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Research Article

Endovascular Therapy for Arteriogenic Erectile Dysfunction with a Novel Sirolimus-Eluting Stent

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Abstract

Aim: To assess the safety and clinical success rate of endovascular revascularization of erection-related arteries with the angiolite BTK® stent in patients with arteriogenic erectile dysfunction.

Methods: From January 2017 to June 2019, a total of 100 consecutive men (61.8 ± 10 years) with atherosclerotic lesions in erection-related arteries agreed to participate and were included into a single-centre all-comers registry. Endovascular therapy with angiolite BTK® drug-eluting stents was performed on a total of 211 lesions. Patients received a baseline IIEF-15 questionnaire at first presentation and 3 and 12 months after stenting. An improvement by 4 points in the erectile function domain consisting of 6 questions (IIEF-6) was defined as minimal clinically important difference (MCID) and was thus considered clinically relevant.

A total of 24 patients with 52 stented arterial lesions underwent angiographic follow-up of the initially treated arterial side during secondary revascularization of the contralateral side (angiographic sub-study).

Outcome/Results: No major adverse events occurred during endovascular revascularization or within 30 days thereafter. Technical success was achieved in all lesions and procedural success in all patients. At 1 year, 55 of 97 patients (56.7%) improved by at least 4 points in IIEF-6 score and thus achieved a clinically relevant improvement of erectile function.

In the angiographic sub-study, arterial patency and binary restenosis were observed in 46/52 (88.5%) and in 8/52 (15.4%), respectively, after a mean follow-up of 9.6 ± 5.8 months.

Clinical Implications: In patients with arteriogenic erectile dysfunction, endovascular therapy with a novel thin-strut sirolimus eluting stent is a safe and feasible treatment option and associated with lower restenosis rates when compared with earlier-generation drug eluting stents in earlier trials.

Strengths & Limitations: This real-world arterial revascularization registry included patients with a multitude of risk factors for ED thereby representing the heterogeneity in patients in the clinical practice. Furthermore, focus was laid analysing outcomes of patients with arteriogenic ED utilizing a single endovascular device. Further studies are warranted to better define subgroups of patients with impaired clinical outcomes.

Conclusion: Within the present all-comers registry, endovascular therapy of erectile dysfunction with the angiolite BTK® stent was shown to be a safe and feasible treatment option resulting in clinical improvement rates comparable to that of earlier clinical trials. Restenosis rate with the angiolite BTK stent was lower when compared to earlier-generation stents across studies.

INTRODUCTION

In the year 1995, 150 million men worldwide were estimated to suffer from erectile dysfunction (ED). By the year 2025 this number is estimated to have risen to 322 million men [1].

ED is a common disease, with prevalences ranging from 2% in men in their twenties up to over 80% in men aged over 75 years [2]. Recognized risk factors for ED include age, depression, diabetes mellitus, dyslipidaemia, arterial hypertension, obesity, sedentary lifestyle and active as well as passively smoking [2-7]. Thus, risk factors are similar to those of coronary heart disease and peripheral arterial disease.

Among the different pathogenic mechanisms of ED, vascular pathologies represent the most common cause and account for 60-80% of erectile dysfunction [8].

Two of the main clinical difficulties ED patients may experience are the reduced ability to achieve an erection sufficient for penetration and the reduced ability to maintain an erection during intercourse [9]. Treatment options for ED range from lifestyle changes (i.e. dietary measures and risk factor modification as well as physical exercise), over oral medication with phosphodiesterase-5-inhibitors (PDE-5-I) or intracavernosal application prostaglandins to penile implantation surgery [3,10-12].

However, 30-35% of patients on PDE-5-I do not respond to conservative treatment or report insufficient erections for intercourse and may have drug related side effects [13]. With the development and down-sizing of endovascular devices suited for the complex anatomy of the inner pelvic arteries, endovascular therapy is proposed as an alternative strategy in patients presenting with arteriogenic ED and failure of PDE-5-I therapy or contraindications for PDE-5-I [9,14-18].

To date, no specific guidance based on clinical studies exist, as to whether stenting is superior to balloon angioplasty in these oftentimes small-calibre arteries. Balloon angioplasty of the pudendal artery was shown to restore blood flow and substantially improve the symptoms of ED during short-term follow-up [19].

In our experience, the use of plain balloon angioplasty alone or an approach utilizing drug-coated balloons is not ideal, since the pudendo-penile arteries are prone to elastic recoil [16]. This process had also been observed in the coronary arteries and has led to a direct drug eluting stenting approach for most de-novo coronary artery obstructions nowadays.

Purpose of the present study was to assess the clinical and angiographic utility of drug eluting stenting of erection-related arteries in an all-comers registry.

METHODS

The objective of the present investigation is to assess safety and rates of clinical improvement in 100 consecutive ED patients from the swissPOWER registry following endovascular therapy of erection-related arteries with the angiolite BTK® stent. The swissPOWER registry is a prospective, single-centre, all-comers registry, based on data from patients presenting with ED of atherosclerotic aetiology with unsatisfactory response to or severe side-effects from medical treatment [9].

Patients

Patients with ED were referred to our centre by general practitioners and urologists or by self-administration. Endovascular treatment was proposed to patients with arterial aetiology, which was determined through color-coded duplex ultrasound and confirmed by computed tomography angiography and if medical therapy, such as PDE-5-I was not satisfactory, contraindicated or was accompanied by adverse drug events (ADE). Response to medical therapy was categorized into no response, medium response and satisfactory response. Medium response was defined as improvement in erection after intake of PDE-5-I which was not entirely sufficient for intercourse. Satisfactory response was defined as improvement in erection sufficient for intercourse.

Upon providing informed consent for participation in the registry they underwent endovascular revascularization utilizing an angiolite BTK® stent.

A thorough patient history workup was conducted, reviewing risk factors for ED and medical history. Prior to or in parallel to vascular workup, all patients had been investigated by board-certified urologists.

No patients were excluded from the present registry. Withdrawal of study participation was possible at any point of this study.

Vascular Imaging

Duplex Ultrasound of the corpora cavernosa was performed after intracavernosal injection of 10 µg Alprostadil. When maximum possible erection was achieved, peak systolic velocity and diastolic velocity were measured. PSV-values below 30cm/sec marked a reduced arterial flow, whereas EDV-values above 15 cm/sec suggested a venous leak of the pudendal veins [20].

Computed tomography angiography

Following duplex ultrasound, patients with reduced arterial flow underwent contrast-enhanced CTA-imaging by radiologists with a high level of experience in iliac artery imaging [21]. The imaging consisted of two spiral sequences with a 120ml injection of contrast medium at a rate of 4ml/s. The first sequence starts at the aortic bifurcation and end at the lower margin of the scrotum, wherefrom the second sequence continues up to the jugulum. This imaging was conducted in one radiology centre with two radiologists independently reviewing the cases. A glomerular filtration rate lower than 40ml/min and contrast medium allergy were contra-indications for CTA.

Description of Stent

The angiolite BTK ® Sirolimus-eluting Stent (iVascular S. L. U., Barcelona, Spain, CE Mark reference number: 2014 12 0833 ED) is made from a cobalt-chromium alloy backbone (L605), with a strut thickness of 75-80 µm. The stent is manufactured from a metal tube that is laser cut and subjected to various treatments providing a smooth, glossy surface finish. The stent structure has been modified to consist of 8 crowns linked by 3 rows of non-concatenated connectors in a non-continuous sinusoid fashion (Figure 1).

This feature confers a slightly higher metal-to-artery ratio, enabling improved drug distribution to the vessel wall. The metallic backbone is coated with a biostable, durable fluoroacrylate-based polymer. The stent is coated with sirolimus at a dose of 1.4 µg/mm^2, with >80% of the drug being released following 60 days post-implantation.

A preclinical trial was conducted in which the efficacy and safety of the angiolite drug eluting stent (DES) was demonstrated in comparison with drug eluting stents on the market [22].

Also, two coronary clinical trials have been conducted, the ANCHOR study, a first-in-man evaluation of the mechanical and clinical performance of the angiolite DES. The latter is a multi-center prospective observational trial, which includes 103 patients that are evaluated randomized at 3 or 6 months

Figure 1 Angiolite BTK ® Sirolimus-eluting Stent (iVascular S.L.U.,Barcelona, Spain). The stent is made from a cobalt-chromium alloy backbone, with a strut thickness of 75-80 µm and consists of 8 crowns linked by 3 rows of non-concatenated connectors in a non-continuous sinusoid fashion.

for QCA, OCT and clinical behavior and the ANGIOLITE TRIAL, a randomized clinical trial with 223 patients to compare the efficacy of angiolite stent versus Xience stent in patients with indication for percutaneous coronary intervention at 6, 12 and 24 months [23,24].

Endovascular Procedures

Endovascular therapy follows the intervention scheme of our first study [9]. After local anaesthesia, arterial access to the common femoral artery was obtained. Endovascular therapy was started by injecting Heparin (5000 IU). Diagnostic intra-arterial angiography was performed to confirm arterial obstructions.

Lesions were crossed using a 0.014-inch guidewire. Subsequently, lesions were primarily stented with angiolite BTK® drug eluting stent. Stents were chosen to not exceed the arterial diameter by more than 10%. In case arterial diameters were 1.75mm or smaller in diameter, lesions were treated with plain balloon angioplasty.

At the operator's discretion, lesions of the contralateral site were done in the same session or at a second stage. All interventions were done by the same operator under the same circumstances [9,17]. Within the next three to five days, patients were invited to a postinterventional examination.

Medical Therapy

During the endovascular intervention patients received a bolus of 5'000 IU of heparin with the placement of the introducer sheath followed by an oral loading dose of 300mg clopidogrel immediately after stent placement.

After workup of diagnostic and therapeutic interventions, patients showing atherosclerotic ED received acetylsalicylic acid (100 mg/d) as well as a statin, if indicated.

After stent implantation, patients received a 300mg loading of clopidogrel and 75 mg once daily of this substance thereafter. Dual antiplatelet therapy was recommended for 6 months, with a continuation of aspirin 100mg daily thereafter. Moreover, patients were recommended to follow a medication with tadalafil (5 mg/d) for 3 weeks subsequent to endovascular revascularization [9].

Outcome Assessment and study endpoints

To quantify the erectile function before and after endovascular therapy, all patients were assessed with the International Index of Erectile Function-15 (IIEF-15) Questionnaire, consisting of 15 standardized questions divided into the topics erectile function, orgasmic function, sexual desire and sexual satisfaction [25-28].

Patients received a baseline questionnaire at first presentation and follow-up-questionnaires with the same questions 3 months and 12 months after intervention. An improvement by 4 points in the erectile function domain consisting of 6 questions (IIEF-6) was defined as minimal clinically important difference (MCID) [28]. An improvement by ≥ 4 points was therefore considered clinically relevant. Additionally, questions 1-5 and 15 were analysed separately.

The primary safety endpoint was absence of device- or procedure-related death or major adverse events (MAE), such as gangrene or necrosis in the revascularisation area of the internal iliac artery, secondary lesion revascularisation or subsequent penile, perineal or anal surgery [9]. MAEs were defined according to commonly applied study guidelines [29]. The definition of bleedings were in line with the TIMI definitions [30].

The primary feasibility endpoint was a minimally clinically relevant improvement of ≥4 in the IIEF-6 score at 12 months. The feasibility of the treatment was demonstrated when at least 50% of the patients showed an MCRI [9].

In addition, responses to IIEF question 3 on ability to achieve penetration, and on IIEF question 4 on ability to maintain erection sufficient for sexual intercourse, considered as key components of erectile function, were separately evaluated. Finally, the total IIEF-15 at 3 months and 12 months was compared to that prior to endovascular therapy.

Angiographic patency was assessed in a sub study in patients undergoing staged endovascular revascularization of erection-related arteries. Arterial patency was defined as ≥ TIMI 2 flow [30]

Binary restenosis was defined as ≥ 50% diameter stenosis on follow-up angiography by visual estimation of a vascular interventionalists with 20 years of experience in angiographic reading blinded to clinical outcomes [31].

Statistical design and analysis

Continuous variables are reported as mean ± SD and categorical variables as counts and percent. Differences between means of continuous variables were assessed with Students t test, Mann-Whiney U test or Wilcoxon signed-rank test were appropriate. Proportions were compared with Fisher's exact test or Chi-square test. Linear regression and analysis of variance including Fisher's F-test were used for univariable analysis. Logistic regression was used to assess predictors of non-response. P-value cut-off for subsequent multivariable covariance analysis was 0.25. Variable selection for multivariable modelling was continued by backwards regression with an entry and removal threshold p-value of 0.1. Values are presented with their corresponding 95% CIs. A two-sided value of $p < 0.05$ indicated statistical significance. Statistical analyses were performed with XLSTAT software, version 2015.6.01.24026 (Addinsoft SARL).

Statement of Compliance

The swissPOWER registry was approved by the local ethics committee and written informed consent has been provided by

all patients included in the present analysis. Patients had the right to withdraw all their data from the study at any point.

This registry was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice. Data entry into the present registry was financially supported by iVascular S. L. U., Barcelona, Spain.

RESULTS

Study Population and Treatment

From January 2017 to June 2019 a total of 100 men (61.8 ± 10 years) with atherosclerotic lesions in erection related arteries were included in a single centre to undergo endovascular revascularization. To treat 224 lesions, 1.3 consecutive procedures per patient were conducted. More than half of the patients (55%) were former or current smokers, 13% had diabetes mellitus, and nearly a quarter (24%) had atherosclerotic comorbidities (Table 1). At baseline, patients achieved an IIEF-15 score of 32.6 ± 14.8 and an IIEF-6 score of 11.0 ± 6.9. At baseline, 61% of patients showed no response to conservative therapy with PDE-5-I, 22% mentioned severe side effects causing refusal of PDE-5-I therapy. A medium or satisfactory response to PDE-5-I was observed in 17% patients. 22% of patients refused medical therapy from the beginning out of fear of side effects (Table 2). In 72% of patients the distal pudendal artery or distally located arteries were involved. Bilateral penile artery disease was present in 32% of patients (Table 3). A total of 211 lesions (94.2%) were treated with angiolite BTK® drug-eluting stents and 13 lesions (5.8%) with balloon angioplasty alone. All patients received at least one angiolite BTK® stent. Total stented length per patient was 64.3 ± 42.5 mm. PDE-5-I medications was prescribed in 83.8% of patients post procedure for 3 weeks (Table 4). Three-months and 1-year follow-up was completed in 97% and 100% of patients, respectively.

Table 1 Baseline Patient Demographics and Comorbidities.[a]

Characteristics (100 patients)		
Age, yrs	61.8	± 10.0
Smoking	55	(55.0)
Never	45	(45.0)
Former	30	(30.0)
Current	25	(25.0)
Diabetes mellitus	13	(13.0)
Hypertension	46	(46.0)
Hyperlipidaemia	64	(64.0)
Coronary artery disease	14	(14.0)
Peripheral artery disease	8	(8.0)
Cerebrovascular disease	2	(2.0)
Neurological disease	1	(1.0)
Renal insufficiency	2/94	(2.1)
History of, or current dialysis	0	(0.0)
History of prostate surgery	3	(3.0)
Chronic prostatitis	6	(6.0)
Alcoholism	2	(2.0)
Drug abuse	0	(0.0)

[a] Values are mean ± SD or n (%).

Table 2 Baseline Patient Response to Conservative Therapy (PDE5-I).[a]

Characteristics (100 patients)		
No response to PDE5-I	46	(46)
Medium response to PDE5-I	8	(8)
Satisfactory response to PDE5-I	2	(2)
No response & side effects	15	(15)
Medium response & side effects	5	(5)
Satisfatory response & side effects	2	(2)
Refused medical therapy with PDE5-I	22	(22)

[a] Values are n (%).

Table 3 Baseline Patient Characteristics Related to Erectile Dysfunction[a]

Characteristics (100 patients)		
Baseline IIEF-15 score (n = 98)	32.6	± 14.8
Baseline IIEF-6 score	11.0	± 6.9
Ability to achieve penetration (Q3)	1.83	± 1.49
Ability to maintain erection (Q4)	1.38	± 1.24
Affected side		
Left side only	52	(52.0)
Right side only	16	(16.0)
Bilateral	32	(32.0)
PSV left, cm/sec (n = 95)	19.1	± 13.4
PSV right, cm/sec (n = 95)	20.3	± 13.6
PSV target side[b], cm/sec (n = 95)	19.0	± 12.1
EDV left, cm/sec (n = 94)	4.2	± 4.8
EDV right, cm/sec (n = 95)	4.9	± 5.5
EDV target side[b], cm/sec (n = 95)	4.4	± 4.8
Venous leakage	0	(0.0)
Baseline medication		
Phosphodiesterase type 5 inhibitor	32/99	(32.3)
Dosage of sildenafil, mg	80.6	± 30.0
Dosage of tadalafil, mg	8.0	± 6.1
Prostaglandin, intracavernosal	3	(3.0)
Testosterone	1	(1.0)
Medication with impact on EF	44	(44.0)
Antihypertensives	40	(40.0)
Psychotropic drugs	4	(4.0)

EDV, end diastolic velocity; EF, erectile function; IIEF-15, 15-item International Index for Erectile Dysfunction; Q3, IIEF question 3; PSV, peak systolic velocity; Q4, IIEF question 4.
[a] Values are mean ± SD or n (%).
[b] Velocity of the affected side or averaged over right and left cavernosal arteries in case of bilateral involvement

Safety

Safety outcomes of the present registry are summarized in Table 5. No major adverse event occurred during endovascular revascularization or within 30 days thereafter. Puncture related

complications were observed in the following frequencies: Minimal bleeding (moderate puncture site hematomas, in 26.7% of procedures), requiring medical attention (false aneurysms and arterio-venous fistulas, in 3.7%). One arterial venous fistula had to be treated by endovascular intervention and the other was resolved by conservative measures. One arterio-venous fistula was resolved by endovascular and one by conservative treatment. No minor or major bleeding complications were observed.

No patients suffered perineal gangrene or necrosis, underwent repeated target lesion revascularization, or died within 1 year of follow-up.

Effectiveness

Technical success was achieved in all lesions and procedural success in all patients. At 1 year, 55 of 97 patients (56.7%) improved by at least 4 points in IIEF-6 score and thus achieved a clinically relevant improvement of erectile function (Figure 2A). Multivariable analysis revealed total stented length as independent predictor for non-response (no MCRI) (odds ratio [OR] per 10 mmm: 1.1 [95%CI: 1.0 to 1.2], p = 0.02). At 1 year, IIEF-15, Q3, and Q4 score improved in 75.5%, 56.1%, and 57.1% of patients, respectively (Figure 2B).

The IIEF-15 score improved by 17.1 percentage points (95%CI: 12.6 to 21.69) from 43.4 ± 19.7% of the maximum score at baseline to 60.3 ± 24.9% at 1 year (p < 0.001). The IIEF-6 score, representing the erectile function domain, improved by 18.6 percentage points (95%CI: 12.7 to 24.4) from 36.6 ± 22.9% at baseline to 55.0 ± 30.9% of the maximum score at 1 year (p < 0.001). IIEF Q3 and Q4 scores improved by 20.2% (95%CI: 13.1 to 27, p < 0.001) and 21.6% (95%CI: 15.1 to 28.2, p < 0.001), respectively (Figure 3).

Improvement in IIEF-15 score at 1 year was consistent across subgroups (overall improvement: 12.8 [95%CI: 9.4 to 16.2], p < 0.001). However, there was a trend towards less improvement in patients with a total stented length of > 10 mm (Figure 4A). Linear regression revealed a reduction in improvement by 1.1 points (95%CI 1.8 to 0.3) per 10 mm stented length (p < 0.001) (Figure 4B). Likewise, total stented length significantly reduced improvement in the IIEF-6, Q3-, and Q4 scores (Figure 5A,B). Univariable linear regression showed a non-significant tendency of hypertension, bilateral lesion location, and involvement of distal lesions to lower improvement of erectile function after endovascular treatment (Figure 4,5).

Within 1 year from intervention, 36.1% of patients (30 of 83) terminated PDE-5-I medication (Figure 6A). There was no difference in the proportion of responders between patients who discontinued or not even started PDE-5-I medication and those who were on PDE-5-I medication (MCRI achieved: 61.7% (29 of 47) without PDE-5-I vs. 52.8% (28 of 53) with PDE-5-I, p = 0.49; IIEF-15 score improved: 78.4% (37 of 47) without PDE-5-I vs. 73.6% (39 of 53) with PDE-5-I, p = 0.71). Dose of PDE-5-I medication did not change significantly from baseline to 1 year after intervention (Figure 6B).

A total of 24 patients with 52 stented arterial lesions underwent angiographic follow-up of the initially treated arterial side during staged revascularization of the contralateral side.

Table 4. Lesion and Procedure Characteristics of 100 patients undergoing endovascular revascularization.[a]

Characteristics		
Lesions	228	
Internal iliac artery	9	(3.9)
Internal pudendal artery, proximal	72	(31.6)
Internal pudendal artery, mid	32	(14.0)
Internal pudendal artery, distal	50	(21.9)
Common penile artery	22	(9.6)
Dorsal penile artery	13	(5.7)
Cavernosal artery	27	(11.8)
Inferior gluteal artery	3	(1.3)
Treated lesions	224	(98.2)
POBA only	13	(5.8)
Stent implantation	211	(94.2)
Stents/lesion	1.1	
Stents/patient	2.3	
Stented length/patient, mm	64.3	± 42.5
Procedures/patient[b]	1.3	
Radiation exposure, µGym² (n = 128) Per procedure Per patient	 12 103 15 808	 ± 13 658 ± 17 260
Contrast medium, ml Per procedure Per patient	 57.9 77.6	 ± 30.9 ± 47.9
Post procedure medication (n = 99)		
Phosphodiesterase type 5 inhibitor	83	(83.8)
Dosage of sildenafil, mg	93.8	± 17.7
Dosage of tadalafil, mg	6.3	± 4.3
Dosage of vardenafil, mg	10.0	± 0.0
Prostaglandin, intracavernosal	8	(8.1)
Testosterone	1	(1.0)
Medication with impact on EF		
Antihypertensives	41	(41.4)
Psychotropic drugs	6	(6.1)

[a] Values are mean ± SD or n (%).
[b] Two consecutive procedures in 32 patients, three consecutive procedures in 1 patient.

Table 5. Safety Outcomes.[a]

Outcomes	Post procedure	At 3 months	At 12 months
Puncture site complications (TIMI)			
Minimal [c]	36/135 (26.7)		
Requiring medical attention	5/135 (3.7)		
Perineal skin lesion		0/97 (0%)	0/97 (0%)
Mortality		0/100 (0%)	0/100 (0%)

[a] Values are n (%).
[b] In terms of the number of procedures.
[c] All hematomas were resolved by conservative measures.
[d] One fistula was resolved by endovascular and one by conservative treatment.

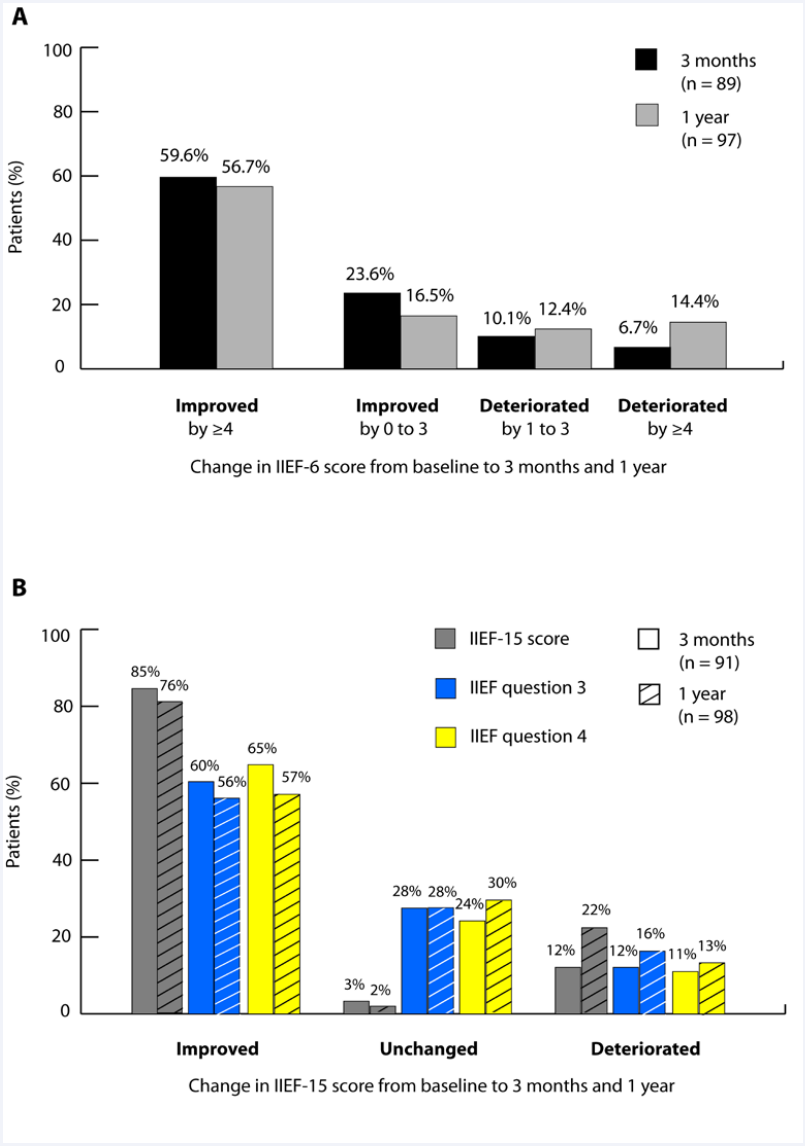


Figure 1 **Treatment success reflected by MCRI of ≥ 4 of the IIEF-6 score (A) and improvement of IIEF-15 score and IIEF-15 questions 3 and 4 at 3 months and 1 year (B).**
IIEF, international index of erectile function; MCRI, mivnimum clinically relevant improvement; Q3, IIEF question 3; Q4, IIEF question 4.

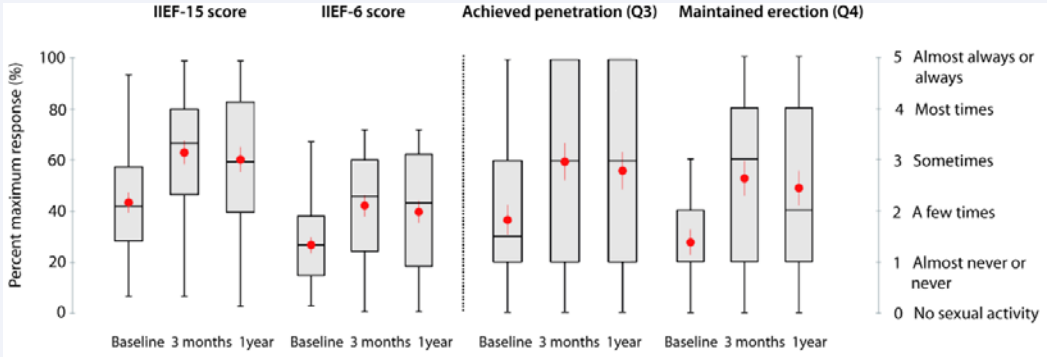
After a mean follow-up of 9.6 ± 5.8 months, arterial patency and binary restenosis were observed in 46/52 (88.5%) and in 8/52 (15.4%) lesions, respectively (Table 6).

DISCUSSION

Endovascular revascularization of erection-related arteries is an emerging interventional option for patients with arteriogenic ED. The recent development of flexible and thin-strut drug eluting stents has facilitated endovascular therapy of more complex disease patterns and small-diameter vessels such as erection-related arteries. Within the present investigation, the safety and clinical efficacy of the angiolite BTK® stent was assessed in an all-comers cohort of 100 consecutive patients. Endovascular revascularization of erection-related arteries was shown to be safe, technically feasible and clinically effective in the majority of patients. Moreover, angiographic restenosis rates were shown to be lower than those reported in previous studies.

In the present series, procedural success was achieved in all patients and no major adverse events were observed. Complications were limited to puncture-site complications mostly attributable to dual antiplatelet therapy. Structural puncture site complications requiring further medical attention were observed in 3.7 percent of patients. This finding is well in line with experiences from endovascular revascularization approaches in other arterial beds [32].

In addition, no local ischemic complications associated with revascularization of erection-related arteries were observed. Thus, in experienced hands, endovascular therapy for ED can be considered equally safe when compared to endovascular revascularization for peripheral arterial disease.



		Baseline	3 months	P-value	1 year	P-value
IIEF-15 score (% maximum response)	Mean ± SD	43.4 ± 19.7	62.9 ± 22.0	p < 0.001	60.3 ± 24.9	p < 0.001
	Median (IQR)	42.0 (28.3-57.3)	66.7 (46.7-80.0)		59.3 (39.7-82.7)	
IIEF-6 score (% maximum response)	Mean ± SD	36.6 ± 22.9	58.4 ± 29.1	p < 0.001	55.0 ± 30.9	p < 0.001
	Median (IQR)	36.7 (20.0-52.5)	63.3 (33.3-83.3)		60.0 (25.0-86.7)	
IIEF Q3	Mean ± SD	1.8 ± 1.5	3.0 ± 1.8	p < 0.001	2.8 ± 1.9	p < 0.001
	Median (IQR)	1.5 (1-3)	3 (1-5)		3 (1-5)	
IIEF Q4	Mean ± SD	1.4 ± 1.2	2.6 ± 1.6	p < 0.001	2.4 ± 1.7	p < 0.001
	Median (IQR)	1 (1-2)	3 (1-4)		2 (1-4)	

Figure 3 Results from the 15-item international index of erectile function (IIEF-15) questionnaire, the erectile function domain (IIEF-6 score), and IIEF questions 3 and 4 on ability to achieve or maintain erection. IIEF, international index of erectile function, Q3, IIEF question 3; Q4, IIEF question 4.

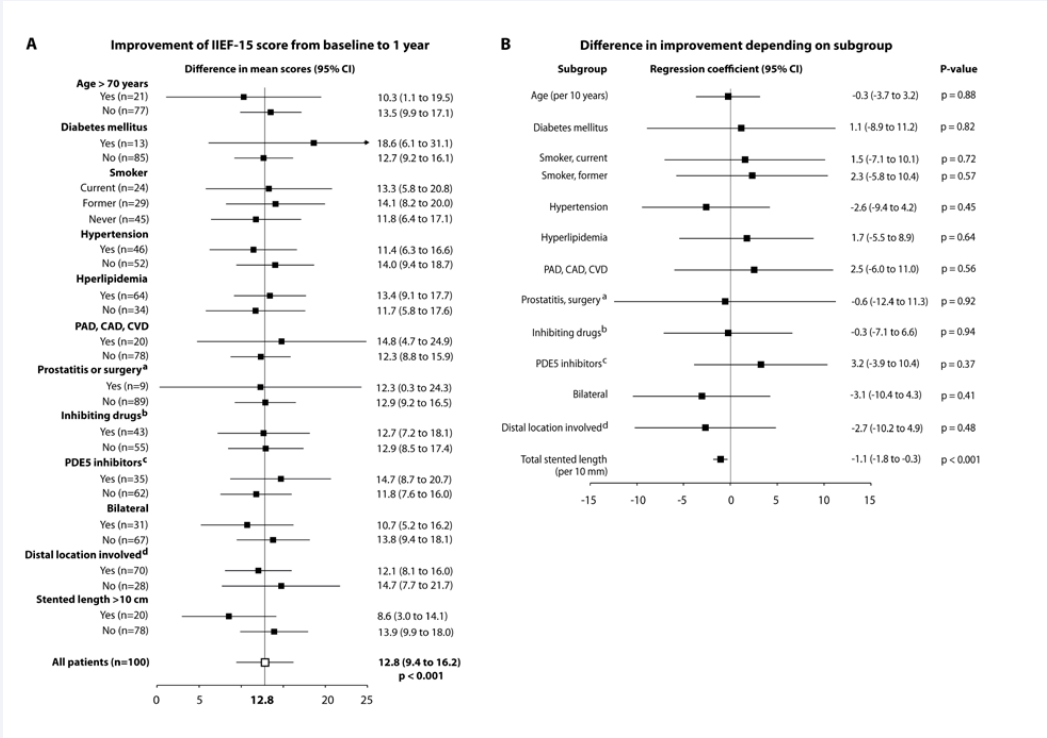


Figure 4 Improvement of mean IIEF-15 score from baseline to 1 year (A) and difference in mean improvement depending on subgroup (B). IIEF, international index of erectile function, PDE5i, phosphodiesterase type 5 inhibitor. [a] Chronic prostatitis or previous prostate surgery, [b] Antihypertensive and psychotropic drugs, [c] PDE5i or intracavernosal prostaglandin prior to intervention, [d] distal pudendal artery or distally located arteries involved.

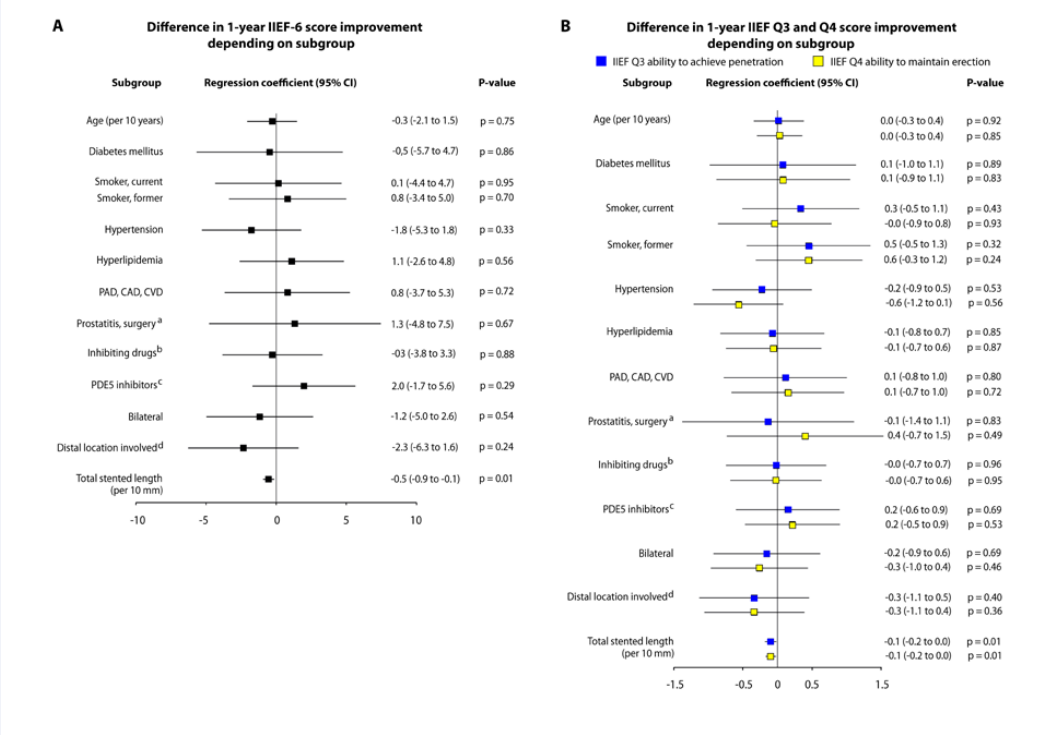


Figure 5 Improvement of mean IIEF-6 score (A) and mean IIEF Q3 and Q4 score (B) from baseline to 1 year (A) and difference in mean improvement depending on subgroup (B). IIEF, international index of erectile function, PDE5i, phosphodiesterase type 5 inhibitor. [a] Chronic prostatitis or previous prostate surgery, [b] antihypertensive and psychotropic drugs, [c] PDE5i or intracavernosal prostaglandin prior to intervention, [d] distal pudendal artery or distally located arteries involved.

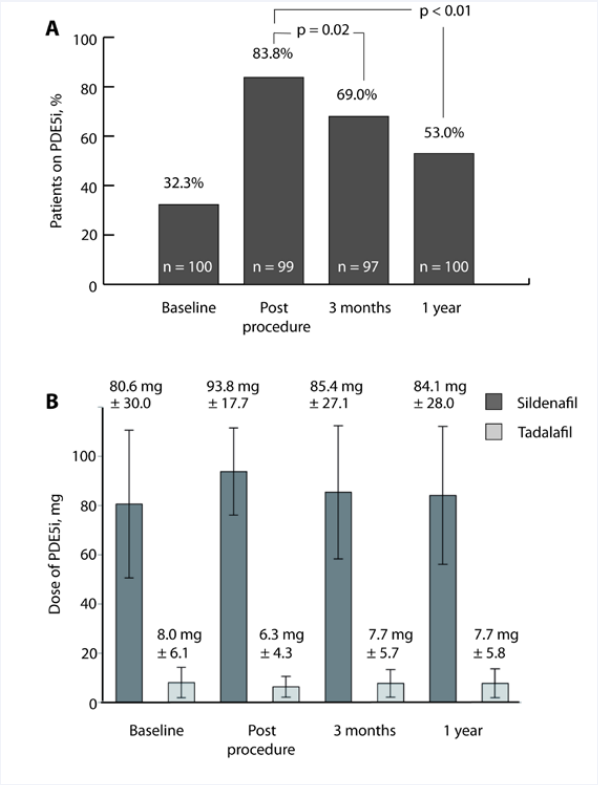


Figure 6 Proportion of patients who are on PDE5 inhibitor medication (A) and dose of PDE5 inhibitor (B). PDE5i, phosphodiesterase type 5 inhibitor.

Table 6. Angiographic Sub-Study [a].

	Lesions, n	Binary restenosis, n	Binary restenosis, %	Mean stent diameter	SD stent diameter	Mean stent length	SD stent length
Lesions	**52**	**8**	**15.4**				
Proximal internal pudendal artery	30	2	6.7	3.7	± 0.4	32.8	± 9.8
Middle internal pudendal artery	7	1	14.3	3.3	± 0.4	29.1	± 9.0
Distal internal pudendal artery	5	2	40.0	2.8	± 0.4	33.0	± 8.2
Common penile artery	4	1	25.0	2.7	± 0.3	31.5	± 8.7
Cavernosal artery	4	2	50.0	2.5	± 0.4	29.0	± 12.2
Dorsal penile artery	2	0	0.0	2.5	± 0.7	19.0	± 7.1

In line with earlier publications, the feasibility endpoint of this study had been defined as a minimal clinically important difference (MCID) of at least 4 points in the IIEF-6 domain in more than 50% of the patient population [9,18]. As described, with this comparatively strict definition, an improvement in 56.7% of patients at the 1-year mark was found. Of note, utilizing the endpoint definition used in initial trials for PDE-5-I, a treatment success could be witnessed in about 80% of patients [11].

The results of the present study are comparable to another all-comers registry, which featured a smaller patient cohort in whom various anti-restenosis concepts had been utilized [9].

Angiographic evidence subsequent to endovascular therapy of erection-related arteries is currently scarce. The ZEN trial by Rogers and colleagues evaluated the use of a drug-eluting stent coated with Zotarolimus for the treatment of ED in patients with suboptimal response to PDE-5-I [18]. Within this prospective single-arm multicenter trial, a total of 30 patients with 45 internal pudendal artery lesions were treated with the Resolute Zotarolimus-coated drug eluting stent (Medtronic, Santa Rosa, CA, USA). Mean lesion length was 18 mm and procedural success rate was 100%. The primary feasibility endpoint, defined as an improvement of IIEF score ≥ 4, was achieved in 59.3% of patients at the six-month follow-up. Binary restenosis (≥ 50 % lumen compromise by angiography) was reported in 34.4% at the same interval. Based on these findings, drug-eluting stenting of the pudendal arteries was considered safe and beneficial to the majority of patients.

The PERFECT-2 Study evaluated balloon angioplasty for isolated penile artery stenoses (n = 34 lesions) in 22 ED patients [15]. The primary endpoint was in-segment restenosis (≥ 50 %) by CTA at the eight- month follow-up. One year sustained clinical success (IIEF-5 score ≥ 22 or maintaining a ≥ 4 improvement to baseline) was considered as secondary endpoint. Mean lesion length was 11.1 ± 9.0 mm and the mean IIEF-5 score at baseline was 10.3 ± 4.5. Procedural success was 91 %. Restenosis at eight months was observed in 14/34 (41.2 %) lesions (13/22 patients). At one year, the secondary endpoint was achieved in 50 % (11/22) of patients [15].

Doppalapudi et al., described in a meta-analysis success rates from 59.8% to 63.2% for endovascular therapy in ED patients undergoing arterial revascularization [33]. Thus, although a comparison across different studies is very difficult, results obtained with the angiolite BTK® stent are well in line with or better than those of earlier publications [14,15,18].

In contrast to the present all-comers registry, key exclusion criteria in the ZEN trial contained prostatectomy, pelvic radiation, diabetes mellitus, myocardial infarction and others. In addition, the ZEN trial was limited to patients with target lesions in the pudendal artery. In contrast, the present series contained patients undergoing endovascular revascularization of all erection-related arteries, especially also smaller-caliper arteries such as the penile arteries in which restenosis rates and clinical outcomes should be worse when compared with larger diameter vessels such as the internal pudendal artery.

Comparing patient outcomes of the present series with other treatment approaches or earlier publications on endovascular therapy, it has to be kept in mind, that this all-comers registry did not exhibit any clinical exclusion criteria. Thus, a multitude of factors potentially affecting clinical outcomes subsequent to revascularization of erection related arteries such as medications (44%), diabetes mellitus (13%), history of prostate surgery (3%), chronic prostatitis (6%) and alcohol abuse (2%) were present in this real-world registry. In a potential prospective randomized trial comparing revascularization with conservative therapy, patients bearing these comorbidities would be excluded thereby positively impacting clinical success rates to be expected. At present, however, no precise tools exist to quantify the individual impact of the above-mentioned co-existing risk factors to facilitate prediction of the response to revascularization. Thus, further studies are warranted to better assess subgroups of ED patients with heterogeneous risk factors and a potential suboptimal response to revascularization.

Within the multi-variable analysis of the present investigation, we found total stented length of more than 10mm to be an independent predictor of impaired outcomes. These results are generally in line with observations from endovascular revascularizations in other arterial beds [34].

In the present series, many ED patients required further PDE-5-I medication subsequent to revascularization. Considering that PDE-5-inhibitors mostly exert their effect on the penile microcirculation, the latter may be required in patients with atherosclerotically caused ED despite successful treatment of macroangiopathy with stents.

CONCLUSION

In conclusion, within this real-world registry, endovascular therapy of ED with the angiolite BTK® stent was shown to be a safe and feasible treatment option. In the angiographic sub-study,

use of a novel thin-strut drug eluting stent was associated with restenosis rates lower than those reported with thicker-strut stents. Further studies will have to focus on patient selection to better define subgroups of patients with poor response to endovascular revascularization.

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