Postimplantation syndrome (PIS) after endovascular repair (EVAR) of infrarenal aortic aneurysms (AAA) is characterized by postoperative fever, leukocytosis, increased C-reactive protein, and blood coagulation disorders [5, 11]. The etiology of this generalized inflammation is still inadequately characterized [2]. Since it was first described in 1999 by Valezquez et al. [21], the existence and clinical relevance of PIS has been continually questioned [17]. However, daily clinical routine suggests that it is an independent complication after EVAR, despite the majority of cases having a harmless and transient course. There are currently no standardized diagnostic criteria available internationally or nationally, which makes it difficult to compile clinical and epidemiological data. Furthermore, recommendations or guidelines for the treatment of this patient population are lacking. The goal of the present survey was, thus, to determine the nationwide incidence and diagnostic criteria and evaluate the perception of PIS as a complication of EVAR in vascular surgery in Germany.

Materials and methods

The current article is a retrospective analysis of data, in which German vascular surgeons were surveyed using a standardized questionnaire. From January 2012 to April 2012, a total of 124 vascular surgery clinics nationwide were sent a questionnaire to inquire about their experience with PIS after EVAR. The clinics contacted were identified using a clinic internal distribution list of German vascular surgery clinics and departments.

Questionnaire

The following categories were included in the questionnaire:

1. Frequency of endovascular repairs (EVAR) at the respective clinic per year
2. Stent grafts used for EVAR at the respective clinic
3. Estimated incidence of PIS at the respective clinic
4. Diagnostic criteria for PIS at the respective clinic
5. Treatment of PIS at the respective clinic
6. Individual perception of PIS as a complication after EVAR at the respective clinic

Re 1. Frequency of endovascular AAA repairs at the respective clinic

Responses concerning EVAR frequency were divided into the categories ≤25/year, 25–50/year, 50–75/year, and 75–100/year.

Re 2. Stent graft devices used for AAA repairs at the respective clinic

The following stent graft devices were included: Medtronic Endurant® (Medtronic, Minneapolis, MN, USA), Medtronic Talent® (Medtronic, Minneapolis, MN, USA), Gore Excluder® (W.L. Gore and Associates, Flagstaff, AZ, USA), Jotec E-vita® (Jotec GmbH, Hechingen, Germany), Cook Zenith® (Cook Inc., Bloomington, IN, USA), Endologix Powerlink® (Endologix, Irvine, CA, USA) and Vascutek Anaconda® (Vascutek, Bad Soden, Germany). Multiple answers were possible. In addition, a free text field was available.

Re 3: Estimated incidence of PIS at the respective clinic

The incidence of PIS was categorized as follows: ≤20%, 20–30%, 30–40%, and ≥40%. In addition, a free text field was available.

Re 4. Diagnostic criteria for PIS used at the respective clinic

The following options were possible: body temperature (<38.0°C, 38.0–38.5°C, 38.5–39.0°C, >39.0°C), increase in C-reactive protein (CRP; 50 mg/l, 50–100 mg/l, 100–200 mg/l, >200 mg/l), and white blood cell count (<10•10^9/l, >10•10^9/l, >12•10^9/l, >14•10^9/l).

Re 5. Treatment of PIS at the respective clinic

The following active ingredients were available for selection: acetylsalicylic acid (aspirin), paracetamol, ibuprofen, diclofenac, and metamizole. In addition, a free text field was available.

Re 6. Individual perception of PIS as a complication after endovascular AAA repair

Concerning the acceptance of PIS as an independent complication after EVAR, two answers were possible: “Yes, PIS is a clinically relevant complication after..."
Redmond, WA, USA). The data were statistically analyzed using IBM SPSS Statistics, Version 20 (IBM GmbH, Ehningen, Germany). The dependence between the number of available stent graft systems and EVAR incidence was analyzed using the Kruskal–Wallis test. The dependence of the incidence and the relevance of PIS on the number of EVAR procedures performed were evaluated for linearity using the χ² test. A significance level of 5% was set for all calculations.

**Results**

The analyzable return rate was 59.7% (74/124). However, 50 of the 124 questionnaires (40.3%) could not be evaluated, because 48 questionnaires were not returned and 2 clinics reported not performing EVAR procedures.

**Frequency of endovascular repair**

The majority of clinics (52/74; 70.2%) reported performing ≥25 EVAR procedures per year. While 22 of 74 clinics (29.7%) performed ≤25 procedures per year, 36 of 74 clinics (48.6%) implanted 25–50 endoprostheses per year. EVAR frequencies of 50–75 and 75–100 per year are reported by 10 of 74 (13.5%) and 6 of 74 (8.1%) of the clinics (Fig. 1).

**Stent graft devices used**

The data concerning the graft devices used during EVAR are shown in Tab. 1. When answering the question, multiple answers were possible. On average, 2 stent graft devices were used per clinic (range: 1–5). Thereby, 1 clinic (1.4%) reported using 5 different types of prostheses; 4, 3 and 2 different devices were used in 4 (5.4%), 13 (17.6%), and 28 (37.8%) clinics. In 28 of 74 clinics (37.8%), only one type of prosthesis was available. No significant correlation was observed between the frequency of EVAR and the number of available stent graft devices (Kruskal–Wallis test, p=0.311).

**Incidence**

The incidence of PIS was estimated by 52 of 74 clinics (70.2%) to be ≤20% (Fig. 2). Thereby one clinic estimated the occurrence of PIS after EVAR to be <10%, while 2 clinics reported that they had not observed any patients to have experienced PIS after having undergone EVAR. On the other hand, 13 of 74 clinics (17.6%) reported PIS after EVAR in 20–30% of patients and 4 clinics (5.4%) in 30–40% of cases. Six of 74 clinics (8.1%) reported the occurrence of PIS in ≥40% of AAA cases undergoing an endovascular procedure. No significant correlation between PIS incidence and EVAR frequency was observed (χ² test for a linear trend, p=0.828).

**Diagnostic criteria**

In 71 of 74 clinics (95.9%), the diagnostic criteria were available for analysis. Three of the 74 clinics (4.1%) made no statement concerning temperature and laboratory values in PIS, but relied more on pure clinical aspects (tachypnea/tachycardia) to diagnose PIS. Only 21 clinics made statements concerning all 3 diagnostic parameters.

An increase in body temperature of ≥38.0°C was reported by all clinics (100%; 71/71) as a diagnostic criterion in PIS, whereas 58 of 71 clinics (81.7%) reported a cut-off value of ≥38.5°C. A total of 11 of 71 clinics (15.5%) reported using only an increase in body temperature as the diagnostic criterion.

Leukocytosis was reported as being used by 50 of 71 (70.4%) clinics for the diagnosis of PIS. A total of 21 clinics (29.6%) made no comment concerning this. The cut-off value of ≥12×10⁹/l was preferred by 84% (42/50) of vascular surgery departments.

An increase of the C-reactive protein was reported by 51 of 71 (71.8%) clinics as a PIS-associated laboratory value/result. No statement concerning CRP was made by 20 clinics (28.2%). For 39 of 51 clinics surveyed (76.4%), a CRP value of 50–100 mg/l was considered a typical laboratory value for PIS.
**Abstract • Zusammenfassung**


**M.S. Bischoff · S. Hafner · T. Able · A.S. Peters · A. Hyhlik-Dürr · D. Böckler**

**Incidence and treatment of postimplantation syndrome after endovascular repair of infrarenal aortic aneurysms**

**Abstract**

**Background.** The goal of the current survey was to evaluate the role of the postimplantation syndrome (PIS) after endovascular repair (EVAR) of infrarenal aortic aneurysms (AAA) in German vascular surgery practice.

**Materials and methods.** From January 2012 to April 2012, a total of 124 German clinical departments for vascular surgery were surveyed regarding their experience with PIS using a standardized questionnaire. Categories were EVAR frequency per year, stent graft devices used, PIS incidence, diagnostic criteria for PIS, treatment of PIS, and relevance of PIS as a complication after EVAR.

**Results.** The analyzable return rate was 59.7% (74/124). In 70.2% (52/74), the number of EVAR procedures performed was ≥25/year. The incidence of PIS was estimated to occur in ≤20% of cases by 70.2% (52/74). The diagnostic cut-off values used were body temperature ≥38.5°C, white blood cell count ≥12/nl, and C-reactive protein levels of 50–100 mg/l.

**Keywords**

Stent graft · Fever · Leukocytosis · C-reactive protein · Anti-inflammatory agents · non-steroidal

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**Inzidenz und Therapie des Postimplantations syndroms nach endovaskulärer Ausschaltung infrarenaler Aortenaneurysmen**

Zusammenfassung

Hintergrund. Ziel der vorliegenden Umfrage war es, den Stellenwert des Postimplantations syndroms (PIS) nach endovaskulärer Ausschaltung (EVAR) infrarenaler Aortenaneurysmen (Bauchaortenaneurysmen (BAA)) in der deutschen Gefäßchirurgie zu evaluieren.


Ergebnisse. Die auswertbare Rücklaufquote betrug 59,7% (74/124). In 70,2% (52/74) der Kliniken lag die Anzahl der EVAR-Prozeduren bei ≥25/Jahr. Die Inzidenz des PIS wird von 70,2% (52/74) mit ≤20% angegeben. Führende Diagnosekriterien waren eine Körpertemperatur ≥38,5°C, eine Leukozytose ≥12/ nl und ein Spiegel des C-Reaktiven Proteins (CRP) von 50–100 mg/l. Für 55,4% (41/74) der Kliniken stellt das PIS eine relevante Komplikation nach EVAR dar. Die Therapie des PIS erfolgt uneinheitlich mit nicht-steroidalen Antiphlogistika.


Schlüsselwörter

Stent graft · Fieber · Leukozytose · C-reactives Protein · Nichtsteroidale Antiphlogistika

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**Discussion**

The exact incidence of PIS after EVAR is unknown. The data in the literature for the incidence of PIS vary between 14 and 60% [2, 10]. Current prospective and retrospective analyses report incidences of about 35% [15, 23]. In the present survey, the incidence of PIS was estimated by 70% of the clinics to be ≤20% (Fig. 2). The hypothesis that clinics with greater numbers of EVAR procedures would perceive a greater incidence could not be verified by the present data ($\chi^2$ test for a linear trend, $p=0.828$). One of the main reasons for the significant differences concerning the published incidences is due to the lack of consensus concerning the symptoms and laboratory values for PIS. For example, Vouïte et al. [23] defined PIS as a fever of ≥38°C in combination with CRP values >10 mg/l, while Arnaoutoglou et al. [2] included a white blood cell count of >12·10^9/l instead of the CRP value for diagnosis. Blum et al. [3] based their diagnosis on an elevated CRP value and a white blood cell count >9.8·10^9/l, but not on fever.

Therefore, it would be advantageous to have uniform diagnostic criteria are nec-
The etiology of PIS is still not adequately known, whereby the clarification of the underlying pathophysiological principles is made more difficult by the variety and complexity of immunobiological processes after EVAR [14, 19]. Factors that are discussed as initiating PIS included, e.g., the contrast agent, intraoperative manipulation of the parietal thrombus, secondary IL-8 and fever occurred more often, whereby no significant differences were observed concerning the IL-6 concentrations. In a retrospective study, Verhagen et al. [23] described that the implantation of a polyester stent graft compared to endografts from PTFE led to a higher PIS incidence after EVAR (56.1% vs. 17.9%, p<0.001). The multivariate analysis performed by the authors only identified polyester as a significant factor for the development of PIS (p=0.007), but not the size of the graft or new-onset thrombosis (p=0.33 and p=0.58, respectively).

In a prospective cytokine-based study (among others IL-6 and IL-10), Moulakakis et al. [15] recently showed postoperative immune response to be dependent on the endograft type. Especially after Anaconda® implantations (Vascutek, Bad Soden, Germany), but also after Zenith® implantations (Cook Inc., Bloomington, IN, USA), a strong inflammatory reaction was observed; both stent grafts are made of polyester. The use of the Excluder® system made from polytetrafluorethylene (W.L. Gore and Associates, Flagstaff, AZ, USA) led to only mild inflammation. Although the increase in the 24-h serum concentration of IL-6 and IL-10 was elevated compared to the preoperative controls with all 3 stent grafts, patients treated with the Excluder® statistically had the smallest IL level increase (IL-6: Anaconda® vs. Excluder®: p<0.01; Zenith® > Excluder®: p<0.02). The influence of the contrast agent or aneurysm thrombus content on the development of PIS could not be proven. The etiology of PIS remains unclear. However, specific macroscopic and microscopic construction of the polyester fabric, the stent graft support and other endograft components, e.g., introducer sheaths [15], are discussed.

There are no established algorithms concerning the type and duration of treatment for PIS. Some authors propagate the preoperative prophylactic administration of corticosteroids to mitigate the inflammatory process, whereby other groups.

Based on 74 clinics (%)

<table>
<thead>
<tr>
<th>Total responses (n)</th>
<th>Based on 74 clinics (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic Endurant®</td>
<td>57</td>
</tr>
<tr>
<td>Gore Excluder®</td>
<td>28</td>
</tr>
<tr>
<td>Zenith® Flex</td>
<td>24</td>
</tr>
<tr>
<td>Vascutek Anaconda®</td>
<td>14</td>
</tr>
<tr>
<td>Medtronic Talent®</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
</tbody>
</table>

The category ‘other’ included: TriVascular Ovation® (TriVascular, Santa Rosa, CA, USA; n=5) Aorfix® (Lombard Medical, Oxfordshire, United Kingdom; n=1), and Cook Zenith® LP (Cook Inc., Bloomington, IN; USA; n=1).

*Multiple answers were possible.

<table>
<thead>
<tr>
<th>Total responses (n)</th>
<th>Based on 74 clinics (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>24</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>22</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>14</td>
</tr>
<tr>
<td>Metamizole</td>
<td>13</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>8</td>
</tr>
<tr>
<td>Indometacin</td>
<td>2</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>No treatment</td>
<td>20</td>
</tr>
</tbody>
</table>

The category ‘other’ includes: ticlopidine (n=2). *Multiple answers were possible.
treat PIS only in acute cases [8, 14]. Ger-
asimidis et al. [13] showed that PIS oc-
curs in 10% of patients despite prophyl-
lactic treatment with intraoperative cor-
ticosteroid administration and periopera-
tive NSAID administration. Similarly, the
perioperative administration of antibiot-
ics by Akin et al. [1] did not have an effect
on the incidence of PIS. The lack of stan-
dardized treatment is also reflected in the
present survey. Nationwide, NSAIDs are
the preferred substance class. However,
there is no consensus concerning the ad-
ministration of the drug and the dosage or
treatment duration ( Tab. 2). Less than
half of the clinics surveyed indicated using
(standardized) monotherapy with a spe-
cific drug in PIS. More than 30% indicat-
ed using ≥2 drugs. From the view of the
authors, prophylactic anti-inflammatory
treatment to avoid PIS after EVAR con-
sidering the comorbidity and side effects
is not justified. In the authors’ experience,
500 mg acetylsalicylic acid i.v. twice dai-
ly for 3 days in the case of acute PIS has
proven efficacy.

The clinical relevance of PIS has been
discussed since it was first described at
the end of the 1990s. Actually, the num-
ber of cases with severe coronary, pulmo-
nary, renal or anticoagulatory dysfunc-
tion described in the literature is small
[8, 9, 16]. In the majority of cases, a tran-
sient condition with flu-like symptoms is
described for PIS [6, 12, 15]. The scientif-
ic research efforts that have been under-
taken more recently concerning PIS have
shown, however, that there is still ambigui-
ity concerning the short- and long-term
consequences of PIS. This is especially
ture due to the fact that the number of en-
dograft implantations is increasing world-
wide. In the present survey—-independent
from the EVAR frequency (χ² test for lin-
ear trend, p=0.895)—only a slight major-
ity (55.4%) of the clinics for vascular sur-
gery surveyed currently indicate PIS as
a relevant complication after EVAR in dai-
ly clinical practice. However, nearly three-
quarters (54/74) of those questioned used
pharmacological treatment.

However, what does relevant mean? In
addition to the individual symptomatol-
ogy of the patients, increased diagnostic
d and nursing effort is required. Further-
more, analysis of prospective data indi-
cates that PIS can lead to prolonged hos-
pital stays [2]. In accordance with current
reporting standards for EVAR, this must
be classified as a moderate complication
[7]. Against the background of individual
patient burden and the limited informa-
tion in the literature, PIS is in the authors’
opinion a clinically and economically rel-
levant complication of endovascular AAA
treatment which requires further clarifica-
 tion. However, this can only be realized
by analyzing patients affected. In the 12-year
data recently published by Trenner et al.
[20] on “Qualitätsicherung BAA” (Qual-
ity assurance AAA) of the Deutsche Ge-
sellschaft für Gefäßchirurgie und Gefäß-
medizin” (DGG, German Society for Vascu-
lar Surgery and Vascular Medicine), PIS
is not listed. More recently, the “Deutsche
Institut für Gefäßmedizinische Gesund-
erassurance AAA) of the Deutsche Ge-
sellschaft für Gefäßchirurgie und Gefäß-
medizin” (DGG, German Insti-
tute for Vascular Medicine and Health
Research) has made available the option
“postimplantation syndrome” in the post-
surgical course—provided clinic-internal
documentation is available—thus, allow-
ing future patients to be registered in par-
ticipating clinics.

The generation of valid data concern-
ing PIS only appears to be possible with-
in the framework of a prospective, multi-
center study with uniform documentation
of PIS cases after EVAR. The data collect-
ed within such a study including periopera-
tive course, morbidity, treatment, and
follow-up of patients with PIS should con-
tribute significantly to the clinical charac-
terization of PIS.

Limitations
The present work has the following limita-
tions: it is a retrospective study of data that
was compiled using a questionnaire and
was partially categorized, which means
it is—in general—the summarization of the
subjective replies given by the vascu-
lar surgeons surveyed. The quality of da-
ta is dependent on the estimates provided.
A selection bias cannot be excluded. Ac-
cordingly, the results only reflect the per-
ception in the clinics questioned, which is,
however, not a representative picture for
Germany as a whole. Furthermore, near-
ly 40% of the questionnaires mailed were
not returned, which limits the evaluable
data further.


Practical conclusion
The incidence of PIS after endograft im-
plantation in AAA is estimated by Ger-
man vascular surgeons to be about 20%. Fever
appears to be accepted as the pre-
dominant diagnostic criterion. Treat-
ment for PIS is generally based on vari-
ous NSAIDs in approximately 75% of the
clinics surveyed. The opinion concern-
ing the clinical relevance of PIS is divid-
ed. Against the background of the limit-
ed data available, the individual burden
of the affected patients, and the other
unknown long-term effects indicate that
further follow-up and characterization of
PIS in the framework of prospective stud-
ies are needed.

Corresponding address
Dr. M. S. Bischoff
Klinik für Gefäßchirurgie und Endovaskuläre
Chirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 110
69120 Heidelberg
Germany
moritz.bischoff@med.uni-heidelberg.de

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A. S. Peters, A. Hylilä-Durr, and D. Böckler declare that
they have no conflict of interest.

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