalım sonuçlarının araştırılmasını amaçlamaktadır.

**Gereç ve Yöntemler:** Çalışmada Ocak 2015 - Ağustos 2019 tarihleri arasında alt ekstremitte arter hastalığı nedeniyle revaskülarizasyon işlemi gerçekleştirilen hastalar retrospektif olarak incelendi. Revaskülarizasyon tipine göre hastalar, endovasküler, cerrahi veya hibrid tedavi olmak üzere üç gruba ayrıldı. Majör amputasyon, oklüzyon ve ölüm primer sonlanım noktaları olarak belirlendi. Beklenen primer açıklık ve genel sağkalım oranları Kaplan-Meier analizleri kullanılarak tahmin edildi.

**Bulgular:** Çalışmaya 285 hastaya uygulanan 338 revaskülarizasyon işlemi dahil edilmiştir. Tedavi grupları arasında primer sonlanım gerçekleşmesi açısından fark saptanmamıştır ( $p=0,080$ ). Olguların %57,1'inde revaskülarizasyon sonrası Rutherford kategorisinde iyileşme gözlenmiştir. Rutherford kategorisindeki değişim açısından gruplar arasında fark bulunmamıştır ( $p=0,230$ ). Kronik ekstremitte tehdit edici iskemi ile başvuran hastalarda ve kronik böbrek yetmezliği olan hastalarda beklenen primer açıklık oranları anlamlı olarak düşük bulunmuştur (sırasıyla;  $p<0,001$ ,  $p=0,020$ ). Gruplar arasında beklenen primer açıklık açısından fark saptanmamıştır. ( $p=0,069$ ). Kronik ekstremitte tehdit edici iskemi, kronik böbrek yetmezliği ve atriyal fibrilasyon varlığında genel sağkalım oranları daha düşük bulunmuştur. (sırasıyla;  $p=0,013$ ,  $p=0,010$  ve  $p<0,001$ ).

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**Sonuç:** Çalışmamızda, kronik ekstremitte tehdit edici iskemi ve böbrek yetmezliği daha kötü sağkalım ve düşük primer açık kalma oranları ile ilişkili bulundu. Revaskülarizasyon grupları arasında sağkalım açısından farklılık saptanmadı Atriyal fibrilasyon ise daha kötü sağkalım beklentisi ile ilişkiliydi.

**Anahtar Kelimeler:** Ampütasyon; endovasküler; periferik arter hastalığı; revaskülarizasyon.

## INTRODUCTION

Peripheral arterial disease (PAD) is a disease of high mortality and morbidity that develops in the setting of atherosclerosis, a systemic disease, and is characterized by narrowing or occlusion of arterial structures. PAD affects more than 200 million people worldwide (1). Similar to coronary artery disease, smoking, dyslipidemia, diabetes mellitus, male sex, and hypertension play a role in its etiology. PAD has a progressive course and a poor prognosis due to underlying chronic diseases. Survival in patients with peripheral arterial disease is worse than for most cancers (2).

PAD affects the lower extremity more than the upper extremity (3). Therefore, a significant proportion of patients present with lower extremity arterial disease (LEAD). While most patients are asymptomatic, symptomatic patients typically complain of intermittent claudication. In advanced stages of the disease, ulcers, or gangrene may occur. The aim of treatment in patients with LEAD is not only to relieve symptoms but also to protect the extremity, and to provide secondary protection against the risk of cardiovascular events (4).

Conservative and medical treatment, surgical treatment, endovascular approaches, and increasingly, hybrid procedures are the treatment options for LEAD. While medical treatment is mainly aimed at reducing cardiovascular risk, endovascular and surgical treatments are mainly aimed at relieving symptoms and preserving limb function. Therefore, it is important to target both cardiovascular risk reduction, and extremity preservation by combining different treatment strategies.

The aim of this study was to determine the expected short and medium-term primary patency and survival outcomes in patients undergoing different revascularization procedures for LEAD.

## MATERIAL AND METHODS

The study was approved by the Non-Interventional Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine with the decision dated 23.01.2020, numbered 17 and protocol number 2020/07. The retrospectively designed study included 285 patients with lower extremity arterial disease who received at least one of the endovascular, surgical or hybrid intervention options between January 01, 2015 and August 01, 2019.

Patients with previous surgical treatment of lower extremity arteries, trauma patients, patients with peripheral arterial aneurysms, and patients with a history of endovascular aneurysm repair were excluded. Revascularization procedures were recorded retrospectively from 31 December 2019 using computerized records. Patients were divided into three groups: surgical, endovascular, and hybrid. Demographic groups ( $p=0.017$ ), with the highest age in the surgical group. There was also a significant difference in the

data, risk factors for peripheral arterial disease, and medications used were obtained from archival records. The Rutherford classification was used in the clinical assessment of the patients' extremities, and the Rutherford categories both before, and after the procedure were recorded by analyzing the patient charts.

The medical status of the patients after the treatment, and the condition of the treated extremity, and the intervention site were recorded by analyzing the outpatient clinic control records. The Rutherford categories of the patients were recorded using data on walking distance, presence of gangrene, or ulcer.

The primary endpoint was imaging-proven occlusion, major amputation, or death at follow-up. The time from revascularization to the primary endpoint was recorded, and an estimate of primary patency was calculated.

Foot amputation, below-the-knee amputation, and above-the-knee amputation were considered to be major amputations. The presence of non-major amputation, wound debridement, and procedural complications were the other parameters recorded. Death information for the 285 patients included in the study was retrieved using the hospital information management system, and the death notification system.

## Treatment Options

In our clinic, the European Society of Cardiology (ESC) guidelines are used to determine the treatment option (surgical/endovascular/hybrid), and the most appropriate treatment protocol is determined by the surgical team on a patient-specific basis. A minimum of 1 mL of intravenous heparin (5000 units) is administered prior to all procedures to achieve target ACT. Prophylactic antibiotics are routinely given to patients prior to surgery. In our clinic, the medical management of patients is organized according to the ESC guidelines, and the patients' concomitant vascular, and systemic diseases. All patients are observed for at least one day, and are routinely evaluated with hand Doppler after the procedure.

## Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (SPSS Inc. Chicago, IL). The conformity of the data to normal distribution was analyzed using the Kolmogorov-Smirnov test. Parametric tests were preferred in the analysis of the data conforming to normal distribution. Descriptive statistics were presented as numbers and percentages. Continuous variables were expressed as mean and standard deviation. T-test, ANOVA and Wilcoxon tests were used in the comparative analysis of continuous variables. Chi-square test was used in the analysis of categorical variables. Expected primary patency and survival analyses were performed using the Kaplan-Meier method. The statistical significance level was accepted as  $p<0.05$ .

## RESULTS

A total of 338 revascularization procedures, and outcomes in 285 patients were analyzed. Of the 338 revascularization procedures that met the inclusion criteria, 123 (36.4%) were surgical, 204 (60.4%) were endovascular, and 11 (3.3%) were hybrid. The mean age was  $65.17\pm 10.89$  years. There was a statistically significant difference in mean age between the treatment presence of Chronic obstructive pulmonary disease (COPD) and smoking between the groups (respectively;

p=0.001, p=0.004). Demographic data and distribution of comorbidities by group are shown in Table 1.

**Table 1.** Distribution of demographic data and comorbidities according to groups

	Surgical (n=123)		Endovascular (n=204)		Hybrid (n=11)		p value
Age (mean ± sd)	68.2 ± 10.37		63.22 ± 10.67		63.91 ± 7.68		0.010
Gender (n, %)							0.520
Male	110	89.4%	184	90.2%	11	100%	
Female	13	10.6%	20	9.8%	0	0%	
Coronary artery disease (n, %)							0.820
(+)	39	31.7%	90	44.22%	4	36.36%	
(-)	84	68.3%	114	55.88%	7	63.64%	
Carotid artery disease (n, %)							0.410
(+)	4	3.25%	12	5.88%	0	0%	
(-)	119	96.75%	192	94.12%	11	100%	
Hypertension (n, %)							0.250
(+)	99	80.49%	163	79.9%	11	100%	
(-)	24	19.51%	41	20.1%	0	0%	
Diabetes mellitus (n, %)							0.540
(+)	66	53.66%	119	58.33%	5	45.45%	
(-)	57	46.34%	85	41.67%	6	54.55%	
Insulin use (n, %)							0.780
(+)	42	34.15%	63	30.88%	3	27.27%	
(-)	81	65.85%	141	69.12%	8	72.73%	
Chronic kidney failure (n, %)							0.700
(+)	13	10.57%	32	15.69%	1	9.09%	
(-)	110	89.43%	172	84.31%	10	90.91%	
COPD (n, %)							0.001
(+)	15	12.2%	11	5.39%	4	36.36%	
(-)	108	87.8%	193	94.61%	7	63.64%	
Hyperlipidemia (n, %)							0.200
(+)	45	36.59%	86	42.16%	2	18.18%	
(-)	78	63.41%	118	57.84%	9	81.82%	
Smoking (n, %)							0.004
(+)	93	75.61%	128	62.75%	11	100%	
(-)	30	24.39%	76	37.25%	0	0%	
Atrial fibrillation (n, %)							0.530
(+)	12	9.76%	13	6.37%	1	9.09%	
(-)	111	90.24%	191	93.63%	10	90.91%	

COPD:Chronic obstructive pulmonary disease

A statistically significant difference between the groups was found only in the use of pentoxifylline (p=0.005). The distribution of medications used before revascularization by group is shown in Table 2.

The mean Rutherford category values before revascularization were significantly higher in the surgical group (surgical: 4±0.95, endovascular: 3.48±0.85, hybrid:

3.67±0.92) (p<0.001) (Table 3). In 57% of the revascularization procedures, there was an improvement in the Rutherford category compared to the pre-procedure period. There was no statistically significant difference in Rutherford category improvement between the groups (p=0.239) (Table 4).

**Table 2.** Distribution of medications used before revascularization according to groups

	Surgical		Endovascular		Hybrid		p value
	(n=123)		(n=204)		(n=11)		
	n	%	n	%	n	%	
Acetylsalicylic acid							0.680
(+)	67	54.47%	117	57.35%	5	45.45%	
(-)	56	45.53%	87	42.65%	6	54.55%	
Clopidogrel							0.070
(+)	25	20.33%	59	28.92%	5	45.45%	
(-)	98	79.67%	145	71.08%	6	54.55%	
Dual antiaggregant							0.500
(+)	11	8.94%	21	10.29%	0	0%	
(-)	112	91.06%	183	89.71%	11	100%	
Cilostazol							0.058
(+)	44	35.77%	48	23.53%	3	72.73%	
(-)	79	64.23%	156	76.47%	8	27.27%	
Pentoxifylline							<u>0.005</u>
(+)	14	11.38%	6	2.94%	0	0%	
(-)	109	88.62%	198	97.06%	11	100%	
Warfarin							0.215
(+)	2	1.63%	10	4.9%	1	90.91%	
(-)	121	98.37%	194	95.1%	10	9.09%	
DOACs							0.830
(+)	4	3.25%	6	2.94%	11	100%	
(-)	119	96.75%	198	97.06%	0	0%	

DOAC: Direct Oral Anticoagulants

**Table 3.** Preoperative and postoperative Rutherford categories of revascularization groups

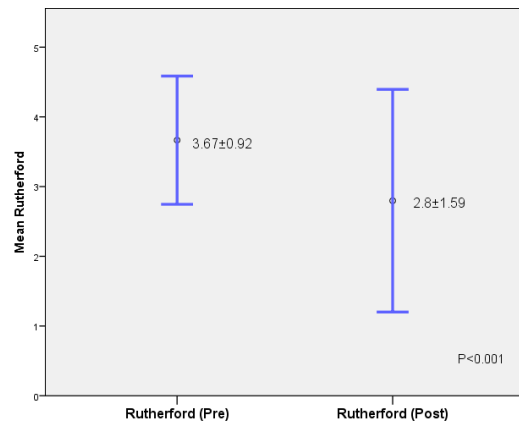
Rutherford Category	Surgical	Endovascular	Hybrid	Total	p value
Pre-procedure (mean±ss)	4±0.95	3.48±0.85	3.36±0.67	3.67±0.92	<u>&lt;0.001</u>
Post-procedure (mean±ss)	2.94±1.73	2.71±1.52	2.64±1.28	2.8±1.59	0.761

**Table 4.** Improvement in rutherford category of revascularization groups

			p* value
	n	%	0.239
Surgical (n=116)	71	61.2	
Endovascular (n=174)	97	55.7	
Hybrid (n=11)	4	36.4	
Total (n=301)	172	57.1	

The mean Rutherford score before revascularization was  $3.67 \pm 0.92$ . When this value was compared with the mean Rutherford score after the procedure ( $2.8 \pm 1.59$ ), the improvement in Rutherford category was significant ( $p < 0.001$ ) (Figure 1). When the pre-revascularization period was evaluated in terms of chronic limb-threatening ischemia (CLTI), there was a statistical difference between the groups ( $p = 0.0001$ ), and the clinic of CLTI was 65.9% in the surgical group.

Of the 310 revascularization procedures for which records of occlusion, death and major amputation were available, 134 (43.2%) had a primary outcome in the post-revascularization process. There was no statistically significant difference between the groups in terms of primary outcome (Table 5).



**Figure 1.** Comparison of mean rutherford score

**Table 5.** Reasons for primary outcome of 310 revascularization procedures with follow-up

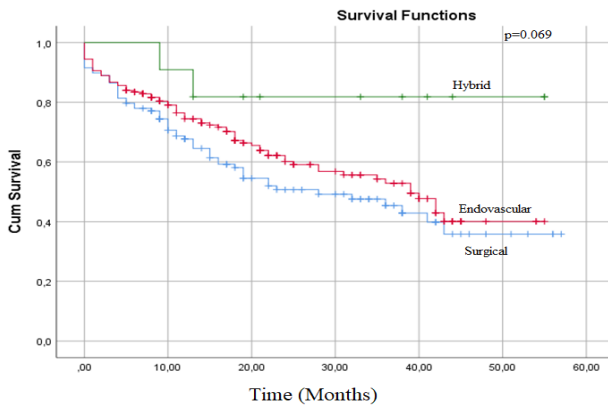
	Surgical (n=118)		Endovascular (n=181)		Hybrid (n=11)		p value
Occlusion (n, %)							0.080
(+)	26	22.03%	35	19.34%	0	0%	
(-)	92	77.97%	146	80.66%	11	100%	
Major amputation (n, %)							0.057
(+)	9	7.63%	5	2.76%	0	0%	
(-)	109	92.37%	176	97.24%	11	100%	
Death (n, %)							0.179
(+)	23	19.49%	34	18.78%	2	18.18%	
(-)	95	80.51%	147	81.22%	9	81.82%	
Primary patency (n, %)							0.086
(+)	60	49.15%	107	59.12%	9	81.82%	
(-)	58	50.85%	74	40.88%	2	18.18%	

**Table 6.** The one-year and three-year primary patency expectations of revascularization groups

	Primary Patency		p value
	1. year	3. year	0.069
Total	72.4%	51.2%	
Hybrid	90.9%	81.8%	
Surgical	67.7%	45.4%	
Endovascular	74.4%	52.8%	

The expected 1-year and 3-year primary patency rates for revascularization were 72.4% and 51.2%, respectively. The one-year and three-year primary patency expectations of revascularization groups were presented in the Table 6.

Although both the one-year and three-year expected primary patency rates were higher in the hybrid group, there was no statistically significant difference between the groups ( $p = 0.069$ ) (Figure 2).



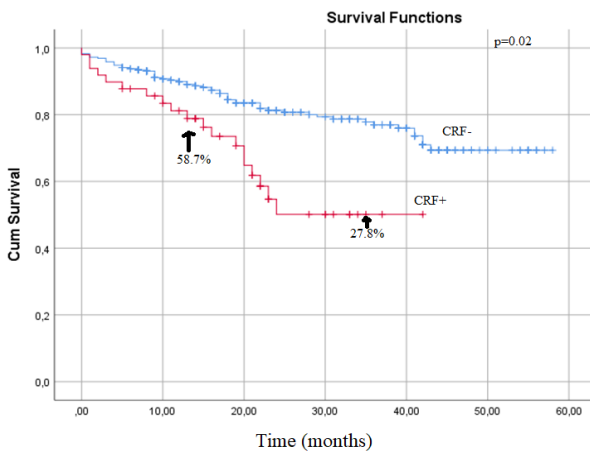
**Figure 2.** Graphical charts of expected primary patency of revascularization groups

The one-year and three-year primary patency expectations of chronic renal failure (CRF) and CLTI groups were presented in the Table 7. The expected primary patency rates in patients with CRF were significantly lower than in patients without CRF ( $p=0.021$ ) (Figure 3). The expected primary patency rates in patients with CLTI were significantly lower than in patients without CLTI ( $p<0.001$ ) (Figure 4).

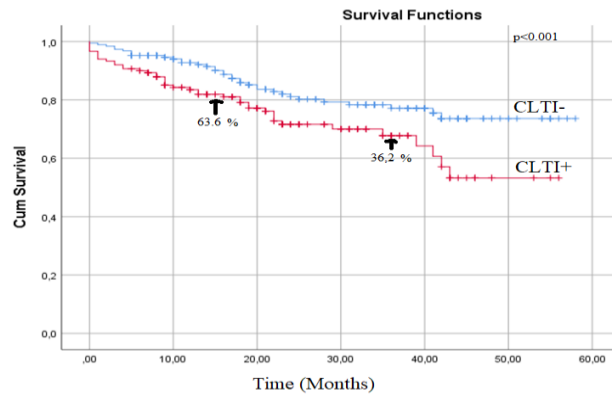
Major amputation was performed in 20 of 338 revascularization procedures (surgical: 12, endovascular: 7, hybrid: 1). There was no statistically significant difference between the revascularization groups in terms of major amputation, and the primary outcome ( $p=0.057$ ) (Table 5).

**Table 7.** The primary patency expectations CRF and CLTI groups.

	Primary Patency	
	1. year	3. year
Chronic renal failure	58.7%	27.8%
Chronic limb-threatening ischemia	63.6%	36.2%



**Figure 3.** The expected primary patency rates in patients with chronic renal failure

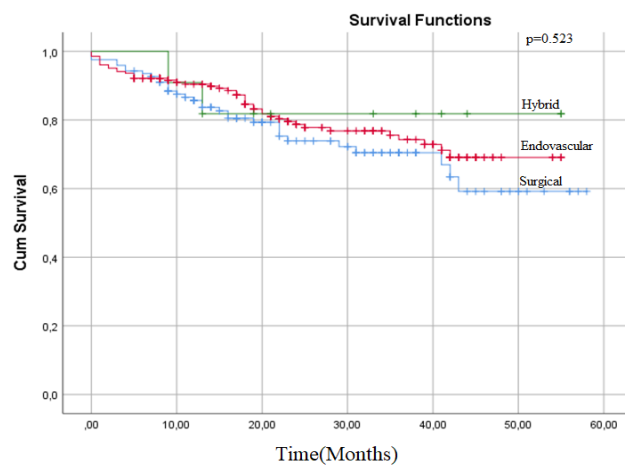


**Figure 4.** The expected primary patency rates in patients with chronic limb-threatening ischemia

Mortality was observed in 63 of the 285 patients in the study. There was no statistical difference in mortality between the revascularization groups ( $p=0.549$ ). The expected 1-year and 3-year rates for all revascularization procedures were 88.6% and 73.1%, respectively. The one-year and three-year survival expectations of revascularization groups were presented in the Table 8. The difference in 1- and 3-year survival between the groups was not statistically significant ( $p=0.523$ ) (Figure 5).

**Table 8.** The one-year and three-year survival expectations of revascularization groups

	Survival		p value
	1. year	3. year	
Total	88.6%	73.1%	0.523
Hybrid	90.9%	81.8%	
Surgical	85.7%	70.5%	
Endovascular	94.1%	74.3%	

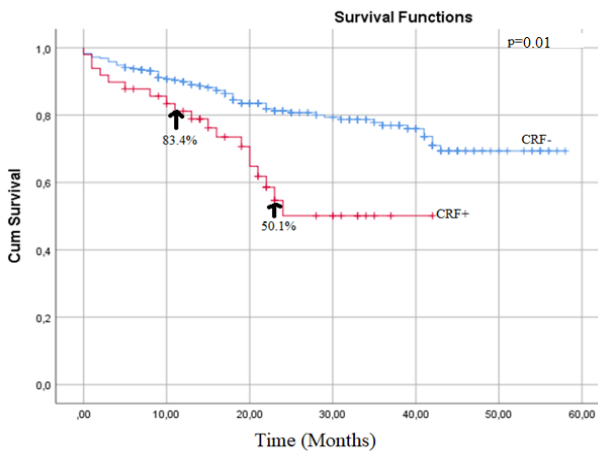


**Figure 5.** Graphical charts of expected survival of revascularization groups

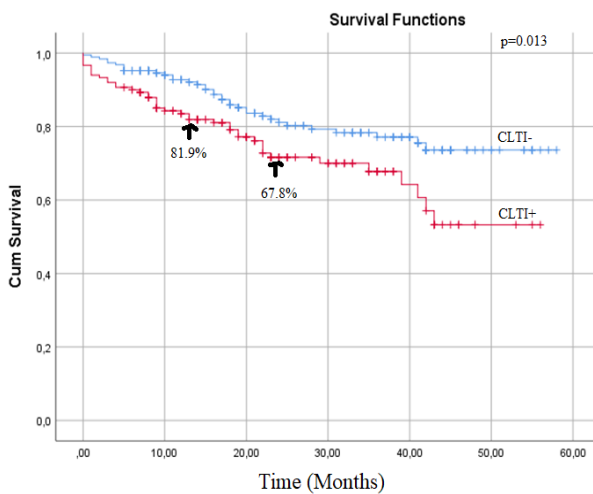
The one-year and three-year primary patency expectations of CRF, CLTI and, AF groups were presented in the Table 9. Expected survival was significantly lower in patients with chronic renal failure compared to patients without chronic renal failure ( $p=0.01$ ) (Figure 6). One-year and three-year survival were significantly lower in patients with pre-procedure CLTI compared to patients without pre-procedure CLTI ( $p=0.013$ ) (Figure 7). Expected survival was significantly lower in patients with a history of atrial fibrillation (AF) compared to patients without AF ( $p<0.001$ ) (Figure 8).

**Table 9.** The Survival Expectations of CRF, CLTI and, AF groups

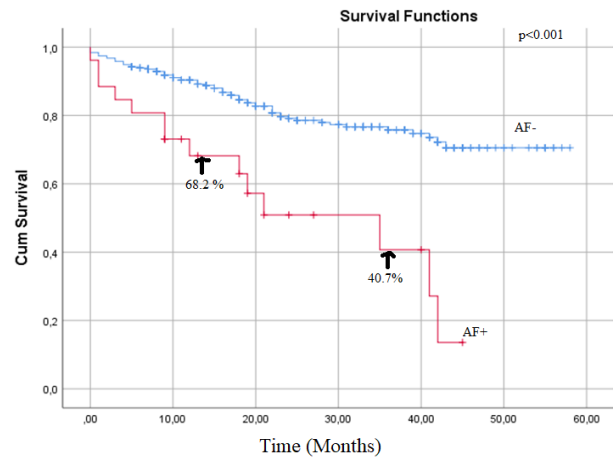
	Survival	
	1. year	3. year
Chronic renal failure	83.4%	50.1%
Chronic limb-threatening ischemia	81.9%	67.8%
Atrial fibrillation	68.2%	40.7%



**Figure 6.** The expected survival in patients with chronic renal failure



**Figure 7.** The expected survival in patients with chronic limb-threatening ischemia



**Figure 8.** The expected survival in patients with atrial fibrillation

**DISCUSSION**

In our study, we analyzed the patency and survival outcomes of 338 procedures of 285 different patients who underwent revascularization procedures for LEAD. Age was significantly higher in the surgical treatment group. The rate of pre-procedural CLTI and the mean Rutherford categories were similarly higher in the surgical group. It is known that CLTI is associated with advanced age (5). This may explain the high mean age and high rate of pentoxifylline use in the surgical group. On the other hand, the fact that CLTI was found to be high in the surgical group indicates that surgical treatment is our predominant revascularization strategy in CLTI despite the fact that we used all three techniques. The surgical treatment option in the treatment of CLTI still maintains its place despite the increase in the success of endovascular treatment (6). Male gender, advanced age, smoking, diabetes mellitus, hyperlipidemia and hypertension are known important risk factors for LEAD (7). It is expected that smoking is more prevalent in the hybrid and surgical groups, which include more complex lesions, compared to the endovascular group.

Clinical improvement was detected in more than half of all revascularization procedures. This rate was similar to the primary patency rate in the study. In the surgical group, there was a difference between the primary patency rate and improvement in the Rutherford category. This suggests that patients may benefit clinically despite radiologic occlusion. It was emphasized in the ESC 2012 guideline that long-term vessel patency is not mandatory when aiming for permanent clinical improvement, especially in the case of CLTI with lesions below the knee (4).

In the study, the expected primary patency rate was found to be significantly lower in patients with a clinic of CLTI. The last stage of peripheral arterial disease, which is a progressive disease, is CLTI and it progresses with high amputation and mortality rates (8). Therefore, it is an expected finding that primary patency is found to be lower in patients with a clinic of CLTI.

Similarly, patients with CRF had poorer expected primary patency results. In a study of 39441 patients who underwent revascularization due to LEAD, the need for

amputation, re-hospitalization within six months and the risk of major cardiovascular events were found to be higher in patients with CRF compared to those without CRF (9). In a study of 6978 patients who underwent revascularization with venous grafts for LEAD, severe CRF was associated with early graft occlusion, postoperative myocardial infarction and a higher rate of reoperation (10). Considering the reported outcomes of lower extremity arterial patients with CRF in the literature, our lower primary patency rates in patients with CRF are expected.

In our study in which there was no significant difference between revascularization groups in terms of survival, the subgroups of CLTI, CRF and AF had poor survival results. In a study evaluating patients who presented with the clinic of CLTI and underwent endovascular treatment, one-year expected survival was reported to be 80% (11). In another study in which 187 patients with CLTI clinic were followed up after endovascular treatment, one-year and three-year expected survival rates were reported as 86% and 79%, respectively (12). When the rates reported in the literature are analyzed, the survival rates found in patients presenting with a clinic of CLTI are similar to the expected survival rates found in our study and are lower than those without a clinic of CLTI.

It is known that the association of CRF and LEAD significantly increases the risk of mortality (13). In a study in which patients who underwent infra-inguinal bypass operation due to the clinic of CLTI were analyzed, one-year and three-year survival rates were reported as 79.6% and 57.9% for patients with CRF, respectively (14). The expected survival rates we found for CRF in our study are also low like the rates reported in the literature.

The other subgroup with poor survival outcomes is Atrial Fibrillation. The low survival rates we found in patients with atrial fibrillation are worse than the survival rates of patients with CRF, which is known to be characterized by high mortality and morbidity. In a recently published study, a high association between AF and major cardiac events and mortality was demonstrated (15). In the study, the likelihood of major cardiac events in patients with newly diagnosed AF was found to be 8.45 times higher than in the healthy population (15). In a subgroup analysis from the registry of the REACH study (16), a significant increase in the risk of cardiovascular death was found in the association of AF and PAH. In our study, the low expected survival rates in patients with AF are consistent with the high mortality expectation in the association of AF and LEAD in the current literature.

## CONCLUSION

The primary patency rates and survival rates found in the study indicate that all revascularization options were successfully applied in our center. Patients with CLTI had poor outcomes in terms of both primary patency and survival. Early recognition and treatment of CLTI, an advanced form of LEAD, will improve outcomes. Similarly, we believe that individualized treatment in the presence of AF and CRF, which are associated with poor outcomes, may contribute to improving outcomes.

**Authors' Contributions:** Idea/Concept: O.F.R., E.A.O.; Design: O.F.R.; Data Collection and/or Processing: O.F.R.; Analysis and/or Interpretation: O.F.R., E.A.O.;

Literature Review: O.F.R.; Writing the Article: O.F.R.; Critical Review: E.A.O.

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