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# A retrospective angiographic study to determine the effect of atherosclerotic stenoses of upstream arteries on the degree of atherosclerosis in distal vascular territories

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## Abstract

**Objective:** Experimental coarctation of the aorta prevents the development of downstream atherosclerosis. The aim of this study was to find out whether or not atherosclerotic stenoses protect distal vascular territories from developing atherosclerosis in humans.

**Design and setting:** A total of 2125 vascular segments from angiographies of 101 patients were evaluated by calculating the maximum degree of stenosis (NASCET criteria), the degree of calcification, and the Friesinger score.

**Results:** Stenosis ≥30%–49% was found in 685 vascular segments (32.2%), ≥50%–69% was found in 490 (23.1%), ≥70–89%% in 373 (17.6%), and ≥90% in 265 (12.5%). If a stenosis of at least ≥70%–89% was present in the common iliac, the external iliac, or the common femoral artery, the degrees of stenosis distal to it were lower than on the contralateral side (19.8±22.3% [CI:11.7-28.0] vs. 25.2±20.7% [CI: 21.2-29.1]; Friesinger scores: 1.1±1.2 [CI:0.6-1.5] vs. 1.4±1.1 [CI:1.2-1.6]; degrees of calcification 0.8±1.0 [CI:0.4-1.1] vs. 1.2±1.1 [CI:1.2-1.6]; $p < 0.05$ each). This effect depended on the degree of proximal stenosis and was most pronounced distally to stenoses of the common iliac, the superficial femoral, and the popliteal artery. Ostial stenoses of the internal iliac artery were not relevant. In regression models, stenoses of the pelvic arteries revealed to be an independent protective factor for the distal vascular territories.

**Conclusions:** Atherosclerotic stenoses protect distal vascular territories from developing atherosclerosis. We hypothesize the pulse pressure reduction to be the crucial mechanism for this phenomenon.

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## Strengths and limitations of this study

- Stenoses in arteries can protect distal vascular territories from developing stenoses, wall irregularities, and calcifications - the observation that vascular territories distal to a stenosis of the pelvic or femoropopliteal arteries are affected by atherosclerosis to a lesser extent has never been circumstantiated before.
- The degree of stenoses of the common iliac artery and the external iliac artery is a protective factor independent of other protective or risk factors.
- The protective effect of stenoses as slight as 30-49% was demonstrated.
- The hypothesis that not just the level of blood pressure itself, but also the pulse pressure is relevant for developing atherosclerosis cannot be proven by present data.
- Further research is needed in order to elucidate the probable pathophysiological mechanism, i.e. the pulse pressure reduction.

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## Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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## Introduction

There are several patterns of "arterial occlusive disease" in great arteries[1] involving either mainly the coronary arteries, the branches of the aortic arch, the visceral branches of the aorta, or the distal aorta and its branches. Combinations of these patterns also occur.[1] The distal aorta and its branches can have iliac, femoropopliteal, or infragenual patterns of occlusive disease depending on the various vascular risk factors.[2] Women are more predisposed to a femoropopliteal, diffuse distribution of the disease,[3] while men tend to have an iliac pattern.[2] Smoking causes an aortoiliac pattern,[2] while diabetes[2] and kidney failure[4] are more likely to affect peripheral vessels. Arterial hypertension puts all vascular territories equally at risk.[2]

Additionally, local anatomical and physiological conditions are also significant,[5] namely the phenomena of "stress concentration"[5] and "wall fatigue due to pulsatile blood pressure".[5] The extent of stress at a given location is a function of the shape of the cross section, the wall thickness, and the outer curvature of the artery[5] as well as the heart rate, blood pressure, and blood pressure amplitude.[5] Therefore, origins of branches of arteries or the inner curvature of a curving artery in patients with a high heart rate are especially at risk.[5]

In animal experiments, the atheroprotective effect of the introduction of stenoses by coarctation of the aorta as a local anatomical protective condition is well established.[6-8] In humans, it is known that intramyocardial segments of the coronary arteries are usually free of atherosclerosis. This is explained by the lower transmural pressure gradients and thus lower mural stress in comparison with free epicardial segments.[9] A similar principle is speculated as an explanation[5] of the rhythmic location of atherosclerotic lesions in the extraosseous – but not in the intraosseous – segments of the vertebral artery.[10] The observation that vascular territories distal to a clinical relevant stenosis of the pelvic or femoropopliteal arteries are affected by atherosclerosis to a lesser extent is familiar to many physicians involved in the treatment of the patients, but has never been circumstantiated.

This study aims to investigate the hypothesis that stenoses of great arteries are capable of protecting distant distal vascular territories from developing atherosclerosis in humans.

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## Patients and methods

Approval to conduct this study was obtained from the local ethics committee (No. AN2015-0198). The study was conducted in compliance with the most recent revision of the Declaration of Helsinki. The digital subtraction angiographies of the pelvis and legs of 101 consecutive Caucasian patients (31 women and 70 men, mean age 66.1 ± 10.8 years [CI:64.0-68.2]) were used. Demographic data of the patients, their clinical condition, and risk factors are presented in Table 1. All 101 patients had atherosclerosis. Ninety-nine patients (98%) had peripheral arterial occlusive disease of at least Fontaine stage IIb (Rutherford classification I/3),[11, 12] one stage II (I/1) patient had a popliteal aneurysm, and one stage 1 (0/0) patient had an infrarenal aortic aneurysm. There were no treatment options for 13 patients (12.9%), 7 patients (6.9%) underwent surgical treatment (patch angioplasty of the CFA and SFA or popliteal bypass), 66 patients were treated with a stent (65.3%), 11 (10.9%) patients with a balloon angioplasty, and two patients (2%) with a stent in one region and a PTA in another region. A total of 86 (85.1%) patients came to at least one follow-up, 11 patients (10.9%) died within the follow-up period of 4 ± 3.6 months, and 7 patients required amputation – one at the thigh, the other 6 of the foot.

The examinations were made on a Siemens Artis Zee angiography system (Siemens Healthcare, Erlangen, Germany) or a Philips Allura Xper FD20 (Philips Healthcare, Best, the Netherlands), using a ruler. The arteries were divided into the following segments: infrarenal aorta, common iliac artery (CIA), external iliac artery (EIA), internal iliac artery (IIA), common femoral artery (CFA), profunda femoris artery (PFA), superficial femoral artery (SFA), popliteal artery (PI, PII, and PIII), tibiofibular trunk (TFT), anterior tibial artery (ATA), posterior tibial artery (PTA), and fibular artery (FA). There were a total of 2125 vascular segments (Table 2). The following parameters were examined and evaluated by consensus of two radiologists:

1. The maximum degree of stenosis in each segment of a vessel quantified using the NASCET criteria.[13] For this purpose, the difference of the diameters in and distal to the stenosis was divided by the distal diameter.

2. The Friesinger score of the segment, a six-point atherosclerosis score developed for coronary angiography.[14] The score 0 indicates no arteriographic abnormality, 1 means trivial irregularities with stenoses from 1–29%, 2 means localized luminal narrowing of 30–68%, 3 means multiple luminal narrowing of 30–68% in the same vessel, 4 means luminal narrowing of 69%–99%, and 5 means total occlusion.

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3. The degree of calcification on a scale of 0–5, with 0 meaning “no calcification”, 1 = discrete, 2 = slight, 3 = moderate, 4 = high-grade, and 5 extreme calcification with voluminous deposits that cause protrusion of the vascular wall.

For these evaluations, a Picture Acquisition and Communication System (IMPAX EE R20 VII P1, Agfa HealthCare NV, Mortsel, Belgium) was used. The 3D data set came from a volume rendering reconstruction of a CT angiography of the pelvis and legs (General Electric Discovery 750 CT, General Electric Company, Fairfield, CT, USA). The reconstruction was made at a 3D post-processing workstation (Advantage Workstation 4.6/VolumeShare 5, General Electric Company, Fairfield, CT, USA).

In addition, a qualitative evaluation was made of the risk factors smoking, hyperlipidemia, arterial hypertension, diabetes, and kidney failure and of the use of statins, antihypertensives, antidiabetics, anticoagulants, or antiplatelets. Blood pressure and pulse wave index were recorded.

To analyze the data, descriptive statistics were first created using Excel (Office 2007, Microsoft, Seattle, WA, USA). Distributions were examined using the Shapiro-Wilk test (Graph Pad Prism, GraphPad Software Inc. La Jolla, CA, USA). Mann-Whitney or Levene tests were used to investigate possible differences in the values or variances between the right and the left side; the Spearman ‘s correlation test was used to measure the agreement of the data between the right and left sides. A $\rho < 0.19$ was considered to be an indicator of a very weak correlation, 0.2–0.39 weak, 0.4–0.59 moderate, 0.6–0.79 strong, and >0.8 was a very strong correlation. After this analysis, the data on sides was discarded, i.e. they were now classified as side affected by a stenosis and contralateral side. Then the stenoses of the pelvic arteries were arbitrarily classified in groups of 0–29%, 30–49%, 50–69%, 70–89%, and 90–100% stenosis. Depending on the degree of stenosis at each level, e.g. of the CIA, two groups of patients were formed, namely those with a stenosis of that degree and those without. The segments of the lower limb distal to the respective “classification level” were assigned to one of the two groups accordingly and compared with one another with respect to the NASCET degree of stenosis, the Friesinger score, and the severity of calcification using the Mann-Whitney test. Frequency analyses of the variables “degree of stenosis (NASCET)”, “Friesinger score”, and “severity of calcification” yielded two groups of histograms: a group with a relatively low percentage of more severe lesions (CIA, EIA, CFA) and a group with a higher percentage of more severe lesions (SFA; PI, PII, PIII). In order to present the effect of stenosis of the pelvic vascular territory as an example of the results, a binning was conducted on the base of the frequency analyses so that the CFA was grouped with the CIA and EIA. The most severe stenosis in the CIA/EIA/CFA was assessed as a classification criterion. The data distal to the lesion were normalized to those on the contralateral side so that they could be expressed in % of the contralateral side (0%). They were entered on an

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ordinate over the corresponding segment location on the abscissa. The classification of the data according to the degree of stenosis of the main stem of the IIA, on which no distal territories of the thigh depend, was used as an internal control. Finally, linear regression analyses were conducted on the factor "degree of stenosis (NASCET)" at every level, first including all factors, and then based on these models in forward stepwise selection procedures (SPSS 23, IBM, Armonk, NY, USA). To present the results, the software Prism 6 (Graph Pad Prism, GraphPad Software Inc. La Jolla, CA, USA), Adobe Illustrator CC (Adobe Systems Inc., San José, CA, USA), and CorelDraw Graphics Suite (X7, Corel Inc., Ottawa, Canada) were used. A $p < 0.05$ was considered to be significant.

## Results

The main risk factors for PAOD in the group were arterial hypertension (n = 76; 75.2%), smoking (n = 64; 63.4%), diabetes (n = 28; 27.7%), and kidney failure (n = 20; 19.8%). Two patients (2%) had Fontaine stage I PAOD, 62 (61.4%) had stage IIb, 16 (15.8%) stage 3, and 21 (20.8%) stage 4. The initial procedure was successful in all 86 patients; 13 patients required a reintervention and/or a second procedure during the follow-up period to improve flow to or from the same limb (Table 1). In 8 cases, this was a femoral bifurcation reconstruction and/or femoropopliteal bypass, in 4 cases an additional endovascular procedure, and lysis in one case. Of a total of 2125 segments of vessels, 685 (32.2%) had stenosis of ≥30%–49%, 490 (23.1%) ≥50%–69%, 373 (17.6%) ≥70%–89%, and 265 (12.5%) ≥90% (Table 2).

The diameters of all segments of vessels were distributed normally; all other parameters were not distributed normally. The medians, means, and variances of all parameters were the same on both sides. The severity of the stenoses, Friesinger scores, and calcification correlated horizontally weakly to moderately ($p < 0.0001$ each), and longitudinally very weakly to moderately (ns; $p < 0.0001$).

If at least one stenosis ≥30%–49% was present along the pelvic axis (CIA, EIA, CFA), the degrees of stenosis distal to it were lower than on the contralateral side (23.3 ± 21.3% [CI:18.9-27.7] vs. 25.3 ± 20.9% [CI:19.2-31.5]; Friesinger scores: 1.3 ± 1.1 [CI:1.0-1.5] vs. 1.5 ± 1.2 [CI:1.1-1.8]; degrees of calcification: 1.0 ± 1.1 [CI:0.8-1.2] vs. 1.2 ± 1.2 [CI:0.9-1.6], $p > 0.05$ each). If at least one stenosis ≥50%–69% was present, the degrees of stenosis distal to it were lower than on the contralateral side (21.0 ± 19.0% [CI:16.1-26.0] vs. 26.2 ± 22.3% [CI:21.1-31.2], $p > 0.05$; Friesinger scores: 1.1 ± 1.0 [CI:0.8-1.4] vs. 1.5 ± 1.2 [CI:1.3-1.8], $p = 0.007$; degrees of calcification: 0.8 ± 1 [CI:0.6-1.1] vs. 1.3 ± 1.2 [CI:1.0-1.5], $p = 0.0225$). If at least one stenosis ≥70%–89% was present, the degrees of stenosis distal to it were lower than on the contralateral side (19.8±22.3% [CI:11.7-28.0] vs. 25.2±20.7% [CI:

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21.2-29.1], p = 0.028; Friesinger scores: 1.1±1.2 [CI:0.6-1.5] vs. 1.4±1.1 [CI:1.2-1.6], p = 0.0245; degrees of calcification 0.8±1.0 [CI:0.4-1.1] vs. 1.2±1.1 [CI:1.2-1.6], p = 0.0195). If at least one stenosis ≥90% was present, the degrees of stenosis distal to it were lower than on the contralateral side (23.3 ± 24.7% [CI:8.4-38.3] vs. 24 ± 20.8% [CI:20.4-27.7]; Friesinger scores: 1.2 ± 1.3 [CI: 0.4-2.0] vs. 1.4 ± 1.1 [CI: 1.1-1.6]; degrees of calcification: 0.7 ± 0.7 [CI:0.3-1.1] vs. 1.1 ± 1.1; p > 0.05 each).

The main stem of the IIA was used as an internal control. If a stenosis of at least ≥30%–49% was present in this location, the degrees of stenosis distal to it were the same as on the contralateral side (24.5 ± 20.5% [CI:19.1-29.9] vs. 23.6 ± 21.6% [CI:18.8-28.4]; Friesinger scores: 1.4 ± 1.1 [CI:1.1-1.7] vs. 1.3 ± 1.2 [CI:1.1-1.6]; degrees of calcification: 1.1 ± 1.1 [CI:0.8-1.4] vs. 1.1 ± 1.1 [CI:0.8-1.3], p > 0.05 each). If a stenosis of at least ≥50%–69% was present, the degrees of stenosis distal to it were the same as on the contralateral side (25.2 ± 21.6% [CI:18.7-31.7] vs. 23.4 ± 20.9% [CI:19.1-27.7]; Friesinger scores: 1.4 ± 1.2 [CI:1.1-1.8] vs. 1.3 ± 1.2 [CI:1.1-1.5]; degrees of calcification: 1.1 ± 1.1 [CI:0.8-1.5] vs. 1.0 ± 1.1 [CI:0.8-1.3], p > 0.05 each). If a stenosis of at least ≥70%–89% was present, the degrees of stenosis distal to it were the same as on the contralateral side (24.4 ± 23% [CI:16.4-32.4] vs. 23.8 ± 20.7% [CI:19.8-27.8]; Friesinger scores: 1.3 ± 1.2 [CI:0.9-1.7] vs. 1.4 ± 1.2 [CI:1.1-1.6]; degrees of calcification 1 ± 1.2 [CI:0.6-1.5] vs. 1 ± 1.2 [CI:0.9-1.3], p > 0.05 each). If a stenosis of at least ≥90% was present, the degrees of stenosis distal to it were the same as on the contralateral side (25.6 ± 24.6% [CI:14.7-36.5] vs. 23.7 ± 20.5% [CI:20.0-127.4]; Friesinger scores: 1.4 ± 1.3 [CI:0.8-1.9] vs. 1.3 ± 1.1 [CI:1.1-1.5]; degrees of calcification: 1.1 ± 1.3 [CI:0.6-1.7] vs. 1.1 ± 1.1 [CI:0.8-1.2], p > 0.05 each).

The significance levels of all tests of the differences between the segments in relation to the respective classification level are shown in Table 3. The effects were most pronounced for stenoses of the CIA and the SFA.

Figure 1 shows the association of stenoses of pelvic vessels (CIA/EIA/CFA) ≥30%–49%; ≥50%–69%, ≥70%–89%, or ≥90% with the extent of the degrees of stenosis distal to them as a percentage comparison with the contralateral side, calcifications, and the Friesinger scores.

Figure 2 shows the standardized coefficients of the independent risk factors identified on the regression models with respect to the degree of maximum stenosis at the pelvic level, femoropopliteal region, and the crural region. While in the pelvis, smoking was found to be the most important risk factor before the pulse wave index, in the femoropopliteal region it was PWI before age, use of statins, and oral anticoagulation. The degree of stenosis in the pelvis (NASCET), and the BMI were found to be independent protective factors. In the crural region, age was the most significant influencing factor before the PWI.

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## Discussion

This study shows that stenoses in arteries can protect distal vascular territories from developing stenoses, wall irregularities, and calcification. This applies to stenosis as mild as 30% (NASCET). If the stenosis is located in the CIA, associated reductions of the degree of stenosis are found in the EIA, not in the CFA, but even more pronounced in the femoropopliteal and infragenual arteries. Stenoses in the EIA or CFA are less significant, but stenoses in the femoropopliteal region have an atheroprotective effect on almost every vascular territory distal to these segments. When the pelvic-leg vascular territory is subdivided into the pelvic level, the femoropopliteal level, and the tibial level,[2] the degree of stenosis in the iliac level located above is a protective factor independent of the other important risk factors. While as expected, smoking[2] and the PWI are the most important risk factors proximal to this, the most important protective factors are PWI and age in the femoropopliteal region and age at the crural level. Stenoses of the main stem of the IIA used as an internal control were not correlated with lesser degrees of atherosclerosis in the distal vascular territories: The slight positive correlations of the degrees of stenosis of the IIA with the degrees of stenosis of all other vascular segments were not statistically significant.

This thus supports the hypothesis that not just the level of blood pressure itself, but also the pulse pressure is relevant for developing atherosclerosis.[5] While flow acceleration and turbulence occurs within stenoses, the flow decelerates in the separation zone immediately downstream. At this location, a recirculation flow causes post-stenotic dilatation due to elevated transmural pressure, while 1–2 cm further distal, laminar flow is restored.[15] Distal to this, flow is characterized by small, late arterial pulses, known as pulsus parvus et tardus, which is found in the entire dependent vascular territory.[16]

In comparison with the EIA, the protective effect of the CIA is considerably stronger. This could be attributed to the fact that stenoses of the CIA cannot be collateralized as well as stenoses of the EIA, since there is no possibility of diverting via the ipsilateral IIA. The lack of significance of the effect of stenoses of the CFA is likely due to the shortness of this vascular segment and the resulting low number of stenoses, while the pronounced and significant associations of stenoses of the SFA, the popliteal artery, and the TFT with less pronounced stenoses, Friesinger scores, and degrees of calcification distal to them can be explained by the poor collateralization options in comparison with the pelvic level. Although no territory distal to the PFA is immediately dependent on it, stenoses at this level appear to be relevant. The reason for this is that most of these cases involved lesions of the bifurcation of the CFA, a pattern that is not rare.[17] This region meets the conditions for high local stress, such as are present at the carotid bifurcation or at the aortic bifurcation: a greater cross

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section, bending effects, reduced thickness, and opposite curvatures.[5] The femoral bifurcation is therefore considered to be a vulnerable site where an isolated stenosis of the PFA rarely occurs.

This study has limitations. The first limitation that should be mentioned is the retrospective study design, which can be the source of a selection bias. However, the study meets the criteria for evidence level I.[18] The sample consisted of consecutive patients with pronounced atherosclerosis, the main risk factors for atherosclerosis were represented, and the number of 2125 segments evaluated was high. However, the number of patients, although not small at 101, limited the possibilities of multivariate analyses. Additional studies must be conducted to determine the exact extent of the magnitude of the protective effect of stenoses on distal vascular territories. However, the very good agreement of the location-related effects of the standard risk factors with literature indicates that a good estimate of the magnitude was made. The significance of pulse pressure as a cardiovascular risk factor is well established.[19-23] It contributes to the development of atherosclerosis independently of the classical risk factors.[24] While the positive effects of lowering the heart rate[5, 25] and the blood pressure[26, 27] are known, it is still unclear whether or not lowering the pulse pressure results in a protective effect in humans. However, as the study was performed retrospectively, we were not able to measure the pulse pressure distally to the stenoses. This main weakness of the study can only be addressed with prospective, longitudinal observational studies.

Clinical implications of this observation are conceivable. Dilatations of not clinically manifest stenoses detected as incidental findings “in passing” in coronary angiographies, for example, could possibly be counterproductive for the distal vascular territory. A stenosis that is not relevant is dilated and the atherosclerosis distal to it could progress even more. In the kidney, for example, this could mean faster progression of glomerulosclerosis, in the supraaortic region faster progression of cerebral microangiopathy. By analogy with the studies of animal experiments in which the atheroprotective effect of coarctation was proven,[6-8] it would be possible to introduce low-grade stenoses using vascular or endovascular surgery, e.g. proximal to aneurysms of the aorta or the cerebral vessels that require treatment that is either technically difficult or risky or which cannot be treated with other methods for clinical reasons. This modification of the pulse pressure would be possible, for example with a simple bending, but also with stents, which could be similar to those used for reducing a TIPS.[28, 29]

Longitudinal, prospective studies will be needed to prove the hypothetical negative effect on the distal vascular territory of treating a stenosis. It is probable that the most suitable patients for this will be those with constellations in which a PAOD IIb is present on one side and a not clinically manifest stenosis is present at the same level on the other side or in which a stenosis of the carotid artery is treated, but not an additional contralateral stenosis.

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In conclusion, this study shows that atherosclerotic stenoses protect distant distal vascular territories from developing atherosclerosis. The practice of automatically performing dilatation of stenoses discovered as an incidental finding during endovascular treatment of clinically relevant stenoses must therefore be reconsidered. Treatment involving the introduction of stenoses to protect a vascular territory is conceivable.

## Contributors

RR, JP, AM, and BG contributed to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; in drafting the work and revising it critically for important intellectual content; and in giving final approval of the version to be published. RR and BG were the main investigators of this study.

AG, HZ, AL, AEG, and JK contributed to the acquisition of data for the work; in partially drafting the work in revising it critically for important intellectual content; and in giving final approval of the version to be published.

All authors (RR, JP, AG, HZ, AM, AL, AEG, JK, and BG) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Data Sharing Statement

If accepted for publication, data will be available on individual request.

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**Table 1**

| | | All | Mean | Women | Mean | Men | Mean |
|---|---|---|---|---|---|---|---|
| **N** | | 101 (100%) | - | 31 (30,7%) | - | 70 (69,3%) | - |
| **Legs** | | 202 (100%) | - | 62 (30,7%) | - | 140 (69,3%) | - |
| **Age** | | 38 - 91 | 66,1 ± 10,8 | 46 - 89 | 69,7 ± 10,8 | 38 - 91 | 64,5 ± 10,5 |
| **BMI** | | 15,8 - 41,1 | 25,8 ± 4,7 | 15,8 - 41,1 | 24,6 ± 5,2 | 16,6 - 39,9 | 25,9 ± 4,4 |
| **BP syst.** | | 113 - 190 | 154,8 ± 18,9 | 113 - 185 | 153,2 ± 18,5 | 117 - 190 | 155,5 ± 19,2 |
| **BP diast.** | | 50 - 109 | 80,7 ± 11,2 | 50 - 105 | 79,0 ± 11,5 | 57 - 109 | 81,5 ± 11,2 |
| **DM** | *y* | 28 (27,7%) | - | 10 (32,3%) | - | 18 (25,7%) | - |
| | *n* | 73 (72,3%) | | 21 (67,7%) | | 52 (74,3%) | |
| **RI** | *y* | 20 (19,8%) | - | 8 (25,8%) | - | 12 (12,1%) | - |
| | *n* | 81 (80,2%) | | 23 (74,2%) | | 58 (82,9%) | |
| **Control** | *y* | 86 (85,1%) | | 27 (87,1%) | | 59 (84,3%) | |
| | *n* | 11 (10,9%) | - | 2 (6,5%) | - | 9 (12,9%) | - |
| | *na* | 4 (4,0%) | | 2 (6,5%) | | 2 (2,9%) | |
| **Major amputation** | *y* | 7 (6,9%) | - | 4 (12,9%) | - | 3 (4,3%) | - |
| | *n* | 94 (93,1%) | | (87,1%) | | (95,7%) | |
| **Deceased** | *y* | 10 (9,9%) | - | 4 (12,9%) | - | 6 (8,6%) | - |
| | *n* | 91 (90,1%) | | (87,1%) | | 64 (91,4%) | |
| **OAC** | *y* | 17 (16,8%) | - | 6 (19,4%) | - | 11 (15,7%) | - |
| | *n* | 84 (83,2%) | | 25 (80,6%) | | 59 (84,3%) | |
| **HMG-CoA RI** | *y* | 85 (84,2%) | - | 22 (71,0%) | - | 63 (90,0%) | - |
| | *n* | 16 (15,8%) | | 9 (29,0%) | | 7 (10,0%) | |
| **APD** | *y* | 91 (90,1%) | - | 28 (90,3%) | - | 63 (90,0%) | - |
| | *n* | 10 (9,9%) | | 3 (9,7%) | | 7 (10,0%) | |
| **Smoker** | *y* | 64 (63,4%) | - | 17 (54,8%) | - | 47 (67,1%) | - |
| | *n* | 37 (36,6%) | | 14 (45,2) | | 23 (32,9%) | |
| **Arterial hypertension** | *y* | 76 (75,2%) | - | 28 (90,3%) | - | 48 (68,6%) | - |
| | *n* | 25 (24,8%) | | 3 (9,7%) | | 22 (31,4%) | |
| **Fontaine** | | | | | | | |
| **1** | | 2 (2,0%) | - | 1 (3,2%) | - | 1 (1,4%) | - |
| **2** | | 62 (61,4%) | - | 17 (54,8%) | - | 45 (64,3%) | - |
| **3** | | 16 (15,8%) | - | 7 (22,6%) | - | 9 (12,9%) | - |
| **4** | | 21 (20,8%) | - | 6 (19,4%) | - | 15 (21,4%) | - |

**Table 1:** Baseline characteristics of the patient group, as well as of the group divided into women and men. [Abbreviations: Y – Yes; n – No; BMI - Body mass index; BP - Blood pressure; DM - Diabetes mellitus; RI - Renal insufficiency; OAC - Oral anticoagulation; RI - Reductase inhibitor; APD - Antiplatelet drug]

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**Table 2**

| | | Degree of stenosis (NASCET) | | | | Friesinger score (0-5) | | | | | | Degree of calcification (0-5) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Vessel** | **N** | **30-50%** | **50-70%** | **70-90%** | **≥90%** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** |
| **AIC** | 202 | 86 | 47 | 27 | 14 | 26 | 87 | 52 | 7 | 17 | 13 | 37 | 40 | 44 | 43 | 24 | 14 |
| | | *42,6%* | *23,3%* | *13,4%* | *6,9%* | *12,9%* | *43,1%* | *25,7%* | *3,5%* | *8,4%* | *6,4%* | *18,3%* | *19,8%* | *21,8%* | *21,3%* | *11,9%* | *6,9%* |
| **AIE** | 202 | 72 | 49 | 24 | 9 | 26 | 87 | 52 | 7 | 17 | 13 | 78 | 50 | 26 | 25 | 19 | 4 |
| | | *35,6%* | *24,3%* | *11,9%* | *4,5%* | *12,9%* | *43,1%* | *25,7%* | *3,5%* | *8,4%* | *6,4%* | *38,6%* | *24,8%* | *12,9%* | *12,4%* | *9,4%* | *2,0%* |
| **AII** | 202 | 82 | 60 | 43 | 27 | 49 | 75 | 34 | 1 | 18 | 25 | 81 | 49 | 35 | 17 | 15 | 5 |
| | | *40,6%* | *29,7%* | *21,3%* | *13,4%* | *24,3%* | *37,1%* | *16,8%* | *0,5%* | *8,9%* | *12,4%* | *40,1%* | *24,3%* | *17,3%* | *8,4%* | *7,4%* | *2,5%* |
| **AFC** | 201 | 36 | 17 | 8 | 2 | 64 | 102 | 26 | 1 | 6 | 2 | 81 | 57 | 35 | 19 | 6 | 3 |
| | | *17,9%* | *8,5%* | *4,0%* | *1,0%* | *31,8%* | *50,7%* | *12,9%* | *0,5%* | *3,0%* | *1,0%* | *40,3%* | *28,4%* | *17,4%* | *9,5%* | *3,0%* | *1,5%* |
| **APF** | 195 | 20 | 9 | 3 | 2 | 107 | 70 | 14 | 1 | 1 | 2 | 120 | 42 | 22 | 7 | 2 | 2 |
| | | *10,3%* | *4,6%* | *1,5%* | *1,0%* | *54,9%* | *35,9%* | *7,2%* | *0,5%* | *0,5%* | *1,0%* | *61,5%* | *21,5%* | *11,3%* | *3,6%* | *1,0%* | *1,0%* |
| **AFS** | 192 | 108 | 87 | 73 | 44 | 50 | 33 | 19 | 19 | 23 | 48 | 60 | 21 | 21 | 33 | 22 | 35 |
| | | *56,3%* | *45,3%* | *38,0%* | *22,9%* | *26,0%* | *17,2%* | *9,9%* | *9,9%* | *12,0%* | *25,0%* | *31,3%* | *10,9%* | *10,9%* | *17,2%* | *11,5%* | *18,2%* |
| **P1** | 166 | 48 | 30 | 25 | 22 | 61 | 56 | 24 | 1 | 3 | 21 | 73 | 38 | 18 | 46 | 8 | 13 |
| | | *28,9%* | *18,1%* | *15,1%* | *13,3%* | *36,7%* | *33,7%* | *14,5%* | *0,6%* | *1,8%* | *12,7%* | *44,0%* | *22,9%* | *10,8%* | *9,6%* | *4,8%* | *7,8%* |
| **P2** | 168 | 34 | 25 | 22 | 21 | 75 | 57 | 11 | 2 | 1 | 22 | 87 | 37 | 19 | 10 | 4 | 11 |
| | | *20,2%* | *14,9%* | *13,1%* | *12,5%* | *44,6%* | *33,9%* | *6,5%* | *1,2%* | *0,6%* | *13,1%* | *43,1%* | *18,3%* | *9,4%* | *5,0%* | *2,0%* | *5,4%* |
| **P3** | 162 | 29 | 21 | 18 | 17 | 104 | 30 | 7 | 0 | 2 | 19 | 109 | 28 | 8 | 6 | 2 | 9 |
| | | 17,9% | 13,0% | 11,1% | 10,5% | 64,2% | 18,5% | 4,3% | 0,0% | 1,2% | 11,7% | 67,3% | 17,3% | 4,9% | 3,7% | 1,2% | 5,6% |
| **TTF** | 150 | 26 | 19 | 15 | 15 | 92 | 31 | 8 | 2 | 1 | 16 | 105 | 18 | 9 | 5 | 3 | 10 |
| | | 17,3% | 12,7% | 10,0% | 10,0% | 61,3% | 20,7% | 5,3% | 1,3% | 0,7% | 10,7% | 70,0% | 12,0% | 6,0% | 3,3% | 2,0% | 6,7% |
| **ATA** | 166 | 58 | 48 | 44 | 33 | 86 | 24 | 8 | 3 | 6 | 39 | 114 | 16 | 5 | 9 | 9 | 13 |
| | | 34,9% | 28,9% | 26,5% | 19,9% | 51,8% | 14,5% | 4,8% | 1,8% | 3,6% | 23,5% | 68,7% | 9,6% | 3,0% | 5,4% | 5,4% | 7,8% |
| **ATP** | 157 | 53 | 50 | 47 | 36 | 79 | 27 | 3 | 1 | 3 | 44 | 102 | 22 | 10 | 4 | 5 | 14 |
| | | 33,8% | 31,8% | 29,9% | 22,9% | 50,3% | 17,2% | 1,9% | 0,6% | 1,9% | 28,0% | 65,0% | 14,0% | 6,4% | 2,5% | 3,2% | 8,9% |
| **AF** | 164 | 33 | 28 | 24 | 23 | 85 | 40 | 8 | 0 | 0 | 31 | 113 | 22 | 16 | 3 | 2 | 8 |
| | | 20,1% | 17,1% | 14,6% | 14,0% | 51,8% | 24,4% | 4,9% | 0,0% | 0,0% | 18,9% | 68,9% | 13,4% | 9,8% | 1,8% | 1,2% | 4,9% |

**Table 2:** Absolute and relative numbers of stenoses within the arbitrarily stated ranges of degree in the respective arterial segments; numbers of Friesinger scores, and degrees of calcification. [Abbreviations: CIA - common iliac artery; EIA - external iliac artery; IIA - internal iliac artery; CFA - common femoral artery; PFA - profunda femoris artery; SFA - superficial femoral artery; PI, PII and PIII - popliteal artery segment I, II, or III; TFT - tibiofibular trunk; ATA - anterior tibial artery (ATA), PTA - posterior tibial artery; FA - fibular artery.]

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**Table 3**

| Difference | Nascet | EIA N | EIA F | EIA C | IIA N | IIA F | IIA C | CFA N | CFA F | CFA C | PFA N | PFA F | PFA C | SFA N | SFA F | SFA C | PI N | PI F | PI C | PII N | PII F | PII C | PIII N | PIII F | PIII C | TFT N | TFT F | TFT C | ATA N | ATA F | ATA C | PTA N | PTA F | PTA C | FA N | FA F | FA C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CIA | 30-49% | *n* | y | *n* | n | n | n | *n* | *n* | *n* | n | n | n | y | y | y | y | y | n | y | y | y | y | y | n | y | y | y | n | n | n | y | *n* | *n* | n | n | n |
| | 50-69% | y | *n* | *n* | n | n | n | *n* | *n* | *n* | y | y | y | y | y | y | y | y | n | y | y | y | y | y | y | y | y | y | n | n | n | *n* | *n* | y | n | n | n |
| | 70-89% | y | *n* | *n* | n | n | n | *n* | *n* | *n* | y | y | y | y | y | y | y | y | n | y | y | *n* | y | y | y | *n* | y | y | n | n | y | y | *n* | y | n | n | y |
| | ≥90 | y | *n* | *n* | n | n | n | *n* | *n* | *n* | y | n | n | *n* | y | y | n | n | n | y | *n* | *n* | y | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | y | n | n | y |
| EIA | 30-49% | | | | n | n | n | y | y | y | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| | 50-69% | | | | n | n | n | y | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | y | *n* | y | *n* | n | n | y | *n* | *n* | *n* | n | n | y | *n* | *n* | *n* | n | n | n |
| | 70-89% | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | y | y | n |
| | ≥90 | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| ***IIA*** | ***30-49%*** | | | | | | | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** |
| | ***50-69%*** | | | | | | | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** |
| | ***70-89%*** | | | | | | | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** |
| | ≥90 | | | | | | | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | n | n |
| CFA | 30-49% | | | | | | | | | | n | n | n | y | y | y | n | n | n | *n* | y | *n* | n | y | n | *n* | *n* | *n* | y | n | n | *n* | *n* | *n* | n | n | n |
| | 50-69% | | | | | | | | | | n | n | n | y | y | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| | 70-89% | | | | | | | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| | ≥90 | | | | | | | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| PFA | 30-49% | | | | | | | | | | | | | y | y | *n* | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | *n* | n | y | n |
| | 50-69% | | | | | | | | | | | | | y | y | *n* | y | y | n | y | y | *n* | n | y | n | y | y | *n* | y | y | y | *n* | *n* | *n* | n | y | n |
| | 70-89% | | | | | | | | | | | | | *n* | *n* | y | n | n | n | y | y | *n* | n | y | n | y | y | *n* | y | y | y | n | n | n | n | y | n |
| | ≥90 | | | | | | | | | | | | | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | y | n | n | y | *n* | *n* | n | n | y | n | *n* | *n* | y | y | y |
| SFA | 30-49% | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | n | y | y |
| | 50-69% | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | y | n | y | y | y | y | y | n | y | y |
| | 70-89% | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | n | y | *n* | y | n | y | *n* | *n* | n | n | n | n | n |
| | ≥90 | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | n | y | *n* | y | n | y | *n* | *n* | n | n | n | n | n |
| $P^{1st}$ | 30-49% | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y |
| | 50-69% | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | n | y | y | y | y | y | y | y | y |
| | 70-89% | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | *n* | y | y | y | n | y | y | y | n | n | n |
| | ≥90 | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | n | y | y | y | y | n | n | n |
| $P^{2nd}$ | 30-49% | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | | y | y |
| | 50-69% | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | y | y | y | y |
| | 70-89% | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | y | y | y | n |
| | ≥90 | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | y | y | y | n |
| $P^{3rd}$ | 30-49% | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | n | y | y |
| | 50-69% | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | n | y | y | y | n | y | n |
| | 70-89% | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | n | y | y | y | y | y | n |
| | ≥90 | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y | y | y | n |
| TFT | 30-49% | | | | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y |
| | 50-69% | | | | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y |
| | 70-89% | | | | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y |
| | ≥90 | | | | | | | | | | | | | | | | | | | | | | | | | | | | y | y | y | y | y | y | y | y | y |

**Table 3:** Significance levels of all tests of the differences between the segments in relation to the respective classification level. The effects are most pronounced for stenoses of the common iliac artery and the superficial femoral artery. No effects of stenoses of the internal iliac arteries, representing a segment without further distant distal depending territories as a virtual internal control. [Abbreviations: N - NASCET; C - calcification; F - Friesinger score]

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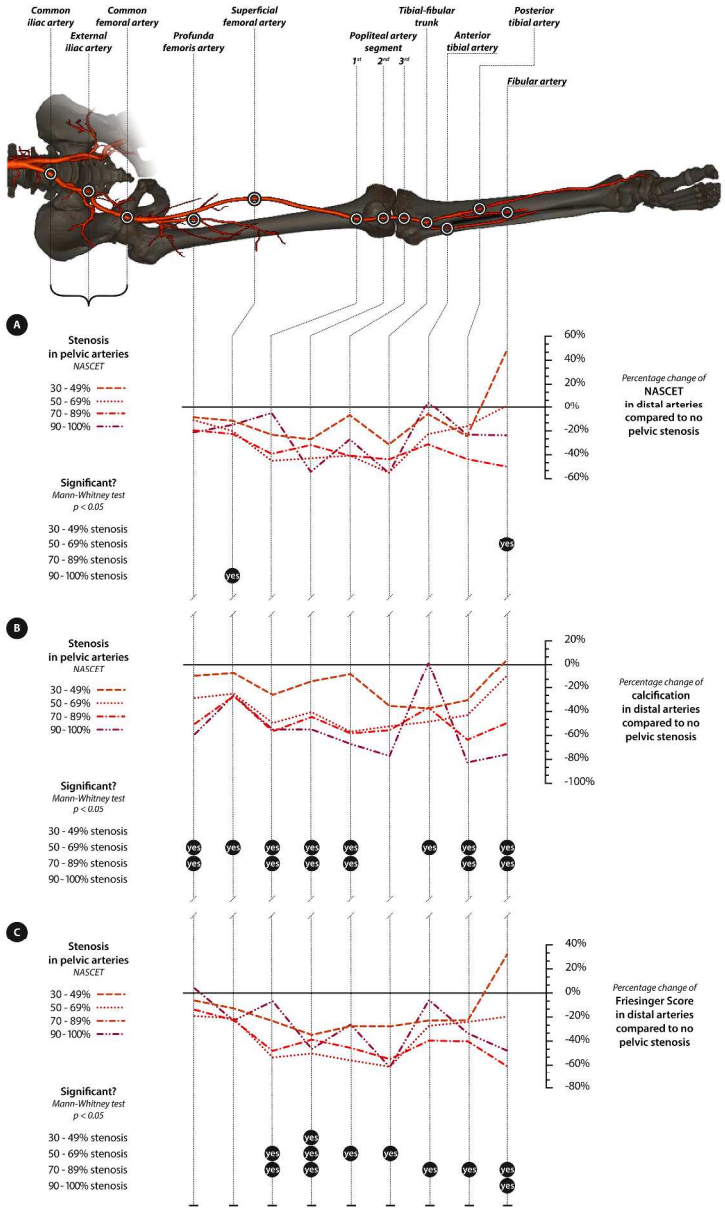


Association of stenoses of pelvic vessels (CIA/EIA/CFA) 30%–49%; 50%–69%, 70%–89%, or 90% with the extent of the degrees of stenosis distal to them as a percentage comparison with (A) the contralateral side, (B) calcifications, and (C) the Friesinger scores. Lower degrees of atherosclerotic burdens distal to stenoses of arteries of the pelvic level are striking.
292x478mm (300 x 300 DPI)

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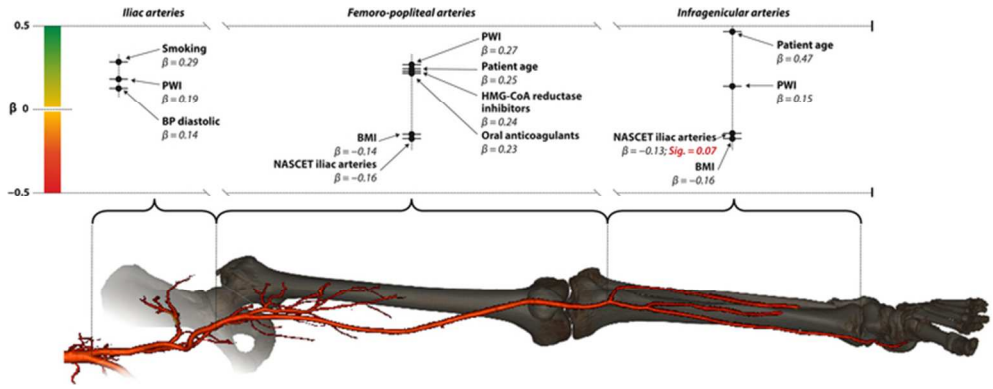


Standardized coefficients of the independent risk factors identified on the regression models with respect to the degree of maximum stenosis at the pelvic level, femoropopliteal region, and the crural region. The degree of stenosis in the pelvis was found to be an independent protective factor of the femoropopliteal region with respect to atherosclerosis.
67x25mm (300 x 300 DPI)

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5, 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5, 6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | n.a. |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5, 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *5, 6* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5, 6 |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6, 7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6, 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6, 7 |
| | | (*c*) Explain how missing data were addressed | 6, 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | n.a. |
| | | (*e*) Describe any sensitivity analyses | n.a. |
| **Results** | | | |

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| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5 |
| | | (b) Give reasons for non-participation at each stage | n.a. |
| | | (c) Consider use of a flow diagram | n.a. |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 5 |
| | | (b) Indicate number of participants with missing data for each variable of interest | n.a. |
| | | (c) Summarise follow-up time (eg, average and total amount) | n.a. |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | n.a. |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7, 8 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 7, 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n.a. |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 7, 8 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 9 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10, 11 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 4 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# A retrospective angiographic study to determine the effect of atherosclerotic stenoses of upstream arteries on the degree of atherosclerosis in distal vascular territories

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# A retrospective angiographic study to determine the effect of atherosclerotic stenoses of upstream arteries on the degree of atherosclerosis in distal vascular territories

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## Abstract

**Objective:** Experimental coarctation of the aorta prevents the development of downstream atherosclerosis. The aim of this study was to find out whether or not atherosclerotic stenoses protect distal vascular territories from developing atherosclerosis in humans.

**Design and setting:** A total of 2125 vascular segments from angiographies of 101 patients were evaluated by calculating the maximum degree of stenosis (NASCET criteria), the degree of calcification, the degree of collaterals, and the Friesinger score.

**Results:** Stenosis ≥30%–49% was found in 685 vascular segments (32.2%), ≥50%–69% in 490 (23.1%), ≥70–89%% in 373 (17.6%), and ≥90% in 265 (12.5%). If a stenosis of at least ≥70%–89% was present in the common iliac, the external iliac, or the common femoral artery, the degrees of stenosis distal to it were lower than on the contralateral side (19.8±22.3% [CI: 11.7-28.0] vs. 25.2±20.7% [CI: 21.2-29.1]; Friesinger scores: 1.1±1.2 [CI: 0.6-1.5] vs. 1.4±1.1 [CI: 1.2-1.6]; degrees of calcification 0.8±1.0 [CI: 0.4-1.1] vs. 1.2±1.1 [CI: 1.2-1.6]; $p < 0.05$ each). This effect depended on the degree of proximal stenosis, but not on collaterals and was most pronounced distal to stenoses of the common iliac, the superficial femoral, and the popliteal artery. In regression models, stenoses of the pelvic arteries were shown to be an independent protective factor for the distal vascular territories.

**Conclusions:** Atherosclerotic stenoses seem to protect distal vascular territories from developing atherosclerosis. The underlying pathophysiological mechanism of this phenomenon remains to be determined. It could be based on pulse pressure reduction.

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## Strengths and limitations of this study

- Stenoses in arteries can protect distal vascular territories from developing stenoses, wall irregularities, and calcifications – the observation that vascular territories distal to a stenosis of the pelvic or femoropopliteal arteries are affected by atherosclerosis to a lesser extent has never been circumstantiated before.
- The degree of stenosis of the common iliac artery and the external iliac artery is a protective factor independent of other protective or risk factors.
- The protective effect of stenoses as slight as 30-49% was demonstrated.
- The hypothesis that not just the level of blood pressure itself, but also the pulse pressure is relevant for developing atherosclerosis cannot be proven by present data.
- Further research is needed in order to elucidate the probable pathophysiological mechanism, i.e. the pulse pressure reduction.

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## Introduction

There are several patterns of "arterial occlusive disease" in great arteries[1] involving either mainly the coronary arteries, the branches of the aortic arch, the visceral branches of the aorta, or the distal aorta and its branches. Combinations of these patterns also occur.[1] The distal aorta and its branches can have iliac, femoropopliteal, or infragenual patterns of occlusive disease depending on the various vascular risk factors.[2] Women are more predisposed to a femoropopliteal, diffuse distribution of the disease,[3] while men tend to have an iliac pattern.[2] Smoking causes an aortoiliac pattern,[2] while diabetes[2] and kidney failure[4] are more likely to affect peripheral vessels. Arterial hypertension puts all vascular territories equally at risk.[2]

Additionally, local anatomical and physiological conditions are also significant,[5] namely the phenomena of "stress concentration"[5] and "wall fatigue due to pulsatile blood pressure".[5] The extent of stress at a given location is a function of the shape of the cross section, the wall thickness, and the outer curvature of the artery[5] as well as the heart rate, blood pressure, and blood pressure amplitude.[5] Therefore, origins of branches of arteries or the inner curvature of a curving artery in patients with a high heart rate are especially at risk.[5]

In animal experiments, the atheroprotective effect of the introduction of stenoses by coarctation of the aorta as a local anatomical protective condition is well established.[6-8] In humans, it is known that intramyocardial segments of the coronary arteries are usually free of atherosclerosis. This is explained by the lower transmural pressure gradients and thus lower mural stress in comparison with free epicardial segments.[9] A similar principle is speculated as an explanation[5] of the rhythmic location of atherosclerotic lesions in the extraosseous – but not in the intraosseous – segments of the vertebral artery.[10] The observation that vascular territories distal to a clinical relevant stenosis of the pelvic or femoropopliteal arteries are affected by atherosclerosis to a lesser extent is familiar to many physicians involved in the treatment of the patients, but has never been circumstantiated.

This study aims to investigate the hypothesis that stenoses of great arteries are capable of protecting distant distal vascular territories from developing atherosclerosis in humans.

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## Patients and methods

Approval to conduct this study was obtained from the Ethics Committee of the Medical University of Innsbruck (No. AN2015-0198). The study was conducted in compliance with the most recent revision of the Declaration of Helsinki. The digital subtraction angiographies of the pelvis and legs of 101 consecutive Caucasian patients (31 women and 70 men, mean age 66.1 ± 10.8 years [CI: 64.0-68.2]) were used. Demographic data of the patients, their clinical condition, and risk factors are presented in Table 1. All 101 patients had atherosclerosis. Ninety-nine patients (98%) had peripheral arterial occlusive disease of at least Fontaine stage IIb (Rutherford classification I/3),[11, 12] one stage II (I/1) patient had a popliteal aneurysm, and one stage 1 (0/0) patient had an infrarenal aortic aneurysm. There were no treatment options for 13 patients (12.9%), 7 patients (6.9%) underwent surgical treatment (patch angioplasty of the CFA and SFA or popliteal bypass), 66 patients were treated with a stent (65.3%), 11 (10.9%) patients with a balloon angioplasty, and two patients (2%) with a stent in one region and a PTA in another region. A total of 86 (85.1%) patients came to at least one follow-up, 11 patients (10.9%) died within the follow-up period of 4 ± 3.6 months, and 7 patients required amputation – one at the thigh, the other 6 of the foot.

The examinations were made on a Siemens Artis Zee angiography system (Siemens Healthcare, Erlangen, Germany) or a Philips Allura Xper FD20 (Philips Healthcare, Best, the Netherlands), using a ruler. The arteries were divided into the following segments: infrarenal aorta, common iliac artery (CIA), external iliac artery (EIA), internal iliac artery (IIA), common femoral artery (CFA), deep femoral artery (DFA), superficial femoral artery (SFA), popliteal artery (PI, PII, and PIII), tibiofibular trunk (TFT), anterior tibial artery (ATA), posterior tibial artery (PTA), and fibular artery (FA). There were a total of 2125 vascular segments (Table 2). The following parameters were examined and evaluated by consensus of two radiologists:

1. The maximum degree of stenosis in each segment of a vessel quantified using the NASCET criteria.[13] For this purpose, the difference of the diameters in and distal to the stenosis was divided by the distal diameter.

2. The Friesinger score of the segment, a six-point atherosclerosis score developed for coronary angiography.[14] The score 0 indicates no arteriographic abnormality, 1 = trivial irregularities with stenoses from 1–29%, 2 = localized luminal narrowing of 30–68%, 3 = multiple luminal narrowing of 30–68% in the same vessel, 4 = luminal narrowing of 69%–99%, and 5 = total occlusion.

3. The degree of calcification on a scale of 0–5, with 0 meaning “no calcification”, 1 = slight, 2 = low grade, 3 = moderate, 4 = high-grade, and 5 extreme calcification with voluminous deposits that cause protrusion of the vascular wall.



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4. The degree of collaterals in each vascular segment, beginning with “0” in segments with no collaterals. Slight collaterals at the detection limit were classified as “1”, low-grade collaterals as “2”, moderate collaterals as “3”, good collaterals as “4”, and very pronounced collaterals as “5”.

For these evaluations, a Picture Acquisition and Communication System (IMPAX EE R20 VII P1, Agfa HealthCare NV, Mortsel, Belgium) was used. The 3D data set came from a volume rendering reconstruction of a CT angiography of the pelvis and legs (General Electric Discovery 750 CT, General Electric Company, Fairfield, CT, USA). The reconstruction was made at a 3D post-processing workstation (Advantage Workstation 4.6/VolumeShare 5, General Electric Company, Fairfield, CT, USA).

In addition, a qualitative evaluation was made of the risk factors smoking, arterial hypertension, diabetes, and kidney failure and of the use of statins, antihypertensives, antidiabetics, anticoagulants, or antiplatelets. Blood pressure and pulse wave index (PWI) were recorded.

To analyze the data, descriptive statistics were first created using Excel (Office 2007, Microsoft Corp., Seattle, WA, USA). Distributions were examined using the Shapiro-Wilk test (Graph Pad Prism, GraphPad Software Inc., La Jolla, CA, USA). Mann-Whitney or Levene tests were used to investigate possible differences in the values or variances between the right and the left side; the Spearman ‘s correlation test was used to measure the agreement of the data between the right and left sides. A $\rho < 0.19$ was considered to be an indicator of a very weak correlation, 0.2–0.39 weak, 0.4–0.59 moderate, 0.6–0.79 strong, and >0.8 was a very strong correlation. After this analysis, the data on sides was discarded, i.e. they were now classified as side affected by a stenosis and contralateral side. Then the stenoses of the pelvic arteries were arbitrarily classified in groups of 0–29%, 30–49%, 50–69%, 70–89%, and 90–100% stenosis. Depending on the degree of stenosis at each level, e.g. of the CIA, two groups of patients were formed, namely those with a stenosis of that degree and those without. The segments of the lower limb distal to the respective “classification level” were assigned to one of the two groups accordingly and compared with one another with respect to the NASCET degree of stenosis, the Friesinger score, and the severity of calcification using the Mann-Whitney test. Frequency analyses of the variables “degree of stenosis (NASCET)”, “Friesinger score”, and “severity of calcification” yielded two groups of histograms: a group with a relatively low percentage of more severe lesions (CIA, EIA, CFA) and a group with a higher percentage of more severe lesions (SFA, PI, PII, PIII). In order to present the effect of stenosis of the pelvic vascular territory as an example of the results, a binning was conducted on the base of the frequency analyses so that the CFA was grouped with the CIA and EIA. The most severe stenosis in the CIA/EIA/CFA was assessed as a classification criterion. The data distal to the lesion were normalized to those on the contralateral side so that they could be expressed in % of the contralateral side (0%). They were entered on an

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ordinate over the corresponding segment location on the abscissa. The classification of the data according to the degree of stenosis of the main stem of the IIA, on which no distal territories of the thigh depend, was used as an internal control. Finally, linear regression analyses were conducted on the factor "degree of stenosis (NASCET)" at every level, first including all factors, and then based on these models in forward stepwise selection procedures (SPSS 23, IBM Corp., Armonk, NY, USA). Other significant risk factors for peripheral arterial occlusive disease were also considered. Adjustment was made for diabetes mellitus, smoking, age, arterial hypertension, and the use of statins. To present the results, the software Prism 6 (Graph Pad Prism, GraphPad Software Inc., La Jolla, CA, USA), Adobe Illustrator CC (Adobe Systems Inc., San José, CA, USA), and CorelDraw Graphics Suite (X7, Corel Inc., Ottawa, Canada) were used. A $p < 0.05$ was considered to be significant.

## Results

The main risk factors for PAOD in the group were arterial hypertension (n = 76; 75.2%), smoking (n = 64; 63.4%), diabetes (n = 28; 27.7%), and kidney failure (n = 20; 19.8%). Two patients (2%) had Fontaine stage I PAOD, 62 (61.4%) had stage IIb, 16 (15.8%) stage 3, and 21 (20.8%) stage 4. The initial procedure was successful in all 86 patients; 13 patients required a reintervention and/or a second procedure during the follow-up period to improve flow to or from the same limb (Table 1). In 8 cases, this was a femoral bifurcation reconstruction and/or femoropopliteal bypass, in 4 cases an additional endovascular procedure, and lysis in one case. Of a total of 2125 segments of vessels, 685 (32.2%) had stenosis of ≥30%–49%, 490 (23.1%) ≥50%–69%, 373 (17.6%) ≥70%–89%, and 265 (12.5%) ≥90% (Table 2).

The diameters of all segments of vessels were distributed normally; all other parameters were not distributed normally. The medians, means, and variances of all parameters were the same on both sides. The severity of the stenoses, Friesinger scores, and calcification correlated horizontally weakly to moderately ($p < 0.0001$ each), and longitudinally very weakly to moderately ($p < 0.0001$).

If at least one stenosis ≥30%–49% was present along the pelvic axis (CIA, EIA, CFA), the degrees of stenosis distal to it were lower than on the contralateral side (23.3 ± 21.3% [CI: 18.9-27.7] vs. 25.3 ± 20.9% [CI: 19.2-31.5]; Friesinger scores: 1.3 ± 1.1 [CI: 1.0-1.5] vs. 1.5 ± 1.2 [CI: 1.1-1.8]; degrees of calcification: 1.0 ± 1.1 [CI: 0.8-1.2] vs. 1.2 ± 1.2 [CI: 0.9-1.6], $p > 0.05$ each). If at least one stenosis ≥50%–69% was present, the degrees of stenosis distal to it were lower than on the contralateral side (21.0 ± 19.0% [CI: 16.1-26.0] vs. 26.2 ± 22.3% [CI: 21.1-31.2], $p > 0.05$; Friesinger scores: 1.1 ± 1.0 [CI: 0.8-1.4] vs. 1.5 ± 1.2 [CI: 1.3-1.8], $p = 0.007$; degrees of calcification: 0.8 ± 1 [CI: 0.6-1.1] vs. 1.3 ± 1.2

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[CI: 1.0-1.5], p = 0.0225). If at least one stenosis ≥70%–89% was present, the degrees of stenosis distal to it were lower than on the contralateral side (19.8±22.3% [CI: 11.7-28.0] vs. 25.2±20.7% [CI: 21.2-29.1], p = 0.028; Friesinger scores: 1.1±1.2 [CI: 0.6-1.5] vs. 1.4±1.1 [CI: 1.2-1.6], p = 0.0245; degrees of calcification 0.8±1.0 [CI: 0.4-1.1] vs. 1.2±1.1 [CI: 1.2-1.6], p = 0.0195). If at least one stenosis ≥90% was present, the degrees of stenosis distal to it were lower than on the contralateral side (23.3 ± 24.7% [CI: 8.4-38.3] vs. 24 ± 20.8% [CI: 20.4-27.7]; Friesinger scores: 1.2 ± 1.3 [CI: 0.4-2.0] vs. 1.4 ± 1.1 [CI: 1.1-1.6]; degrees of calcification: 0.7 ± 0.7 [CI: 0.3-1.1] vs. 1.1 ± 1.1; p > 0.05 each).

The main stem of the IIA was used as an internal control. If a stenosis of at least ≥30%–49% was present in this location, the degrees of stenosis distal to it were the same as on the contralateral side (24.5 ± 20.5% [CI: 19.1-29.9] vs. 23.6 ± 21.6% [CI: 18.8-28.4]; Friesinger scores: 1.4 ± 1.1 [CI: 1.1-1.7] vs. 1.3 ± 1.2 [CI: 1.1-1.6]; degrees of calcification: 1.1 ± 1.1 [CI: 0.8-1.4] vs. 1.1 ± 1.1 [CI: 0.8-1.3], p > 0.05 each). If a stenosis of at least ≥50%–69% was present, the degrees of stenosis distal to it were the same as on the contralateral side (25.2 ± 21.6% [CI: 18.7-31.7] vs. 23.4 ± 20.9% [CI: 19.1-27.7]; Friesinger scores: 1.4 ± 1.2 [CI: 1.1-1.8] vs. 1.3 ± 1.2 [CI: 1.1-1.5]; degrees of calcification: 1.1 ± 1.1 [CI: 0.8-1.5] vs. 1.0 ± 1.1 [CI: 0.8-1.3], p > 0.05 each). If a stenosis of at least ≥70%–89% was present, the degrees of stenosis distal to it were the same as on the contralateral side (24.4 ± 23% [CI: 16.4-32.4] vs. 23.8 ± 20.7% [CI: 19.8-27.8]; Friesinger scores: 1.3 ± 1.2 [CI: 0.9-1.7] vs. 1.4 ± 1.2 [CI: 1.1-1.6]; degrees of calcification 1 ± 1.2 [CI: 0.6-1.5] vs. 1 ± 1.2 [CI: 0.9-1.3], p > 0.05 each). If a stenosis of at least ≥90% was present, the degrees of stenosis distal to it were the same as on the contralateral side (25.6 ± 24.6% [CI: 14.7-36.5] vs. 23.7 ± 20.5% [CI: 20.0-127.4]; Friesinger scores: 1.4 ± 1.3 [CI: 0.8-1.9] vs. 1.3 ± 1.1 [CI: 1.1-1.5]; degrees of calcification: 1.1 ± 1.3 [CI: 0.6-1.7] vs. 1.1 ± 1.1 [CI: 0.8-1.2], p > 0.05 each).

The significance levels of all tests of the differences between the segments in relation to the respective classification level are shown in Table 3. The effects were most pronounced for stenoses of the CIA and the SFA.

The mean value of the iliac collaterals was estimated to be 0.5 ± 0.9 [CI: 0.3-0.6], femoropopliteal collaterals 0.5 ± 0.7 [CI: 0.4-0.6], and infragenual collaterals 0.3 ± 0.5 [CI: 0.2-0.4] (Table 1). The degree of stenosis of the arteries based on the NASCET correlated poorly, with a Spearman ρ = 0.3, but highly significantly (p=0.002) with the degree of collaterals. The degree of stenosis of the CIA and EIA did not correlate with the collaterals of the CIA and EIA (ρ=0.079; p=0.264), but correlated very weakly negatively with the femoropopliteal and crural arteries respectively (ρ=-0.158, p=0.046; ρ=-0.166, p=0.046). The degree of stenosis in the femoropopliteal arteries did not correlate with the collaterals of the CIA and EIA (ρ=-0.075, p=0.347), but correlated moderately with those of the

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femoropopliteal and crural arteries (ρ=0.565, p<0.0001; ρ=0.412, p<0.0001). The degree of stenosis in the crural arteries did not correlate with the collaterals of the CIA and EIA (ρ=-0.161, p=0.052), but correlated weakly to moderately with those of femoropopliteal and crural arteries respectively (ρ=0.36, p<0.0001; ρ=0.525, p<0.0001).

Figure 1 shows the association of stenoses of pelvic vessels (CIA/EIA/CFA) ≥30%–49%; ≥50%–69%, ≥70%–89%, or ≥90% with the extent of the degrees of stenosis distal to them as a percentage comparison with the contralateral side, calcifications, and the Friesinger scores.

Figure 2 shows the standardized coefficients (standardized for the risk factors diabetes mellitus, smoking, age, hypertension, etc.) of the independent risk factors identified on the regression models with respect to the degree of maximum stenosis at the pelvic level and in the femoropopliteal region and the crural region. While in the pelvis, smoking was found to be the most important risk factor before the IIA collaterals, the diastolic blood pressure, and the pulse wave index; in the femoropopliteal region it was PWI before SFA collaterals, HMG-CoA reductase inhibitors, popliteal artery first segment collaterals, and oral anticoagulation. The degree of stenosis in the pelvis (NASCET) was found to be an independent protective factor. In the crural region, the degree of FA collaterals was the most significant influencing factor before the TFT collaterals, patient age, PTA collaterals, and PWI.

## Discussion

This study shows that stenoses in arteries can protect distal vascular territories from developing stenoses, wall irregularities, and calcification. This applies to stenosis as mild as 30% (NASCET). If the stenosis is located in the CIA, associated reductions of the degree of stenosis are found in the EIA, not in the CFA, but even more pronounced in the femoropopliteal and infragenual arteries. Stenoses in the EIA or CFA are less significant, but stenoses in the femoropopliteal region have an atheroprotective effect on almost every vascular territory distal to these segments. When the pelvic-leg vascular territory is subdivided into the pelvic level, the femoropopliteal level, and the infragenual level,[2] the degree of stenosis at the iliac level is a protective factor, before the development of femoropopliteal stenoses, independent of the other important risk factors.

As expected, smoking[2] was the most important risk factor for the degree of iliac stenoses, before IIA collaterals, diastolic blood pressure, and PWI. The most important risk factor for femoropopliteal stenoses was PWI, before SFA collaterals, statins as a surrogate parameter for hypercholesterolemia, the PA first segment collaterals, and oral anticoagulation. The only protective factor was the degree



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of iliac stenosis: A high NASCET degree of iliac stenosis protects the femoropopliteal vascular region. The risk factors for the infragenual arteries included the familial disposition, TFT, PTA collaterals, age, and PWI.

Stenoses of the main stem of the IIA used as an internal control were not correlated with lesser degrees of atherosclerosis in the distal vascular territories: The slight positive correlations of the degrees of stenosis of the IIA with the degrees of stenosis of all other vascular segments were not statistically significant.

This thus supports the hypothesis that not just the level of blood pressure itself, but also the pulse pressure may be relevant for developing atherosclerosis.[5] While flow acceleration and turbulence occurs within stenoses, the flow decelerates in the separation zone immediately downstream. At this location, a recirculation flow causes post-stenotic dilatation due to elevated transmural pressure, while 1–2 cm further distal, laminar flow is restored.[15] Distal to this, flow is characterized by small, late arterial pulses, known as *pulsus parvus et tardus*, which is found in the entire dependent vascular territory.[16]

In comparison with the EIA, the protective effect of the CIA is considerably stronger. This could be attributed to the fact that stenoses of the CIA cannot be collateralized as well as stenoses of the EIA, since there is no possibility of diverting via the ipsilateral IIA. The lack of significance of the effect of stenoses of the CFA is likely due to the shortness of this vascular segment and the resulting low number of stenoses, while the pronounced and significant associations of stenoses of the SFA, the popliteal artery, and the TFT with less pronounced stenoses, Friesinger scores, and degrees of calcification distal to them can be explained by the poor collateralization options in comparison with the pelvic level. Although no territory distal to the DFA is immediately dependent on it, stenoses at this level appear to be relevant. The reason for this is that most of these cases involved lesions of the bifurcation of the CFA, a pattern that is not rare.[17] This region meets the conditions for high local stress, such as are present at the carotid bifurcation or at the aortic bifurcation: a greater cross section, bending effects, reduced thickness, and opposite curvatures.[5] The femoral bifurcation is therefore considered to be a vulnerable site where an isolated stenosis of the DFA rarely occurs.

The degree of collaterals – both iliac as well as femoropopliteal and infragenual – seems to be a risk factor for the severity of stenoses (NASCET) (Figure 2). This can be interpreted to indicate that existing collaterals reverse the protective effect of the stenoses. This is consistent with the hypothesis that a stenosis can protect from atherosclerosis by reducing pulse pressure and slowing the flow of blood: This effect could also be attenuated again depending on how pronounced the collaterals are. However, this hypothesis is highly speculative and must be verified in future studies.

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However, it can be assumed with certainty that the formation of collaterals does not in itself have a protective effect on distal vascular territories. It cannot be tested based on available data how long a stenosis has already been present or how much time has thus passed in which collaterals could have formed. The role of collaterals as a risk factor for stenosis in the model (Figure 2) can probably be explained only by the fact that the collaterals are an epiphenomenon of long-existing stenoses, but are not a "risk factor." The weak negative correlation between femoropopliteal and infragenual collaterals and the degree of stenosis in the CIA or EIA is noteworthy. It could be attributable to the fact that the inflow of blood from proximal is less in these cases and that collaterals around another, more distal femoropopliteal or infragenual stenosis therefore remain narrower or do not arise at all. One explanation for the lack of a correlation between iliac stenoses (CIA and EIA) and collaterals is that the collaterals in this vascular territory are highly variable. They can stem from regions that were not contrasted in the same angiography, such as the contralateral IIA and the IMA.

This study has limitations. The first limitation that should be mentioned is the retrospective study design, which can be the source of a selection bias. However, the study meets the criteria for evidence level I.[18] The sample consisted of consecutive patients with pronounced atherosclerosis, the main risk factors for atherosclerosis were represented, and the number of 2125 segments evaluated was high. However, the number of patients, although not small at 101, limited the possibilities of multivariate analyses. Additional studies must be conducted to determine the exact extent of the magnitude of the protective effect of stenoses on distal vascular territories. However, the very good agreement of the location-related effects of the standard risk factors with literature indicates that a good estimate of the magnitude was made. The significance of pulse pressure as a cardiovascular risk factor is well established.[19-23] It contributes to the development of atherosclerosis independently of the classical risk factors.[24] While the positive effects of lowering the heart rate[5, 25] and the blood pressure[26, 27] are known, it is still unclear whether or not lowering the pulse pressure results in a protective effect in humans. However, as the study was performed retrospectively, we were not able to measure the pulse pressure distal to the stenoses. This main weakness of the study can only be addressed with prospective, longitudinal observational studies.

If the pulse pressure is confirmed in prospective, longitudinal observational studies to be a risk factor, there would be no immediate clinical consequences. Since the overwhelming majority of patients (75.2%) have arterial hypertension as a risk factor for atherosclerosis, these patients at least should be given strict pharmacological antihypertensive treatment. The pulse pressure is thus far not accessible as an independent treatment target. Every antihypertensive treatment also affects the pulse pressure and vice versa. Any existing antihypertensive treatment should never be negatively affected, so if the pulse pressure hypothesis is confirmed, the next step should be to answer the

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question of whether there are antihypertensive drugs or combinations of standard antihypertensive agents that have a greater effect on the pulse pressure than others and whether a better preventive effect could be achieved with them than with others.

At the moment, the results of this study cannot and should not lead to any changes in patient treatment. If a hemodynamically significant stenosis or occlusion is present, the lesion should be treated by angioplasty, stent angioplasty, or bypass – providing there is a clinical necessity – in accordance with the guidelines.[28-30] Treatment should not be delayed for clinically symptomatic patients, even with less pronounced stenoses, but should be determined on a case-by-case basis and not postponed until critical limb ischemia develops. It would also not be acceptable to leave a slight residual stenosis untreated in the belief that this could protect the periphery. Every lesion should be treated as well as possible without causing restenosis because residual stenoses can be the cause of restenosis or even thrombosis in a stented segment.

However, dilatations of not clinically manifest, low-grade stenoses that may possibly never become clinically relevant, which are detected as incidental findings “in passing” in coronary angiographies, for example, may possibly be counterproductive for the distal vascular territory. In the kidney, for example, this could mean faster progression of glomerulosclerosis, in the supraaortic region faster progression of cerebral microangiopathy. These hypotheses are another argument for strict compliance with the treatment guidelines, and their proof is pending.

By analogy with the studies of animal experiments, in which the atheroprotective effect of coarctation was proven,[6-8] it is conceivable to attempt experimental modification of the pulse pressure, for example with simple slight bending, but also with flow-modulated stents, which could be similar to those used for reducing a TIPS[31, 32]. Bending should naturally not be so narrow that it would lead to symptoms, but not so wide that no flow modulation occurs. If a feasible middle ground were found, it would have to be tested in long-term studies.

Longitudinal, prospective studies will be needed to prove the hypothetical negative effect on the distal vascular territory of treating a stenosis. It is probable that the most suitable patients for this will be those with constellations in which a PAOD IIb is present on one side and a not clinically manifest stenosis is present at the same level on the other side or in which a stenosis of the carotid artery is treated, but not an additional contralateral stenosis.

In conclusion, this study shows that atherosclerotic stenoses seem to protect distant distal vascular territories from developing atherosclerosis. The underlying pathophysiological mechanism for this phenomenon remains to be determined, but could be the reduction of pulse pressure.

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## Contributors

RR, JP, AM, and BG contributed to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; in drafting the work and revising it critically for important intellectual content; and in giving final approval of the version to be published. RR and BG were the main investigators of this study.

AG, HZ, AL, AEG, and JK contributed to the acquisition of data for the work; in partially drafting the work in revising it critically for important intellectual content; and in giving final approval of the version to be published.

All authors (RR, JP, AG, HZ, AM, AL, AEG, JK, and BG) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## Data Sharing

The original data set is available on individual request by emailing the corresponding author, johannes.petersen@i-med.ac.at.

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## Table 1

| | | All | Mean ± SD | Women | Mean ± SD | Men | Mean ± SD |
|---|---|---|---|---|---|---|---|
| **N** | | 101 (100%) | - | 31 (30.7%) | - | 70 (69.3%) | - |
| **Legs** | | 202 (100%) | - | 62 (30.7%) | - | 140 (69.3%) | - |
| **Age** | | 38 - 91 | 66.1 ± 10.8 | 46 - 89 | 69.7 ± 10.8 | 38 - 91 | 64.5 ± 10.5 |
| **BMI** | | 15.8 - 41.1 | 25.8 ± 4.7 | 15.8 - 41.1 | 24.6 ± 5.2 | 16.6 - 39.9 | 25.9 ± 4.4 |
| **BP syst.** | | 113 - 190 | 154.8 ± 18.9 | 113 - 185 | 153.2 ± 18.5 | 117 - 190 | 155.5 ± 19.2 |
| **BP diast.** | | 50 - 109 | 80.7 ± 11.2 | 50 - 105 | 79.0 ± 11.5 | 57 - 109 | 81.5 ± 11.2 |
| **DM** | *y* | 28 (27.7%) | - | 10 (32.3%) | - | 18 (25.7%) | - |
| | *n* | 73 (72.3%) | | 21 (67.7%) | | 52 (74.3%) | |
| **CKD** | *y* | 20 (19.8%) | - | 8 (25.8%) | - | 12 (12.1%) | - |
| | *n* | 81 (80.2%) | | 23 (74.2%) | | 58 (82.9%) | |
| **Control** | *y* | 86 (85.1%) | | 27 (87.1%) | | 59 (84.3%) | |
| | *n* | 11 (10.9%) | - | 2 (6.5%) | - | 9 (12.9%) | - |
| | *n.a.* | 4 (4.0%) | | 2 (6.5%) | | 2 (2.9%) | |
| **Major amputation** | *y* | 7 (6.9%) | - | 4 (12.9%) | - | 3 (4.3%) | - |
| | *n* | 94 (93.1%) | | (87.1%) | | (95.7%) | |
| **Deceased** | *y* | 10 (9.9%) | - | 4 (12.9%) | - | 6 (8.6%) | - |
| | *n* | 91 (90.1%) | | 27 (87.1%) | | 64 (91.4%) | |
| **OAC** | *y* | 17 (16.8%) | - | 6 (19.4%) | - | 11 (15.7%) | - |
| | *n* | 84 (83.2%) | | 25 (80.6%) | | 59 (84.3%) | |
| **HMG-CoA RI** | *y* | 85 (84.2%) | - | 22 (71.0%) | - | 63 (90.0%) | - |
| | *n* | 16 (15.8%) | | 9 (29.0%) | | 7 (10.0%) | |
| **APD** | *y* | 91 (90.1%) | - | 28 (90.3%) | - | 63 (90.0%) | - |
| | *n* | 10 (9.9%) | | 3 (9.7%) | | 7 (10.0%) | |
| **Smoker** | *y* | 64 (63.4%) | - | 17 (54.8%) | - | 47 (67.1%) | - |
| | *n* | 37 (36.6%) | | 14 (45.2%) | | 23 (32.9%) | |
| **Arterial hypertension** | *y* | 76 (75.2%) | - | 28 (90.3%) | - | 48 (68.6%) | - |
| | *n* | 25 (24.8%) | | 3 (9.7%) | | 22 (31.4%) | |
| **Fontaine stages** | | | | | | | |
| **1** | | 2 (2.0%) | - | 1 (3.2%) | - | 1 (1.4%) | - |
| **2** | | 62 (61.4%) | - | 17 (54.8%) | - | 45 (64.3%) | - |
| **3** | | 16 (15.8%) | - | 7 (22.6%) | - | 9 (12.9%) | - |
| **4** | | 21 (20.8%) | - | 6 (19.4%) | - | 15 (21.4%) | - |
| **Collaterals** | | | | | | | |
| **Iliac arteries** | | **404 (100%)** | **-** | **124 (100%)** | **-** | **280 ( 100%)** | **-** |
| **0** | | 339 (83.9%) | - | 109 (87.9) | - | 230 (82.1%) | - |
| **1** | | 11 (2.7%) | - | 0 (0.0%) | - | 11 (3.9%) | - |
| **2** | | 12 (3.0%) | - | 5 (4.0%) | - | 7 (2.5%) | - |
| **3** | | 19 (4.7%) | - | 5 (4.0%) | - | 14 (5.0%) | - |
| **4** | | 21 (5.2%) | - | 5 (4.0%) | - | 16 (5.7%) | - |
| **5** | | 2 (0.5%) | - | 0 (0.0%) | - | 2 (0.7%) | - |
| **Femoropopliteal arteries** | | **1084 (100%)** | **-** | **316 (100%)** | **-** | **768 (100%)** | **-** |
| **0** | | 929 (85.7%) | - | 258 (81.6%) | - | 671 (87.4%) | - |
| **1** | | 11 (1.0%) | - | 5 (1.6%) | - | 6 (0.8%) | - |
| **2** | | 26 (2.4%) | - | 14 (4.4) | - | 12 (1.6%) | - |
| **3** | | 53 (4.9%) | - | 15 (4.7%) | - | 38 (4.9%) | - |
| **4** | | 33 (3.0%) | - | 14 (4.4) | - | 19 (2.5%) | - |
| **5** | | 32 (3.0%) | - | 10 (3.2) | - | 22 (2.9%) | - |
| **Infragenual arteries** | | **637 (100%)** | **-** | **175 (100%)** | **-** | **462 (100%)** | **-** |
| **0** | | 526 (82.6%) | - | 143 (81.7%) | - | 383 (82.9%) | - |
| **1** | | 52 (8.2%) | - | 14 (8.0%) | - | 38 (8.2%) | - |
| **2** | | 31 (4.9%) | - | 11 (6.3%) | - | 20 (4.3%) | - |
| **3** | | 20 (3.1%) | - | 5 (2.9%) | - | 15 (3.2%) | - |
| **4** | | 8 (1.3%) | - | 2 (1.1%) | - | 6 (1.3%) | - |
| **5** | | 0 (0.0%) | - | 0 (0.0%) | - | 0 (0.0%) | - |

**Table 1:** Baseline characteristics of the patient group, as well as of the group divided into women and men. [Abbreviations: Y – Yes; n – No; BMI - Body mass index; BP - Blood pressure; DM - Diabetes mellitus; CKD – Chronic Kidney Disease; OAC - Oral anticoagulation; RI – (HMG-CoA-) reductase inhibitor; APD - Antiplatelet drug]

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**Table 2**

| | | Degree of stenosis (NASCET) | | | | Friesinger score (0-5) | | | | | | Degree of calcification (0-5) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Vessel** | **N** | **30-50%** | **50-70%** | **70-90%** | **≥90%** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** |
| **CIA** | 202 | 86 | 47 | 27 | 14 | 26 | 87 | 52 | 7 | 17 | 13 | 37 | 40 | 44 | 43 | 24 | 14 |
| | | *42.6%* | *23.3%* | *13.4%* | *6.9%* | *12.9%* | *43.1%* | *25.7%* | *3.5%* | *8.4%* | *6.4%* | *18.3%* | *19.8%* | *21.8%* | *21.3%* | *11.9%* | *6.9%* |
| **EIA** | 202 | 72 | 49 | 24 | 9 | 26 | 87 | 52 | 7 | 17 | 13 | 78 | 50 | 26 | 25 | 19 | 4 |
| | | *35.6%* | *24.3%* | *11.9%* | *4.5%* | *12.9%* | *43.1%* | *25.7%* | *3.5%* | *8.4%* | *6.4%* | *38.6%* | *24.8%* | *12.9%* | *12.4%* | *9.4%* | *2.0%* |
| **IIA** | 202 | 82 | 60 | 43 | 27 | 49 | 75 | 34 | 1 | 18 | 25 | 81 | 49 | 35 | 17 | 15 | 5 |
| | | *40.6%* | *29.7%* | *21.3%* | *13.4%* | *24.3%* | *37.1%* | *16.8%* | *0.5%* | *8.9%* | *12.4%* | *40.1%* | *24.3%* | *17.3%* | *8.4%* | *7.4%* | *2.5%* |
| **CFA** | 201 | 36 | 17 | 8 | 2 | 64 | 102 | 26 | 1 | 6 | 2 | 81 | 57 | 35 | 19 | 6 | 3 |
| | | *17.9%* | *8.5%* | *4.0%* | *1.0%* | *31.8%* | *50.7%* | *12.9%* | *0.5%* | *3.0%* | *1.0%* | *40.3%* | *28.4%* | *17.4%* | *9.5%* | *3.0%* | *1.5%* |
| **DFA** | 195 | 20 | 9 | 3 | 2 | 107 | 70 | 14 | 1 | 1 | 2 | 120 | 42 | 22 | 7 | 2 | 2 |
| | | *10.3%* | *4.6%* | *1.5%* | *1.0%* | *54.9%* | *35.9%* | *7.2%* | *0.5%* | *0.5%* | *1.0%* | *61.5%* | *21.5%* | *11.3%* | *3.6%* | *1.0%* | *1.0%* |
| **SFA** | 192 | 108 | 87 | 73 | 44 | 50 | 33 | 19 | 19 | 23 | 48 | 60 | 21 | 21 | 33 | 22 | 35 |
| | | *56.3%* | *45.3%* | *38.0%* | *22.9%* | *26.0%* | *17.2%* | *9.9%* | *9.9%* | *12.0%* | *25.0%* | *31.3%* | *10.9%* | *10.9%* | *17.2%* | *11.5%* | *18.2%* |
| **PI** | 166 | 48 | 30 | 25 | 22 | 61 | 56 | 24 | 1 | 3 | 21 | 73 | 38 | 18 | 46 | 8 | 13 |
| | | *28.9%* | *18.1%* | *15.1%* | *13.3%* | *36.7%* | *33.7%* | *14.5%* | *0.6%* | *1.8%* | *12.7%* | *44.0%* | *22.9%* | *10.8%* | *9.6%* | *4.8%* | *7.8%* |
| **PII** | 168 | 34 | 25 | 22 | 21 | 75 | 57 | 11 | 2 | 1 | 22 | 87 | 37 | 19 | 10 | 4 | 11 |
| | | *20.2%* | *14.9%* | *13.1%* | *12.5%* | *44.6%* | *33.9%* | *6.5%* | *1.2%* | *0.6%* | *13.1%* | *43.1%* | *18.3%* | *9.4%* | *5.0%* | *2.0%* | *5.4%* |
| **PIII** | 162 | 29 | 21 | 18 | 17 | 104 | 30 | 7 | 0 | 2 | 19 | 109 | 28 | 8 | 6 | 2 | 9 |
| | | 17.9% | 13.0% | 11.1% | 10.5% | 64.2% | 18.5% | 4.3% | 0.0% | 1.2% | 11.7% | 67.3% | 17.3% | 4.9% | 3.7% | 1.2% | 5.6% |
| **TFT** | 150 | 26 | 19 | 15 | 15 | 92 | 31 | 8 | 2 | 1 | 16 | 105 | 18 | 9 | 5 | 3 | 10 |
| | | 17.3% | 12.7% | 10.0% | 10.0% | 61.3% | 20.7% | 5.3% | 1.3% | 0.7% | 10.7% | 70.0% | 12.0% | 6.0% | 3.3% | 2.0% | 6.7% |
| **ATA** | 166 | 58 | 48 | 44 | 33 | 86 | 24 | 8 | 3 | 6 | 39 | 114 | 16 | 5 | 9 | 9 | 13 |
| | | 34.9% | 28.9% | 26.5% | 19.9% | 51.8% | 14.5% | 4.8% | 1.8% | 3.6% | 23.5% | 68.7% | 9.6% | 3.0% | 5.4% | 5.4% | 7.8% |
| **PTA** | 157 | 53 | 50 | 47 | 36 | 79 | 27 | 3 | 1 | 3 | 44 | 102 | 22 | 10 | 4 | 5 | 14 |
| | | 33.8% | 31.8% | 29.9% | 22.9% | 50.3% | 17.2% | 1.9% | 0.6% | 1.9% | 28.0% | 65.0% | 14.0% | 6.4% | 2.5% | 3.2% | 8.9% |
| **FA** | 164 | 33 | 28 | 24 | 23 | 85 | 40 | 8 | 0 | 0 | 31 | 113 | 22 | 16 | 3 | 2 | 8 |
| | | 20.1% | 17.1% | 14.6% | 14.0% | 51.8% | 24.4% | 4.9% | 0.0% | 0.0% | 18.9% | 68.9% | 13.4% | 9.8% | 1.8% | 1.2% | 4.9% |

**Table 2:** Absolute and relative numbers of stenoses within the arbitrarily stated ranges of degree in the respective arterial segments; numbers of Friesinger scores and degrees of calcification. [Abbreviations: CIA - common iliac artery; EIA - external iliac artery; IIA - internal iliac artery; CFA - common femoral artery; DFA – deep femoral artery; SFA - superficial femoral artery; PI, PII and PIII - popliteal artery segment I. II. or III; TFT - tibiofibular trunk; ATA - anterior tibial artery (ATA). PTA - posterior tibial artery; FA - fibular artery]



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**Table 3**

| Difference | | EIA | | | IIA | | | CFA | | | DFA | | | SFA | | | PI | | | PII | | | PIII | | | TFT | | | ATA | | | PTA | | | FA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NASCET | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C | N | F | C |
| CIA | 30-49% | *n* | *y* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *y* | *y* | *y* | y | y | n | *y* | *y* | *y* | y | y | n | *y* | *y* | *y* | n | n | n | *y* | *n* | *n* | n | n | n |
| | 50-69% | *y* | *n* | *n* | n | n | n | *n* | *n* | *n* | *y* | *y* | *y* | *y* | *y* | *y* | y | y | n | *y* | *y* | *y* | y | y | y | *y* | *y* | *y* | n | n | n | *n* | *n* | *y* | n | n | n |
| | 70-89% | *y* | *n* | *n* | n | n | n | *n* | *n* | *n* | *y* | *y* | *y* | *y* | *y* | *y* | y | y | n | *y* | *y* | *n* | y | y | y | *n* | *y* | *y* | n | n | *y* | *y* | *n* | *y* | n | n | *y* |
| | ≥90 | *y* | *n* | *n* | n | n | n | *n* | *n* | *n* | *y* | n | n | *n* | *y* | *y* | n | n | n | *y* | *n* | *n* | *y* | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *y* | n | n | *y* |
| EIA | 30-49% | | | | n | n | n | *y* | *y* | *y* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| | 50-69% | | | | n | n | n | *y* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | *y* | *n* | *y* | *n* | n | n | *y* | *n* | *n* | *n* | n | n | *y* | *n* | *n* | *n* | n | n | n |
| | 70-89% | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | y | y | n |
| | ≥90 | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| ***IIA*** | ***30-49%*** | | | | | | | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** |
| | ***50-69%*** | | | | | | | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** |
| | ***70-89%*** | | | | | | | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** | ***n*** |
| | ≥90 | | | | | | | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | n | n |
| CFA | 30-49% | | | | | | | | | | n | n | n | *y* | *y* | *y* | n | n | n | *n* | *y* | *n* | n | y | n | *n* | *n* | *n* | y | n | n | *n* | *n* | *n* | n | n | n |
| | 50-69% | | | | | | | | | | n | n | n | *y* | *y* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| | 70-89% | | | | | | | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| | ≥90 | | | | | | | | | | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | n | n | n |
| DFA | 30-49% | | | | | | | | | | | | | *y* | *y* | *n* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *n* | n | *y* | n |
| | 50-69% | | | | | | | | | | | | | *y* | *y* | *n* | *y* | *y* | n | *y* | *y* | *n* | n | *y* | n | *y* | *y* | *n* | *y* | *y* | *y* | *n* | *n* | *n* | n | *y* | n |
| | 70-89% | | | | | | | | | | | | | *n* | *n* | *y* | n | n | n | *y* | *y* | *n* | n | *y* | n | *y* | *y* | *n* | *y* | *y* | *y* | *n* | *n* | *n* | n | *y* | n |
| | ≥90 | | | | | | | | | | | | | *n* | *n* | *n* | n | n | n | *n* | *n* | *n* | *y* | n | n | *y* | *n* | *n* | n | n | *y* | *n* | *n* | *n* | *y* | *y* | *y* |
| SFA | 30-49% | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* |
| | 50-69% | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* | *y* | n | *y* | *y* |
| | 70-89% | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *n* | *y* | *y* | *y* | *y* | n | *y* | *n* | *n* | n | n | n |
| | ≥90 | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* | *n* | *y* | *y* | n | *y* | *n* | *n* | n | n | n |
| PI | 30-49% | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* |
| | 50-69% | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* | *y* | *y* | *y* | *y* |
| | 70-89% | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *n* | *y* | *y* | n | *y* | *y* | *y* | n | n | n |
| | ≥90 | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* | *y* | *y* | n | n |
| PII | 30-49% | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | | *y* | *y* |
| | 50-69% | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* |
| | 70-89% | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n |
| | ≥90 | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n |
| PIII | 30-49% | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* |
| | 50-69% | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* | *y* | n | *y* | n |
| | 70-89% | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | n | *y* | *y* | *y* | *y* | *y* | n |
| | ≥90 | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | n |
| TFT | 30-49% | | | | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* |
| | 50-69% | | | | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* |
| | 70-89% | | | | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* |
| | ≥90 | | | | | | | | | | | | | | | | | | | | | | | | | | | | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* | *y* |

**Table 3:** Significance levels of all tests of the differences between the segments in relation to the respective classification level. The effects are most pronounced for stenoses of the common iliac artery and the superficial femoral artery. No effects of stenoses of the internal iliac arteries. representing a segment without further distant distal depending territories as a virtual internal control. [Abbreviations: N - NASCET; C - calcification; F - Friesinger score]

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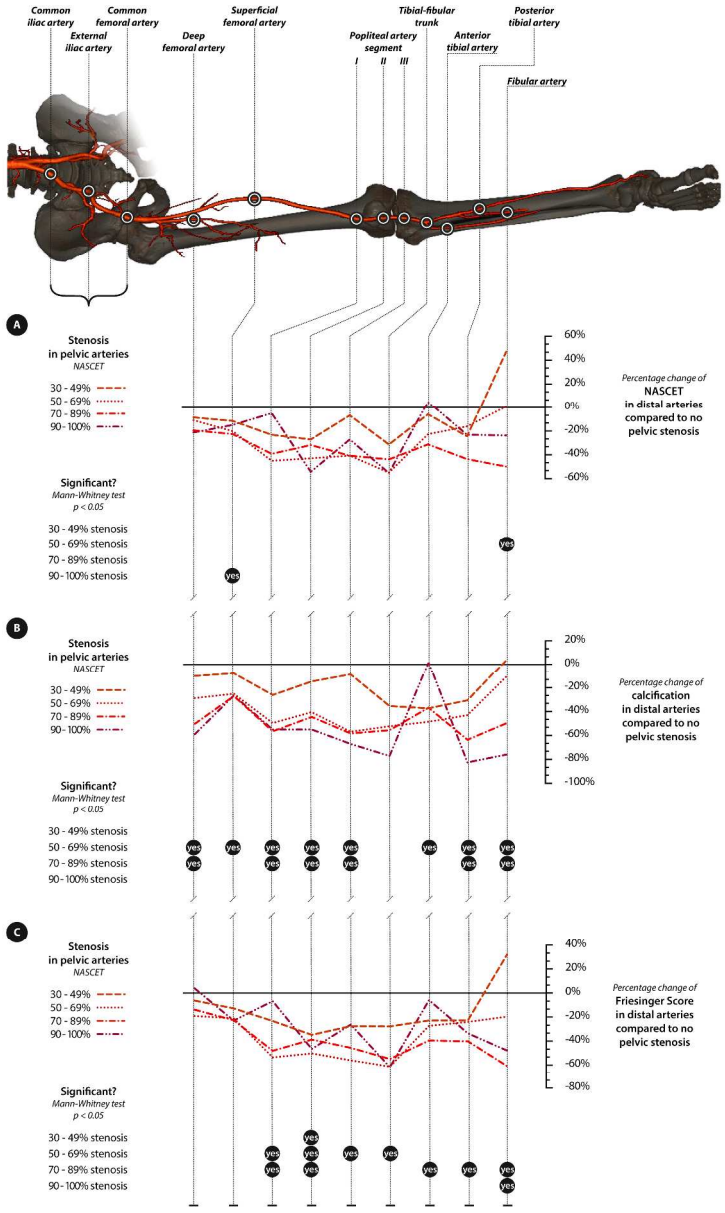


Association of stenoses of pelvic vessels (CIA/EIA/CFA) 30%–49%; 50%–69%, 70%–89%, or 90%–100% with the extent of the degrees of stenosis distal to them as a percentage comparison with (A) the contralateral side, (B) calcifications, and (C) the Friesinger scores. Lower degrees of atherosclerotic burdens distal to stenoses of arteries of the pelvic level are striking.
320x524mm (300 x 300 DPI)

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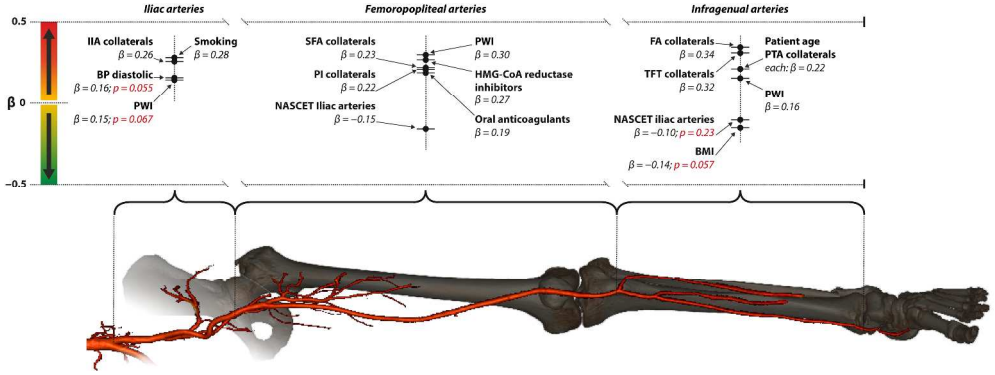


Standardized coefficients of the independent risk factors identified on the regression models with respect to the degree of maximum stenosis at the pelvic level, femoropopliteal region, and the crural region. The degree of stenosis in the pelvis was found to be an independent protective factor of the femoropopliteal region with respect to atherosclerosis.
388x142mm (300 x 300 DPI)

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2, 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5, 6, 7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5, 6, 7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | n.a. |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5, 6, 7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *5, 6, 7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5, 6, 7 |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5, 6, 7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6, 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6, 7 |
| | | (*c*) Explain how missing data were addressed | 6, 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | n.a. |
| | | (*e*) Describe any sensitivity analyses | n.a. |
| **Results** | | | |

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| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5 |
| | | (b) Give reasons for non-participation at each stage | n.a. |
| | | (c) Consider use of a flow diagram | n.a. |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 5 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 17 |
| | | (c) Summarise follow-up time (eg, average and total amount) | n.a. |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | n.a. |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7, 8, 9 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 5, 6, 7, 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n.a. |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 6, 7, 8, 9 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 9 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 9, 10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10, 11, 12 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 3 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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