Predictors of mortality and outcomes after retrograde endovascular angioplasty in patients with peripheral artery disease

Pawel Kleczynski¹, Zoltan Ruzsa²,³, Joanna Wojtasik-Bakalarz¹, Andras Nyerges³, Artur Dziewierz¹, Rafał Januszek⁴, Tomasz Rakowski¹, Dariusz Dudek¹, Stanislaw Bartus¹

¹2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
²Cardiology Department, Heart and Vascular Center, Semmelweis University, Budapest, Hungary
³Invasive Cardiology Department, Bács-Kiskun County Hospital, Teaching Hospital of the Szent-Györgyi Albert Medical University, Kecskemét, Hungary
⁴Department of Clinical Rehabilitation, University of Physical Education, Krakow, Poland

Adv Interv Cardiol 2019; 15, 2 (56): 234–239
DOI: https://doi.org/10.5114/aic.2019.81727

A b s t r a c t

Introduction: Endovascular revascularization (ER) techniques in patients with peripheral artery disease (PAD) have been developed and became more accessible in recent years. The ER is a first-line treatment in the majority of patients with symptomatic PAD. However, data on assessment of predictors of long-term outcomes of retrograde ER in patients with PAD are scarce.

Aim: To evaluate predictors of long-term outcomes of retrograde ER in patients with chronic total occlusion in lower limb arteries.

Material and methods: We analyzed data of 834 patients who underwent retrograde ER. Baseline clinical characteristics and procedural data were collected. Patients were followed up for 36 months, and the primary endpoint was all-cause mortality.

Results: All patients were symptomatic and had failed antegrade ER. The procedural success rate was 92%. Cumulative all-cause mortality was 13.4% at 36-month follow-up. In multivariate analysis history of stroke, Rutherford category, chronic limb ischemia, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and previous ER of other lesion were independent predictors of a higher mortality rate after 36 months (hazard ratio (HR) for stroke 2.4, 95% confidence interval (CI): 1.55–3.66; p = 0.0002; HR for age per 10 years 1.37, 95% CI: 1.15–1.64; p = 0.0002; HR for Rutherford category 1.63, 95% CI: 1.35–1.98; p < 0.0001, HR for chronic limb ischemia 0.44, 95% CI: 0.25–0.8, p = 0.007; HR for CKD 1.73, 95% CI: 1.14–2.56, p = 0.01; HR for COPD 2.4, 95% CI: 1.5–3.7, p = 0.0004; HR for previous ER 0.59, 95% CI: 0.35–0.94, p = 0.02).

Conclusions: History of stroke, Rutherford category, chronic limb ischemia, CKD, COPD, and previous ER of other lesion were independently associated with increased risk of all-cause death.

Key words: peripheral artery disease, endovascular revascularization, retrograde, mortality, outcomes.

S u m m a r y

The endovascular revascularization (ER) techniques in patients with peripheral artery disease (PAD) have been developed and became more accessible in recent years. However data on assessment of predictors of long-term outcomes of retrograde ER in patients with PAD are scarce. In the present study, we identified predictors of long-term outcomes including mortality in patients with PAD undergoing retrograde ER. Predictors of the composite endpoint (death, reER and amputation) were diabetes, history of stroke and Rutherford grade. Moreover, Rutherford grade, the presence of coronary artery disease and history of stroke were independent predictors of composite end point (death, reER, amputation, myocardial infarction, lower extremity bypass and thrombendarterectomy).

Corresponding author:
Stanislaw Bartus MD, PhD, 2nd Department of Cardiology, Jagiellonian University Medical College, 17 Mickiewicza Kopernika St, 31-501 Krakow, Poland, phone: +48 12 424 7181, e-mail: stanislaw.bartus@uj.edu.pl
Received: 22.10.2018, accepted: 6.01.2019.
Introduction
The prevalence of peripheral artery disease (PAD) increases in the aging population and therefore represents a growing problem with diagnostics and management of patients affected by cardiac diseases sharing the same etiology and risk factors [1]. Endovascular revascularization (ER) techniques in patients with PAD have been developed and became more accessible in recent years. The ER is a first-line treatment in the majority of patients with symptomatic PAD. In patients with chronic total occlusion (CTO) of the lower limb arteries and failure of antegrade ER, the retrograde access is a treatment option before referral for vascular surgery or conservative treatment. Several studies estimating long-term results of antegrade ER have been published so far, including those comparing antegrade and retrograde access sites [2, 3]. However, data on assessment of predictors of long-term outcomes of retrograde ER in patients with PAD are scarce.

Aim
Thus, we aimed to evaluate predictors of long-term outcomes of retrograde ER in patients with CTOs in lower limb arteries.

Material and methods
Patients
This study was a prospective, observational registry of 939 consecutive patients in two experienced academic centers, who underwent retrograde recanalization of CTO localized in the iliac artery, superficial femoral artery (SFA), popliteal artery (PA) or below the knee arteries after at least one unsuccessful antegrade attempt. Finally, data of 834 patients with available follow-up were analyzed. Baseline clinical characteristics and procedural data were collected.

Study endpoints
Patients were followed up for 36 months, and the primary endpoint was all-cause mortality. The secondary composite endpoint consisted of death, re-ER, and amputation. The tertiary composite endpoint consisted of death, re-ER, amputation, stroke, myocardial infarction, arterial bypass, and thromboendarterectomy. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki with later amendments and was approved by the institutional ethical board. All patients provided informed consent.

Procedural characteristics
Antegrade failure was defined as an inability to wire the distal part of the vessel after the occlusion via the access site, located in the contralateral artery or proximal to the CTO lesion. According to the local protocol, patients were screened for concomitant diseases, risk factors, and medications. In all patients, the ankle-brachial index (ABI) was determined and severity of PAD was assessed according to the Rutherford, Fontaine and Wagner scales before the procedure. The decision on the use of retrograde recanalization and access site was based on previous angiography. Retrograde recanalization was performed under local anesthesia and required two access sites: antegrade and retrograde. Both proximal and distal punctures were done under the guidance of Doppler ultrasound and/or fluoroscopy. After crossing the occlusion with a wire through the retrograde approach, predilatation with a balloon catheter was done. Stent implantation was left to the operator's decision. After the procedure, the distal sheet was removed immediately and the proximal sheet was maintained up to 4 h. In some cases, due to dissection, the balloon inflations were performed from both ante- and retrograde access (kissing balloons technique) to tear the dissection and facilitate the capture of the wire with a diagnostic catheter.

Pharmacotherapy
As periprocedural treatment all patients received dual antiplatelet therapy: aspirin 75 mg permanently and clopidogrel 75 mg for 3 months, high dose of statin and according to the local protocol low-molecular-weight heparin for 4 weeks. Additional treatment was accordant to individual risk factors and comorbidities, including beta blockers, statins, and angiotensin-converting-enzyme inhibitors.

Statistical analysis
Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean ± standard deviation or median and interquartile range. Normality was assessed with the Shapiro-Wilk test. Equality of variances was assessed using Levene's test. Multivariable Cox regression analysis was performed to find significant predictors of mortality and outcomes and presented as hazard ratios (HR) with 95% confidence intervals (CI). All baseline characteristics and procedural data were tested. Forward selection with a probability value for covariates to enter the model was set at the 0.05 level. All tests were two-tailed, and a p-value of < 0.05 was considered statistically significant. All statistical analyses were performed with JMP, Version 13.1.0 (SAS Institute INC., Cary, NC, USA).

Results
A total of 939 consecutive patients with PAD requiring revascularization were enrolled between 2009 and 2015 and then followed up. Of them, 834 patients were available for detailed analysis. All patients were symptomatic and had failed antegrade ER. The median age was 68 (60–76) years, and the majority of patients were male.
Baseline clinical characteristics are presented in Table I. The procedural success rate was 92%. Angiographic and procedural data are shown in Table II. Study endpoints are presented in Figure 1. Cumulative all-cause

**Table I.** Baseline clinical characteristics (n = 834)

| Variable                                                                 | All          |
|-------------------------------------------------------------------------|--------------|
| Age, median (IQR) [years]                                               | 68.0 (60.0–76.0) |
| Men                                                                     | 522 (62.6%)  |
| Body mass index, median (IQR) [kg/m²]                                   | 27.0 (23.71–30.1) |
| Arterial hypertension                                                  | 735 (88.2%)  |
| Diabetes mellitus                                                       | 342 (41.1%)  |
| Chronic kidney disease                                                  | 135 (16.2%)  |
| Chronic obstructive pulmonary disease                                   | 98 (11.8%)   |
| Coronary artery disease                                                 | 339 (40.7%)  |
| Hyperlipidemia                                                          | 708 (84.9%)  |
| History of stroke/transient ischemic attack                             | 74 (8.9%)    |
| Smoking                                                                 | 463 (55.6%)  |
| Previous endovascular revascularization of other lesion                | 183 (22.0%)  |
| Estimated glomerular filtration rate, median (IQR) [ml/min/1.73 m²]    | 50.0 (40.0–60.0) |
| Rutherford classification:                                             |              |
| 0                                                                      | 0            |
| 1                                                                      | 23 (2.8%)    |
| 2                                                                      | 131 (15.7%)  |
| 3                                                                      | 112 (13.5%)  |
| 4                                                                      | 157 (18.9%)  |
| 5                                                                      | 134 (16.1%)  |
| 6                                                                      | 276 (33.1%)  |
| Fontaine scale:                                                        |              |
| 1                                                                      | 1 (0.1%)     |
| 2a                                                                     | 36 (4.4%)    |
| 2b                                                                     | 256 (30.7%)  |
| 3                                                                      | 149 (17.9%)  |
| 4                                                                      | 389 (46.7%)  |
| 5                                                                      | 1 (0.1%)     |
| Acute limb ischemia                                                     | 42 (5%)      |
| Chronic limb ischemia                                                  | 468 (56.1%)  |
| Intermittent claudication < 50 m                                       | 322 (39%)    |
| Ankle brachial index, median (IQR)                                      | 0.6 (0.3–0.7) |

**Table II.** Angiographic and procedural data (n = 834)

| Variable                                                                 | All          |
|-------------------------------------------------------------------------|--------------|
| TASC II                                                                |              |
| A                                                                      | 157 (18.9%)  |
| B                                                                      | 167 (20.1%)  |
| C                                                                      | 125 (15%)    |
| D                                                                      | 383 (46%)    |
| Angiography first access site:                                          |              |
| Brachial                                                                | 30 (3.6%)    |
| Femoral                                                                | 599 (71.8%)  |
| Radial                                                                 | 204 (24.5%)  |
| Iliac artery – chronic total occlusion                                  | 105 (12.6%)  |
| Deep femoral artery – significant lesion                                | 42 (5%)      |
| Common femoral artery:                                                 |              |
| Chronic total occlusion                                                 | 33 (4%)      |
| Calcification:                                                          |              |
| Slight                                                                  | 316 (37.9%)  |
| Severe                                                                  | 131 (15.7%)  |
| Lesion length [mm]                                                      | 14.1 ±15.8   |
| Superficial femoral artery:                                            |              |
| Tortuosity                                                              |              |
| Severe                                                                  | 22 (2.7%)    |
| Slight                                                                  | 285 (34.2%)  |
| Chronic total occlusion                                                 | 415 (49.8%)  |
| Calcification:                                                          |              |
| Extreme                                                                | 26 (3.1%)    |
| Severe                                                                  | 363 (43.6%)  |
| Slight                                                                  | 248 (35.7%)  |
| Lesion length [mm]                                                      | 127.9 ±110.3 |
| Popliteal artery:                                                       |              |
| Lesion length [mm]                                                      | 52.3 ±48.7   |
| Chronic total occlusion                                                 | 99 (11.9%)   |
| Tibio-fibular trunk:                                                    |              |
| Significant lesion                                                     | 206 (24.7%)  |
| Chronic total occlusion                                                 | 82 (9.8%)    |
| Tibialis anterior artery:                                              |              |
| Significant lesion                                                     | 387 (46.5%)  |
| Chronic total occlusion                                                 | 30 (3.6%)    |
| Peroneal artery – significant lesion                                    | 305 (36.6%)  |
| Tibialis posterior artery:                                             |              |
| Significant lesion                                                     | 391 (47.5%)  |
| Chronic total occlusion                                                 | 70 (8.4%)    |
| Fluoroscopy time [s]                                                    | 825.1 ±697.4 |
| Contrast volume [ml]                                                    | 120.9 ±84.5  |
| Time from procedure to discharge [days]                                 | 3.3 ±2.1     |
| Hospitalization time [days]                                            | 5.5 ±2.2     |
artery. SFA-CTO prevalence reaches around 50% in sy-
mp-
bleeding complications and damage of the punctured
fluoroscopy or ultrasound guidance to avoid additional
tery, and pedal artery. The procedure is performed under
be chosen: the distal segment of the SFA, PA, tibial ar-
for retrograde puncture, there are a few arteries that can
the proximal cap, and with diffuse calcification [9–11].
CTOs are harder, more fibrous within
of the plaque as CTOs are harder, more fibrous within
20% in CTO lesions in lower limb arteries [8]. Difficulties
failure rate of antegrade recanalization can reach up to
patients treated with subintimal recanalization depend-
tional option of choice after antegrade attempt failure,
rer-grade technique. Retrograde technique is an interven-
der in PAD patients have improved significantly since initial
surgical treatment. Importantly, the results of percutaneous
CEA history of stroke, Rutherford category and in-
history of stroke and Rutherford grade. Moreover, Ruth-
erford grade, the presence of coronary artery disease
history of stroke were independent predictors of the ter-
deprecated in high-risk patients who are not suitable can-
dates for surgical treatment. Importantly, the results of
percutaneous angioplasty from the retrograde approach in
PAD patients have improved significantly since initial
reports [2, 4–7]. Montero-Baker et al. reported that the
failure rate of antegrade recanalization can reach up to
20% in CTO lesions in lower limb arteries [8]. Difficulties
in crossing the occlusion are related to the morphology
of the plaque as CTOs are harder, more fibrous within
the proximal cap, and with diffuse calcification [9–11].
For retrograde puncture, there are a few arteries that can
be chosen: the distal segment of the SFA, PA, tibial ar-
tery, and pedal artery. The procedure is performed under
fluoroscopy or ultrasound guidance to avoid additional
bleeding complications and damage of the punctured
artery. SFA-CTO prevalence reaches around 50% in symp-

Discussion
In the present study, we identified predictors of long-
term outcomes including mortality in patients with PAD
undergoing retrograde ER. Predictors of the composite
endpoint (death, reER and amputation) were diabetes
HR = 1.3, 95% CI: 1.07–1.55, p < 0.0075), Ruther-
ford category (HR = 1.27, 95% CI: 1.18–1.37, p < 0.0001)
and history of stroke (HR = 1.41, 95% CI: 1.05–1.86,
p = 0.02), all age-adjusted. Rutherford grade (HR = 1.21,
95% CI: 1.13–1.3, p < 0.0001), coronary artery disease
HR = 1.4, 95% CI: 1.16–1.67, p = 0.0003) and history of
stroke (HR = 1.38, 95% CI: 1.03–1.81, p = 0.02) were in-
dependent predictors of the tertiary composite end point
(death, reER, amputation, myocardial infarction, lower
extremity bypass and thromboendarterectomy). Figure 2
presents all-cause mortality during 36 months of follow-up.

tomatic patients with PAD [12]. Nevertheless, there are
still scarce data on large populations that estimate the
predictors of long-term treatment results in this group of
patients, especially those treated from the retro-
grade approach. In the current study, the mortality after
36 months of follow-up was 13.4%, which was relatively
low compared to previous publications, where mortality
in the overall group of patients with PAD treated with end-
ovascular interventions reached 6–50% with a similar
mean age of participants to the current study at baseline
and depended on the length of follow-up [13–15]. How-
ever, compared to previous studies, the rate of CKD was
lower, impacting the mortality. Additionally, the patients
were strictly oriented towards drug compliance and ad-
mistration of the drugs was monitored during every
follow-up visit. In another study assessing effectiveness
and outcomes after pedal vascular access in critical limb
ischemia mortality was 23% during the mean follow-up
of 17 months [16]. A systematic review with more than
1500 patients reported that the 1-year survival rate in
patients treated with subintimal recanalization depend-
ed on the location of the culprit artery or symptoms be-
fore angioplasty and ranged between 65% and 78% in
patients with critical limb ischemia and crural lesions,
and between 86% and 100% in those with mixed dis-

Figure 1. Study endpoints and days-to-event
*Lower extremity bypass

Figure 2. Kaplan-Meier survival curve for patients
undergoing retrograde endovascular revascular-
ization at 3-year follow-up
ease and femoral lesions [17]. The study published by Kim et al. reported 1-year mortality following subintimal angioplasty in patients with more advanced and disseminated atherosclerosis (TASC C and D) at 5.5% [18]. In contrast, in some studies performed in patients with critical or subcritical lower limb ischemia the mortality rate after 5 years of follow-up reached almost 50% [15]. History of stroke and previous ER of another lesion were also associated with increased mortality risk. However, there are no data available so far regarding this problem. Rutherford category represents the grade of clinical symptoms which are directly affected by the extent of lower limb artery atherosclerosis. The culprit lesion length, clinical state before angioplasty, and the degree of dissemination of atherosclerotic lesions (TASC stage) are among confirmed predictors of clinical outcomes in patients with PAD treated with endovascular interventions [15]. The study published by Murata et al. including 1088 patients, comprising 1306 limbs with critical ischemia treated with endovascular therapy, confirmed the previously discovered relationship in patients with CAD treated with percutaneous intervention [19]. Also, one of several factors for which there is a strong relationship with endovascular outcomes in the follow-up period is CKD. The CKD was found to be a predictor of increased mortality after 4 years of follow-up in patients with PAD treated with ER, and it was strictly correlated with the stage of CKD. The projected 4-year mortality in patients with known CKD was 27%, while in patients with other stages it was 46% (stage 2), 52% (stage 3), 72% (stage 4) and 78% (stage 5) [20]. In a study by Willenberg et al. the presence of CKD was an independent predictor of higher mortality in patients with chronic limb ischemia undergoing ER [21]. Among the most influential mechanisms responsible for worse outcomes after ER of lower limb arteries we can distinguish prothrombotic state related to COPD, elevated proinflammatory markers and markers of oxidative stress [22, 23]. The relationship between COPD and future cardiovascular adverse events in patients with CAD has repeatedly been demonstrated so far [24, 25]. Diabetes mellitus is a well-established risk factor for poor outcomes in cardiovascular diseases. In a study by Neupane et al. with 714 patients, diabetes mellitus was independently associated with higher mortality, major amputations and repeat revascularization at 5 years [26].

**Study limitations**

Only patients with available long-term follow-up were enrolled in the current analysis. Due to drop-offs, the baseline risk characteristics and mortality rates might be underestimated.

**Conclusions**

History of stroke, Rutherford category, chronic limb ischemia, CKD, COPD, and previous ER of other lesions were independently associated with increased risk of long-term all-cause death.

**Conflict of interest**

The authors declare no conflict of interest.

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