

Research Article

Long-term results for post-interventional systemic heparinization following angioplasty of peripheral vessels

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Abstract

Objective: The long-term outcome of percutaneous transluminal angioplasties is mainly determined by restenoses, either by progression of the underlying disease or by intimal hyperplasia. Pharmacological substances on the one hand and the implantation of stents on the other have been developed with the intention of preventing precisely this complication. While patients are treated after PTA of peripheral vessels with different low-molecular-weight heparins, the indication for stent implantation is determined individually rather by experience. The aim of this study was to determine gender-specific risk factors of long-term outcome after percutaneous transluminal angioplasty (PTA) of peripheral vessels with or without stentimplantation.

Methods: In the present study, we examined the long-term results of percutaneous transluminal angioplasty (PTA) of peripheral vessels. Between 2007 and 2017, in total, 3,276 patients underwent PTA with or without stent implantation in our clinic. All patients were treated postinterventionally for 48 hours with 25,000 IU heparin (Unfractionated Heparin (UFH), heparinsodium-Braun, 25,000 I.E./5 ml, 2 ml/h) monitored by the partial thromboplastin time and subsequently underwent a control investigation every 6 months. The endpoint of the study was determination of symptomatic stenosis larger than 50% that required reintervention.

Results: 239 (68.2% with mean age 68.02 years) male patients and 111 female patients (31.71% with mean age 62.92 years) were evaluated with complete follow-up. A total of 470 PTAs were performed on male patients and 213 on female patients in multiple interventions. The majority of patients at the time of treatment were in stage IIb according to the classification of Fontaine (81.6% of male patients and 68% of females). In our sample, peripheral arterial disease stage III and IV according to Fontaine classification occurred twice as frequently in female patients as in male patients (stage III in 12.6% in female versus 6.1% in male, and stage IV in 18% in female versus 8.9% in males). In both groups, the femoral superficialis artery was most frequently dilated (64 cases, 30% in female and 155 cases, 32.9% in male), followed by the iliacal communis artery (46 cases in female and 99 cases in male, both with 21.5%). A balloon angioplasty of the tibialis anterior and posterior arteries was performed twice as frequently in female patients as in male patients (28 cases with 13.1% of tibialis ant. artery in female versus 32 cases with 6.8% in male patients, and in 17 cases with 7.9% of tibialis post. artery in female versus 16 cases with 3.4% in male patients). In this study, without consideration of gender, patency rates of 79% after 2.5 years, 67% after 5 years, 49% after 7.5 years and 37% after 10 years were determined for PTA without stent implantation. Between the 7th and 10th year in follow-up, the cumulative patency rates for stent implantation was 49%, whereas it was 31% for PTA alone. The results of this study show that the stent assisted PTA's of comm. artery and external iliacal artery are significantly independent of risk factors better than the femoral vessels, and these in female patients better than in male patients. Male patients do not benefit significantly from stent implantation in the long term. As the COX1 and II regression analyses show, gender-linked results are most evident for renal insufficiency and diabetes mellitus, and less pronounced also for the number of open lower leg vessels.

Conclusion: Under consideration of gender and risk factors, while male patients with diabetes mellitus, renal insufficiency and/or poor run-off did not benefit from stent implantation in the long-term, female patients with similar risk factors showed higher patency rates after stent therapy. In addition, the long-term results after PTA of femoral superficialis artery and poplitea artery are significantly worse than PTA of the pelvic vessels in both genders.

Introduction

Percutaneous angioplasty with stenting of the superficial femoral and popliteal artery is the treatment of choice in the majority of patients with peripheral artery disease (PAD) [1,2]. The secondary long-term outcome of percutaneous transluminal angioplasty is mainly determined by in-stent stenosis (ISR) [3,4]. Advancements such as drug-eluting stents (DES), covered stents, and drug-coated balloons (DCB) were developed to reduce the rate of in-stent stenosis and improve long-term results [5-9]. Within the first year after treatment, ISR occurs in 18% - 40% of patients undergoing stenting in the femoro-popliteal segment [10,11]. The vascular injury caused by balloon dilatation and stent implantation can lead to an inflammatory reaction and as a result to excessive neointima hyperplasia and ISR [12,13], which develop within a period of weeks to months [14]. The routine therapy of platelet aggregation inhibitors and the administration of anticoagulants are recommended to reduce thrombogenicity after stent implantation using different therapeutic approaches [15,16]. Until the year 2003, the experience gained from coronary stenting with heparin was mainly adopted as standard therapy for stent implantation in peripheral vessels. The studies focused on complications occurring after heparin administration rather than on the efficacy of heparin administration [17,18]. Experience from the management of cardiac patients has shown that due to the lack of routine anti-thrombin III (AT-III) determination, the effects mediated by heparin can be difficult to predict, as the determination of the activated clotting time (ACT) or the partial thromboplastin time (PTT) alone may not be sufficient for the assessment of heparin effects [19]. In addition, the role of risk factors in long-term outcomes after PTA has rarely been systematically investigated so far. Therefore, the aim of this study was to determine gender-specific risk factors of long-term outcome following post-interventional 48-hour heparinization after peripheral PTA. In addition, the role of stent implantation was examined for long-term results depending on the vessels treated.

Materials and methods

In a prospective study conducted between 2007 and 2017, in total 3,276 patients underwent peripheral vascularization at the Clinic for Vascular Surgery in collaboration with the Institute for Interventional Radiology. As inclusion criteria, patients with peripheral arterial occlusive disease in stage IIa, IIb, III and IV according to Fontaine classification were defined. The vascular status was determined by clinical findings, determination of ABI (ankle-arm index), of the TASC classification, of the open lower legs vessels, and the classification to Fontaine. All risk factors and comorbidity such as arterial hypertension, diabetes mellitus, hyperlipidemia, nicotine consumption, hyperuricemia, coronary heart disease, possible tumor diseases and medication were documented. The exclusion criteria were a previous intervention on

peripheral vessels, previous bypass operations or patients scheduled for a hybrid intervention, so that PTA was only part of the primary treatment. Patients were divided into 3 groups, GI: PTA of the pelvic vessels, always with stent implantation, GII: PTA of the femoral superficialis artery, the popliteal artery with or without stent implantation and GIII: PTA of the lower leg vessels without stent implantation. The majority of these patients ($n = 2,956$) were treated post-interventionally for 48 hours with 25,000 IU heparin/24 hours (unfractionated heparin, heparin-sodium-Braun, 25,000 I.E./5 ml, 2 ml/h, Braun, Germany). The heparin therapy was controlled with PTT. Patients underwent follow-up examinations at 6-month intervals. The complete vascular status was determined at each follow-up examination. Symptomatic patients were undergoing to invasive diagnostics. The endpoint of the study was defined as the patency rate of the treated vessel section with stenoses less than 50%, the changes in the Fontaine classification and the symptoms of patients. In this analysis all 350 patients who had undergone all follow-up examinations were considered. In total, 213 interventions in 111 female (31.71%) and 470 interventions in 239 men (68.29%) were performed.

Statistical analyses

Numerical variables are expressed as means \pm SD. Count variables expressed with Kaplan-Meier curves were used to compare the cumulative probability risk of patency. Time zero for the Kaplan-Meier survival analysis was taken as the date on which the primary intervention was undertaken. For event-free patients, the follow-up was censored at the last visit. The log-rank test was used to determine any statistical differences in the Kaplan-Meier curves between the groups. For multiple-comparison analyses, the statistical significance value was adjusted by the Bonferroni Holm procedure. The association between the time to event occurrence and clinical covariates was examined with the use of a multivariate Cox regression model. The multivariate model was adjusted for intervention type (PTA/STENT), gender, smoking status. Comorbidities (coronary heart disease: CHD, diabetes mellitus: DM, renal insufficiency: RF, hyperlipoproteinemia: HLP, arterial hypertension: AH, hyperuricaemia: HU), Vessels type and PTA device type. The proportional hazards assumption was tested by Schoenfeld residuals (phtest). No statistically significant violation was found. Hazard ratios (HR) along with their standard errors and the corresponding p-values for the associations are presented. A reduced model with gender alone as covariate is also considered. The significance level was set to $\alpha = 5\%$ for all statistical tests. All analyses were performed with the statistic software R (version 3.4.4) using the packages `survminer` and `survMisc`.

Results

Characterization of the study cohort

The majority of patients were male (68.3%). The mean



age for men was 62.9 ± 11.9 years and for females 68.0 ± 15.0 years. While the males clearly predominated until the age of 60 years, the number of female patients increased from the age of 60. The gender distribution of the cohort is shown in table 1. As expected, arterial hypertension, hyperlipoproteinemia and nicotine abuse were common risk factors in this cohort of patients, followed by diabetes mellitus and renal insufficiency. More than 85% of the patients had multiple risk factors. Comorbid coronary heart disease was diagnosed in approximately one-third of study participants (30%) and cancers in about one-tenth (10%). Stenosis or occlusion of the subclavian artery as well as aneurysms were only rarely diagnosed in our population. At the time of treatment, 81% of males and 68% of female patients were in stage IIb according to the Fontaine classification. Surprisingly, almost twice as many female patients were at stage III and IV (12.6% versus 6.3% for stage III and 18% versus 8.9% for stage IV) (Tables 1, 2). For the statistical evaluation, the aneurysms, subclavian artery and aorta were not taken into consideration.

Localization of lesions in affected arteries

In both genders, the femoral superficial artery was the most frequently treated vessel with 30% and 32.9%, respectively, followed by the PTA of the common iliac artery with 21%. PTA of the external iliac artery was performed twice as frequently in male patients with 14.4% as in females (with 7.5%). While the proportion of PTAs in the I. and III. Segment of the popliteal artery did not differ between the two genders, a PTA of the II. Segment was performed twice as frequently in male patients (8.5%) as in female patients (4.7%). Correspondingly, in female patients, PTAs of the anterior and posterior tibial artery were performed in 13.1% and 6.8%, respectively (Table1).

Severity of clinical symptoms in PAD patients

The superficial femoral artery was most frequently affected ($n = 219$), leading in more than 80% of cases to the development of PAD in stage IIb ($n = 177, 80.5\%$), in 13.2% in stage IV ($n = 29$) and in 5.91% in stage III ($n = 13$). A relevant stenosis of the common iliac artery led in 86.4% to stage IIb ($n = 127$), in 8.2% to stage III ($n = 12$), and in 4.8% to stage IV ($n = 7$). Less frequently diagnosed was a stenosis of the external iliac artery ($n = 81$), and its clinical severity was similar to the stenosis of the common iliac artery with 85.4% ($n = 70$) of the patients presenting with stage IIb, 8.5% ($n = 7$) in stage III and with 4.9% ($n = 4$) in stage IV. Hemodynamically relevant lesions in the I. segment of the popliteal artery caused in 62.8% ($n = 32$) stage IIb, in 17.7% stage III and in 15.7% ($n = 8$) stage IV symptoms. Similar results were found in the second segment of the popliteal artery with 49.0% IIb ($n = 25$), 17.7% stage III ($n = 9$) and 21.6% ($n = 11$) stage IV symptoms. The third segment of the popliteal artery led to stage IIb symptoms in 61.1% ($n = 11$), to stage III symptoms in 11.1% ($n = 2$), and to stage IV symptoms in 22.2% ($n = 4$) (Table 3).

Cumulative patency rate of both groups depending on coronary heart disease and gender as risk factors

In male patients without coronary heart disease (CHD),

Table 2: Comorbid diseases (percentage).

Arterial hypertension	78.3
Coronary heart disease	30.3
Diabetes mellitus	29.1
Hyperlipoproteinemia	59.7
Hyperurikemia	10.1
Renal insufficiency	27.4
Smoking	78.9
Tumor	10.2

Categorical variables are presented as an absolute percentage.

Table 1: Baseline characteristics of the study population.

	Male (percentage)	Female (percentage)
	239 (68.29)	111 (31.71)
Age (mean ± SD)	68.02 (14.95)	62.92 (11.93)
Fontaine classification of PAD (Peripheral Artery Disease)	359	150
IIa	2 (0.55)	0 (0)
IIb	293 (81.6)	102 (68)
III	22 (6.1)	19 (12.6)
IV	32 (8.9)	27 (18)
Treated Vessels	470	213
I-1	99 (21.5)	46 (21.5)
I-2	66 (14.04)	16 (7.5)
I-3	3 (0.63)	0 (0)
II-1	155 (32.9)	64 (30)
II-2	31 (6.5)	18 (8.4)
II-3	40 (8.5)	10 (4.6)
II-4	13 (2.7)	5 (2.3)
III-1	32 (6.8)	28 (13.1)
III-2	16 (3.4)	17 (7.9)
III-3	14 (2.9)	6 (2.8)

Legends: I-1: Iliacal communis artery, I-2: Iliacal external artery, I-3: Iliacal interna artery, II-1: Femoralis superficialis artery, II-2: Popliteal artery I. Segment, II-3: Popliteal artery II. Segment, II-4: Popliteal artery III. Segment, III-1: Tibialis anterior artery, III-2: Tibialis posterior artery, III-3: Fibularis artery

**Table 3:** Severity of clinical symptoms in PAD (Peripheral Artery Disease) patients according to the classification of Fontaine depending on affected arteries.

	Ila	Ilb	III	IV
I-1	1(0.68)	127(86.39)	12(8.16)	7(4.76)
I-2	0(0)	70(85.37)	7(8.54)	4(4.88)
I-3	0(0)	3(100)	0(0)	0(0)
II-1	0(0)	177(80.45)	13(5.91)	29(13.18)
II-2	1(1.96)	32(62.75)	9(17.65)	8(15.69)
II-3	0(0)	25(49.02)	9(17.65)	11(21.57)
II-4	0(0)	11(61.11)	2(11.11)	4(22.22)
III-1	0(0)	32(52.46)	12(19.67)	17(27.87)
III-2	0(0)	16(48.48)	5(15.15)	12(36.36)
III-3	0(0)	7(35)	4(20)	9(45)

I-1: Iliacal communis artery, I-2: Iliacal external artery, I-3: Iliacal interna artery, II-1: Femoralis superficialis artery, II-2: Popliteal artery I. Segment, II-3: Popliteal artery II. Segment, II-4: Popliteal artery III. Segment, III-1: Tibialis anterior artery, III-2: Tibialis posterior artery, III-3: Fibular artery, the percentage in parentheses.

the cumulative patency rate following PTA for up to 7.5 years after intervention was higher than that in females without CHD (85% versus 68% at 2.5 years and 66% versus 55% at 5 years, respectively, $p = 0.213$). However, at 7.5 years both genders showed identical outcome (50% versus 51%). The cumulative patency was higher in female CHD patients after PTA in comparison to male CHD patients and up to the 7th post-interventional year, was 71% versus 68% at 2.5 years, and 57% versus 47% at 5 years. After the 7th year of post-intervention, the rates did not significantly differ from each other ($p = 0.341$).

Until the fourth post-interventional year, the cumulative patency rate was higher in male PTA-treated patients without CHD after stenting (as) compared to their female counterparts (75% versus 71% at 2.5-years follow-up). After 7 years after stent implantation, the post-interventional outcome was almost identical in both genders (51% versus 52%, $p = 0.581$). The cumulative patency rate was higher in female patients with CAD after PTA and stenting. At 2.5 years, the rate was 90% in female patients and 76% in males, and it decreased at 5-year-follow-up to 75% and 52% in men, respectively ($p = 0.12$). The highest difference, however, was between female patients with CHD who were treated with and without a stent. The cumulative patency rate in female patients after stent therapy was consistently higher than in those after PTA, although this did not reach statistical significance (90% versus 76% after 2.5 years, 75% versus 52% after 5 years, 75% versus 52% after 7.5 and 10 years, $p = 0.412$) (Table 4).

After PTA and stent therapy of the comm. iliacal artery and externa iliacal artery, male patients without CHD showed slightly better patency rates than female patients only in the first 5 years after the intervention, after that male and female patients show identical results. With CHD as a risk factor, results of stent assisted pelvic vascular PTA are consistently better in male patients than in female patients (Table 5).

After PTA and stent therapy of the femoral vessels without CHD, results are consistently better in male patients than in female patients, but significantly worse than stent assisted PTA of the pelvic vessels. With CHD as a risk factor, female

patients with stent assisted PTA of the femoral vessels consistently have better results than male patients, but again worse than PTA of the pelvic vessels. The results of pure PTA from lower leg vessels, usually without stent implantation, are not statistically usable due to the small numbers involved (Table 5).

In summary, the results of stent supported PTA of pelvic vessels show no gender dependency in the long term. The results of PTA of the femoral vessels are consistently worse than PTA of the pelvic vessels in both genders, regardless of CHD, but significantly better in female patients than in male patients. Male patients with or without CHD do not benefit from a stent implantation.

Cumulative patency rate of both groups depending on diabetes mellitus and gender as risk factors

The cumulative patency rate in non-diabetic patients following PTA alone was consistently higher in male patients than in female patients (85% versus 74% after 2.5 years, 70% versus 47% after 5 years, 52% versus 47% after 7.5 years and 46% versus 39% after 10 years, $p = 0.0594$). In nondiabetic patients, male and female patients showed similar values after PTA and stent treatment at each follow-up time point. Similarly, in diabetic patients treated with PTA alone, the cumulative patency rate at 5-year-follow-up was higher in male patients than in female study participants (81% versus 67% after 2.5 years). Between the 5th and 8th year post interventionem, the patency rates did not significantly differ between the two genders, and at the end of the follow-up period the rates were 23% and 22% in the two genders ($p = 0.555$). The cumulative patency rate of diabetic patients after PTA and stent therapy did not differ from each other in the first 3 years after treatment: it was 73% for male patients versus 67% for female patients. The cumulative patency rate of female patients remained at 67% until the end of follow-up and this was significantly higher than that in males at 42% ($p = 0.696$) (Table 6). In summary, male patients without diabetes benefited more from PTA than from stent therapy. Female patients with diabetes mellitus showed better outcome after stent therapy than male patients.



Table 4: Cumulative patency rates of both groups depending on coronary heart disease and gender as risk factors.

	2.5 Years (percentage)	5 Years (percentage)	7.5 Years (percentage)	10 Years (percentage)
Male, CHD=0, PTA	85	66	50	36
Female, CHD=0, PTA	68	55	51	41
Male, CHD=1, PTA	71	57	44	44
Female, CDH=1, PTA	68	47	47	23
Male, CDH=0, Stent	75	61	51	49
Female, CHD=0, Stent	71	58	52	52
Male, CHD=1, Stent	76	52	52	52
Female, CHD=1, Stent	90	75	75	75

Legends: Cumulative patency rates are presented in percentages. Male, CHD 0, PTA and female, CHD 0, PTA $p = 0.213$; Male, CHD 1, PTA and female, CHD 1, PTA $p = 0.341$; Male, CHD 0, Stent and female CHD 0, Stent $p = 0.581$; Male CHD 1, Stent and female CHD 1, Stent $p = 0.12$; The most significant difference. Male, CHD 1, Stent and female CHD1, Stent

Table 5: Cumulative patency rates of treated vessels groups depending on coronary heart disease and gender as risk factors.

	2.5 years (percentage)	5 years (percentage)	7.5 years (percentage)	10 years (percentage)
G-I, CHD=0, M	87	72	60	57
G-I, CHD=0, W	76	67	67	67
G-I, CHD=1, M	84	69	69	69
G-I, CHD=1, W	90	56	56	56
G-II, CHD=0, M	76	52	40	27
G-II, CHD=0, W	53	41	26	19
G-II, CHD=1, M	62	42	26	26
G-II, CHD=1, W	71	53	53	38
G-III, CHD=0, M	75	75	57	57
G-III, CHD=0, W	100	100	100	100
G-III, CHD=1, M	100	100	100	100
G-III, CHD=1, W	100	75	75	75

Legends: Cumulative patency rates are presented in percentages. GI: Iliaca communis and externa artery, GII: femoralis superficialis artery, prof. fem. artery, poplitea artery I, II and III. segment; GII, CHD 0, male versus GI, CHD 0, male, $p = 0.00578$; GII, CHD 0, female versus GI, CHD 0, male, $p = 0.0000161$; GII, CHD 0, female versus GI, CHD 0, female, $p = 0.00621$; GII, CHD 0, male versus GI, CHD 1, male, $p = 0.00114$ GII, CHD 0, male versus GI, CHD 0, male, $p = 0.00135$; The most significant difference. GII, CHD 0, female versus GI, CHD 0, male, $p = 0.0000161$

Table 6: Cumulative patency rates of both groups depending on diabetes mellitus and gender as risk factors.

	2.5 Years (percentage)	5 Years (percentage)	7.5 Years (percentage)	10 Years (percentage)
Male, DM=0, PTA	85	70	52	46
Female, DM=0, PTA	74	47	47	39
Male, DM=1, PTA	81	52	42	23
Female, DM=1, PTA	67	57	45	22
Male, DM=0, Stent	76	59	44	44
Female, DM=0, Stent	76	64	55	42
Male, DM=1, Stent	73	52	42	42
Female, DM=1, Stent	67	67	67	67

Legends: Cumulative patency rates are presented in percentages. Male, DM 0, PTA and female, MD 0, PTA $p = 0.0594$; Male, DM 1, PTA and female, MD 1, PTA $p = 0.555$; Male, DM 0, Stent and female MD 0, Stent $p = 0.693$; Male DM 1, Stent and female MD 1, Stent $p = 0.696$; The most significant difference. Male, DM 0, PTA and female MD 0, PTA (0.0594), and female DM 1 (0.0745), PTA and male, DM 1, Stent (0.0756).

Table 7: Cumulative patency rates of treated vessels groups depending on diabetes mellitus and gender as risk factors.

	2.5 years (percentage)	5 years (percentage)	7.5 years (percentage)	10 years (percentage)
G-I, DM=0, M	91	76	63	49
G-I, DM=0, W	77	61	61	61
G-I, DM=1, M	73	57	57	57
G-I, DM=1, W	88	88	85	85
G-II, DM=0, M	69	56	41	37
G-II, DM=0, W	66	46	41	19
G-II, DM=1, M	76	57	35	18
G-II, DM=1, W	50	34	34	18
G-III, DM=0, M	50	50	50	50
G-III, DM=0, W	100	100	100	100
G-III, DM=1, M	100	67	67	67
G-III, DM=1, W	100	75	75	75

Legends: Cumulative patency rates are presented in percentages. GI: Iliaca communis and externa artery, GII: femoralis superficialis artery, prof. fem. artery, poplitea artery I, II and III. segment; GII, DM 0, male versus GI, DM 0, male, $p = 0.000412$; GII, DM 0, female versus GI, DM 0, male, $p = 0.0000317$; GII, DM 1, male versus GI, DM 0, male, $p = 0.000128$; GII, DM 1, female versus GI, DM 0, male, $p = 0.0000259$; The most significant difference. GII, DM 1, female versus GI, DM 0, male, $p = 0.0000259$



With regard to the treated vessel sections, the patency rate after stent assisted PTA of the pelvic vessels is better in male patients than in female patients only within the first 5 years. Female patients with diabetes mellitus show consistently better results than male patients after stent assisted PTA of the pelvic vessels. After stent assisted PTA of the femoral vessels, male patients without diabetes mellitus show slightly better results than female patients, but significantly worse results than PTA of the pelvic vessels. With diabetes mellitus, the patency rates after stent supported PTA of the femoral vessels are better in male patients within the 5 years than in female patients, after that they did not differ from each other. Again, the results of PTA from lower leg vessels are usually not statistically usable without stent implantation (Table 7).

In summary, the results of stent supported PTA of pelvic vessels show no gender dependence in the long-term course without diabetes mellitus. In patients with diabetes mellitus, only female patients benefit from stent implantation of the pelvic vessels. The results of PTA of the femoral vessels are consistently worse than PTA of the pelvic vessels in both genders independent of diabetes, but better in male patients in the first 5 years postintervention than in female patients.

Cumulative patency rate of both groups depending on renal insufficiency and gender as risk factors

The cumulative patency rate is better in male patients without renal insufficiency with only one PTA at each time than in females. The cumulative patency rate of patients after a PTA with renal insufficiency is almost identical for both genders up to 2.5 years after the PTA and hardly differs after 2.5 years for female patients. Between 2.5 and 5 years after the intervention, male patients show significantly better patency rates than female. Without renal insufficiency, the cumulative patency rates of female patients do not differ significantly from those of male patients after PTA and stent implantation. Interestingly, after PTA and stent implantation with renal insufficiency, female patients show consistently better patency rates than male patients (Table 8). The COX I and II analyses show a clear gender-related dependence only in the presence of renal insufficiency ($p = 0.0027$), diabetes

mellitus ($p = 0.076$), with the use of a Boston stent ($p = 0.04$) lower also in the number of open lower leg vessels ($p = 0.106$) (Tables 8,9).

The patency rate of stent assisted PTA of pelvic vessels in male patients with or without renal insufficiency is better than in female patients only during the first 2.5 years, thereafter almost identical. Without renal insufficiency, male patients with stent assisted PTA of femoral vessels consistently outperformed females, whereas female patients with renal insufficiency consistently outperformed females after stent assisted PTA of femoral vessels. The results of PTA of the lower leg vessels, usually without stent implantation, were not statistically significant. In summary, male patients after stent supported PTA of the pelvic vessels do not benefit from a stent, in the femoral vessels only female patients benefit after PTA and stent implantation.

Discussion

Without consideration of the mutual influence of individual risk factors and gender, the systemic heparin administration started immediately after the intervention as a standard anticoagulant therapy in our study allows a better comparison of the final results of this study without the influence of the various anticoagulation regimens.

The main focus of our study was the gender dependence of long-term results. In our study, the cumulative patency rate in male CHD patients after PTA corresponds to the results of male patients without CHD. The cumulative patency rate in male patients after PTA and stenting without CHD is better in female patients until the 4th post-interventional year, after 7 years, the post-interventional outcome is almost identical in both groups.

There is no statistical relevance, but the cumulative patency rate in female patients after PTA and stenting with CHD as a risk factor throughout tends to be better than in male patients with CHD. Male patients benefit from PTA and stent implantation compared to female patients only within the first 4 years after intervention. However, the final results with and without stent implantation in male and female patients were not significantly different in the individual groups.

Table 8: Cumulative patency rates of both groups depending on renal insufficiency and gender as risk factors.

	2.5 Years (percentage)	5 Years (percentage)	7.5 Years (percentage)	10 Years (percentage)
Male, RF=0, PTA	82	59	43	34
Female, RF=0, PTA	54	42	37	22
Male, RF=1, PTA	84	74	51	51
Female, RF=1, PTA	83	63	63	63
Male, RF=0, Stent	72	54	50	50
Female, RF=0, Stent	72	57	51	47
Male, RF=1, Stent	76	58	58	58
Female, RF=1, Stent	81	81	81	81

Cumulative patency rates are presented in percentages.

Male, RF 0, PTA and female, RF 0, PTA $p = 0.0104$; Male, RF 0, PTA and female, RF 1, PTA $p = 0.0187$; Male, RF 0, Stent and female RF 0, Stent $p = 0.703$ Male RF 1; Stent and female RF 1, Stent $p = 0.306$; The most significant difference.

Male, RF 0, PTA and female, RF 0, PTA ($p = 0.0104$), female RF 0, PTA and male, RF 1, PTA ($p = 0.0179$), female, RF 0, PTA and female, RF 1, PTA ($p = 0.0187$), female, RF 0, PTA and male, RF 0, stent ($p = 0.033$), female, RF0, PTA and male, RF 1, stent ($p = 0.0255$), female, RF 0, PTA and female, RF1, stent ($p = 0.0316$)

Table 9: Cumulative patency rates of treated vessels groups depending on renal insufficiency and gender as risk factors.

	2.5 years (percentage)	5 years (percentage)	7.5 years (percentage)	10 years (percentage)
G-I, RF=0, M	83	65	59	56
G-I, RF=0, W	71	66	66	66
G-I, RF=1, M	93	63	63	63
G-I RF=1, W	89	66	66	66
G-II, RF=0, M	70	46	37	25
G-II, RF=0, W	53	35	29	17
G-II, RF=1, M	74	66	42	42
G-II, RF=1, W	71	71	71	71
G-III, RF=0, M	77	77	57	57
G-III, RF=0, W	100	100	100	100
G-III, RF=1, M	100	75	75	75
G-III, RF=1, W	-	-	-	-

Legends: Cumulative patency rates are presented in percentages.

GI: Iliaca communis and externa artery, GII: femoralis superficialis artery, prof. fem. artery, poplitea artery I, II and III. segment.

GII, RF 0, male versus GI, RF 0, male, $p = 0.00173$; GII, RF 0, female versus GI, RF 0, male, $p = 0.00000282$; GII, RF 0, female versus GI, RF 0, female, $p = 0.00929$

GII, RF 0, female versus GI, RF 1, male, $p = 0.000144$; The most significant difference. GII, RF 0 1, female versus GI, RF 0, male, $p = 0.00000282$

The difference in the presence of renal insufficiency becomes even clearer in our study. Without renal insufficiency, the cumulative patency rate is better in male patients after a PTA at any time than in females. The cumulative patency rate of patients after PTA with renal failure is almost identical for both sexes up to 2.5 years after PTA, between 2.5 and 5 years after the intervention, male patients show significantly better patency rates than women. Without renal insufficiency, the cumulative patency rates of female patients do not differ significantly from those of male patients after PTA and stent implantation. Interestingly, female patients after PTA and stent implantation with renal insufficiency consistently show better patency rates than male patients. Essential factors leading to instentstenosis are the patient's risk profile, stenosis characteristics, clinical circumstances of PCI, and stent characteristics. Among the risk factors for patients, diabetes mellitus and chronic renal failure play key roles [14,20,21]. The long-term prognosis after a PTA depends significantly on the patient's gender and age at the time of treatment. The risk factors for the development of instentstenosis after coronary balloon angioplasty, such as female gender, combination of diabetes mellitus and dialysis requiring renal insufficiency together, previous interventions and resistance or hypersensitivity to anticoagulants, can probably also be extrapolated as risk factors to the PTA peripheral vessels [14,22].

The role of nicotine abuse, diabetes mellitus and hypercholesterinaemia in the development of stent stenosis is controversially discussed. Several studies on instentstenosis after coronary PTCA interventions have shown an influence between smoking and atherosclerosis only in patients with elevated serum cholesterol levels and the lack of development of atherosclerosis in patients with a low risk profile [23-25]. In another study, a precise analysis of the data shows that the primary patency rates of crural vessels are independent of nicotine consumption, sex, SIR class [26], outflow and diagnosis of diabetes mellitus [27]. Our results clearly contradict those of this study.

Foley, et al. even reported better long-term results after a PTA paradoxically in smokers [28], which were similarly confirmed by Piatkowski [33]. However, the results of this study depend on the type of stent used [28].

Despite controversial study results, diabetes mellitus is accepted as a predictive factor in the development of restenosis [29,30]. The long-term results in diabetic patients after a sole PTCA with 63% compared to non-diabetics with 36% on the one hand, and after a PTCA and stent implantation in non-diabetics with 27% compared to diabetics with 25% on the other, speak for a protective effect of stent implantation in diabetic patients [31].

Differentiated studies clearly relativises the role of hypercholesterolemia as a risk factor for instentstenosis [29-31].

Previous studies have also reported both a significantly lower patency rate and 2.8 fold increased risk of major amputation in dialysis patients [27].

The long term patency rate taking into account with arterial hypertension and hyperuricemia were collected but not presented in the results, apart from these risk factors, female patients with PTA and stent implantation have better long-term outcomes than male patients with all other risk factors. Male patients do not clearly benefit from stent implantation. Cumulative patency rates in male patients with one of the above risk factors were always worse after PTA and stent implantation than in male patients without stent implantation (Tables 10-12).

A differentiated analysis of the results depending on treated vessel segments shows that the results of stent assisted PTA's of comm. iliacal artery and external iliacal artery are significantly independent of risk factors better than femoral vessels, and these are better in female patients than in male patients. Male patients do not benefit significantly from stent implantation over the long term. As the COXI and II regression analyses show, gender-linked results are most evident for renal insufficiency and diabetes mellitus, and less pronounced also for the number of open lower leg vessels.



Table 10: ICox regression with Intervention (PTA/STENT) and gender as covariates.

Variable	HR	se(HR)	p - value
Intervention (stent)	1.038486	0.1529599	0.8049961
Gender (female)	1.250974	0.1653273	0.1756025

HR: Hazard Ratio; Intervention Basis Category, PTA, Gender Basis Category = Male

Table 11: II Cox regression with Intervention (PTA/stent) and gender and other covariates.

Variable	HR	se(HR)	p - value
Intervention Stent	1.3298519	0.3815454	0.4549795
Lower leg_vessel 2	0.8386196	0.2247841	0.4336476
Lower leg_vessel 3	0.7150981	0.2075761	0.1062062
CHD (Yes)	1.0328982	0.1906820	0.8652052
DM (Yes)	1.3609622	0.1739407	0.0764242
RF (Yes)	0.5249481	0.2152800	0.0027573
HLP (Yes)	1.0557270	0.1769297	0.7592212
AH (Yes)	1.3262374	0.2239902	0.2074790
HU (Yes)	1.0405584	0.2831417	0.8883317
Smoking (Yes)	1.2808951	0.2158999	0.2515311
Gender (Female)	1.3166465	0.1797612	0.1259432

HR: Hazard Ratio, Intervention Basis Category = PTA, Gender Basis Category = Male, Lower leg-vessel Basis Category = lower leg_vessel1
For all variables with (yes) the (no) class is the Basis Category

Table 12: II Cox regression with Intervention (PTA/stent) and gender depending on treated vessel sections.

Variable	HR	se(HR)	p - value
Vessel group GII	1.840906	0.20242	0.002571
Vessel group G III	0.631002	0.550135	0.40261
Lower leg vessel 2	0.828255	0.228407	0.409375
Lower leg vessel 3	0.773616	0.208579	0.218468
CHD (Yes)	0.937663	0.190949	0.736057
DM (Yes)	1.317862	0.176759	0.118405
RF (Yes)	0.526697	0.215915	0.002984
HLP (Yes)	1.133677	0.179511	0.484593
AH (Yes)	1.244156	0.224226	0.329921
HU (Yes)	0.95245	0.288863	0.866071
Smoking (Yes)	1.207825	0.217737	0.385835
Gender (Female)	1.315025	0.179933	0.128013

As this study shows, the long-term results after PTA of peripheral vessels are not only influenced by risk factors, but also by gender, male patients benefited less from stent implantation over the long term. In addition, the long-term results after PTA of femoral superficialis artery and poplitea artery are significantly worse than PTA of the pelvic vessels in both genders.

It appears that male patients tend to benefit less from stent implantation over the long term. In principle, bare stents are distinguished from drug-eluting stents. It is undisputed that nitinol stents show better long-term results than steel stents, which were proven in several studies to provide significantly better results 2 years post interventionem [32,33]. An explicit dependence of the results on implanted stents was not carried out to the high inhomogeneity of the stents used.

While the routine use of DEB in the femoropopliteal current path is based on a meaningful evidence situation with now 5 multicenter RCT studies from previous years, DES implantation is based on only one significantly positive RCT and registry study [34]. The long-term results of the 48-month Zilver PTX study [35,36] with a persistently significantly better

patency rate than in the BMS group, even in long lesions, must be verified by a longer observation period. The coating with polyvalent bound heparin, hirudin and prostacyclin or with immunosuppressants such as the mitosis inhibitor paclitaxel or the T-cell inhibitor sirolimus, which was introduced to reduce the primary thrombogenicity of drug-eluting stents (DES), did not lead to the hoped-for results either [37].

In addition to gender, risk factors, PAD stage at the time of treatment, TASC classification, calcification and previous interventions, intervention-dependent factors (stent types, etc.) in varying degrees also influence the long term patency results. The results of this study suggest, that gender-linked results are most evident for renal insufficiency and diabetes mellitus, and less pronounced also for the number of open lower leg vessels. For other risk factors, too, there seems to be a tendency towards gender dependence. In addition, the long-term results after PTA of femoral superficialis artery and poplitea artery are significantly worse than PTA of the pelvic vessels in both genders. However, further prospective studies will verify the relevance of these results depending on the vascular segments treated.



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