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*Vascular* 2013 21: 137 originally published online 7 May 2013  
DOI: 10.1177/1708538113478773

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# Results from the International Silver Graft Registry for high-risk patients treated with a metallic-silver impregnated vascular graft

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The purpose of this postmarket surveillance registry was to document the efficacy of a vascular prosthesis coated with metallic silver in high-risk patients undergoing vascular reconstructions. Patency (primary endpoint) and freedom from graft infection (secondary endpoint) data were assessed at a minimum of 12 months in patients with significant co-morbidity and/or confirmed graft infections or infected native vessels. Between November 2006 and December 2009, 230 patients with high-risk factors underwent aortic, peripheral and/or extra-anatomic reconstructions with Silver Graft® (SG) in six German, one French and one Polish vascular center. All participating centers used the metallic silver-coated polyester graft (SG) in various diameters and lengths including tubular and bifurcate vascular grafts. Doppler ultrasound follow-ups to determine graft patency were planned at 12 months or done at an earlier time in case the patient became symptomatic. A total of 230 patients were studied. Ten of these 230 patients had graft infections at baseline whereas the remaining 220 subjects had significant risk factors such as coronary artery disease (62.7%, 138/220), vascular access in scar tissue (27.3%, 60/220), Fontaine III/IV (38.2%, 84/220), chronic renal insufficiency (26.8%, 59/220) and diabetes (21.0%, 46/220). The long-term follow-up at  $15.5 \pm 8.3$  months revealed a secondary patency rate of 93.2% (205/220) and an 'all cause' mortality rate of 18.6% (41/220). There was a freedom from *de novo* graft infection rate of 95.9% (211/220) in the high-risk group without graft infections at baseline. One re-graft infection occurred distal of the revisional reconstruction in the 10 patients with graft infection at baseline. The presence of perigraft fluid at follow-up and Fontaine III/IV at baseline were found to be predictors for graft patency whereas perigraft fluid presence was the only predictor for *de novo* graft infections. This registry revealed favorable patency and freedom from *de novo* infections rates in a 'high-risk' population with significant co-morbidities.

**Key words:** vascular; graft; infection; silver-coated; antimicrobial

Accepted March 5, 2012

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## Introduction

The primary objective of this postmarket surveillance study was to assess the secondary patency rate of a silver-releasing vascular graft in a high-risk patient population suitable for vascular reconstructions. Furthermore, the freedom from *de novo* graft infections was determined in various registry subgroups. This registry was proposed as the extension of the First in Man trial conducted by Zegelman *et al.*<sup>1</sup>

## Materials and methods

The International Silver Graft® Registry is an international non-randomized, multicenter, single-armed postmarket surveillance study. Recruitment was open to patients in three

different high-risk groups defined by either significant co-morbidity, infection of a native vessel (e.g. mycotic aortic aneurysm) or vascular graft infection at baseline.

### Materials

Silver Graft® (B.Braun Melsungen AG, Melsungen, Germany) is a polyester, knitted, double-velour vascular prosthesis (SG) whose external textile surface is coated with metallic silver instead of silver acetate for a sustained long-term silver release.<sup>1</sup> Gelatin is used to seal the graft after the silver is deposited. This prosthesis was originally designed for prophylactic use to prevent graft infections. Sustained bactericidal effects have been confirmed *in vitro*<sup>2</sup> and in animal studies<sup>3</sup> with long-term studies indicating a residual graft surface silver content of 98% after 12 months.<sup>2</sup> Further properties relative to inhibition of bacterial growth on the surface of this silver-coated grafts have been described by Strathman *et al.*<sup>4</sup>

The full range of SG was available to all investigators and included bifurcations (14 × 7, 16 × 8, 18 × 9, 20 × 10) and straight tubes ranging from 6 to 20 mm in various lengths from 15 to 80 cm. Vascular reconstructions were done according to each institution's guidelines and experiences.

### Study design and population

The International Silver Graft® Registry is an international non-randomized, multicenter, single-armed, post-market surveillance study on high-risk patients with peripheral occlusive artery disease (POAD) or aneurysms. Patients in need of revisions due to vascular graft infections or infected native vessels were also included.

### Indication

To reflect the clinical reality of vascular surgery patients, all possible vascular reconstructions with the existing product portfolio were permitted.

### Inclusion criteria

Patients suitable for vascular reconstructions with an overall health status permitting vascular surgery had to fulfill at least one of the following criteria in the 'non-graft infection' group:

- Diabetes;
- Dialysis-dependent;
- Fontaine class IV;

- Body mass index of at least 30;
- Immunosuppression;
- Emergency surgery;
- High-risk surgical site (e.g. groin access).

In the other two inclusion categories, the patient must have had either an infection involving a native vessel or an infected previously implanted vascular prosthesis (graft infection at baseline).

### Exclusion criteria

Exclusion criteria for the implantation of SG were:

- Patient not suitable for surgery;
- Pregnancy;
- Documented allergy to silver or silver ions.

### Primary endpoint

The primary endpoint was secondary patency at a follow-up of at least 12 months quantified with duplex ultrasound.

### Secondary endpoints

The secondary endpoints were freedom from graft infection and freedom from perigraft fluid presence at a minimum of 12 months. Duplex ultrasound was used to detect perigraft fluids. Additional clinical indications for inflammation or infections were recorded when necessary.

### Source data monitoring

Key patient data and adverse events were source data verified by an independent contract research organization (Clinical Research Institute Center for Cardiovascular Diseases, Rotenburg, Fulda, Germany). Monitoring visits were conducted after final data were obtained from an Internet-based data acquisition platform ([www.silvergraft.com](http://www.silvergraft.com); Frictionless GmbH, Kiel, Germany).

### Statistical methods

The  $\chi^2$  tests were applied to calculate the confidence intervals for the odds ratios (ORs) and corresponding *P* values. Frequency data were analyzed in SPSS (version 18.0; IBM, Armonk, NY, USA) and ORs were computed in BiAS (version 8.05; Epsilon Verlag, Frankfurt, Germany). The theoretical sample size calculation was done with nQuery advisor (version 7.0; Statistical Solutions, Saugus, MA, USA).

## Patient demographics, risk factors and vascular reconstructions

A total of 230 patients were recruited. Since patients with graft infections at baseline have a higher risk for adverse events, separate analyses for patients with and without graft infections were done to avoid the associated bias relative to this risk factor when interpreting the study outcomes. Associated risk factors are listed in Table 1. In the patient group without graft infection at baseline, ASA scores were 20.1% (ASA 2), 63.0% (ASA 3) and 16.0% (ASA 4), whereas one patient had ASA classification 5. In these 220 patients, the average patient age was  $66.3 \pm 10.8$  years. Patients were predominantly male (77.7%, 171/220). The overall diabetes rate was 21.0% (46/220). Fontaine classifications were IIa 6.8% (15/220), IIb 30.6% (67/220), III 24.2% (53/220) and IV 14.6% (31/220). Other indications besides POAD were aneurysms 7.3% (16/220) and revisions 16.5% (36/220).

As listed in Table 2, 34.6% (76/220) of all vascular reconstructions had an aortic anastomosis. Other bypasses such as iliaco-xxx and femoral-popliteal contributed 18.6% (41/220) and 14.1% (31/220), respectively. Extra-anatomic

**Table 1** Patient demographics in the patient population without graft infections at baseline ( $N = 220$ )

Patients	
Recruitment and long-term follow-up	$N = 230$
Follow-up period	$15.6 \pm 8.3$ months
Age	$66.3 \pm 10.8$ years
Male inclusion	78.7% (181/230)
Diabetics	20.9% (48/230)
Insulin-dependent	10.9% (25/230)
Non-insulin-dependent	10.0% (23/230)
Coronary artery disease	62.2% (143/230)
Access in previous scar tissue	30.0% (69/230)
Chronic renal insufficiency	26.5% (61/230)
COPD	39.1% (90/230)
Body mass index	$26.4 \pm 5.3$
Patient classification	
High risk without infection	91.7% (211/230)
High risk with infection involving a native artery	3.9% (9/230)
High risk with graft infection	4.4% (10/230)
Fontaine classification	
IIa	6.8% (15/220)
IIb	30.6% (67/220)
III	24.2% (53/220)
IV	14.6% (31/220)
Aneurysm repair	7.3% (16/220)
Others, e.g. revisions at anastomoses	16.5% (36/220)

COPD, chronic obstructive pulmonary disease

**Table 2** Types of vascular reconstructions in the patient group without graft infections at baseline

Type of reconstruction	Frequency
Aorto-xxx	34.6% (76/220)
Iliaco-xxx	18.6% (41/220)
Femoropopliteal	14.1% (31/220)
xxx-crural	5.5% (12/220)
<b>Extra-anatomic</b>	27.3% (60/220)
Crossover with a. fem	4.5% (10/220)
Protheto-xxx	3.2% (7/220)
Other extra-anatomic	19.6% (43/220)

reconstructions were done in 60 out of 220 patients (27.3%).

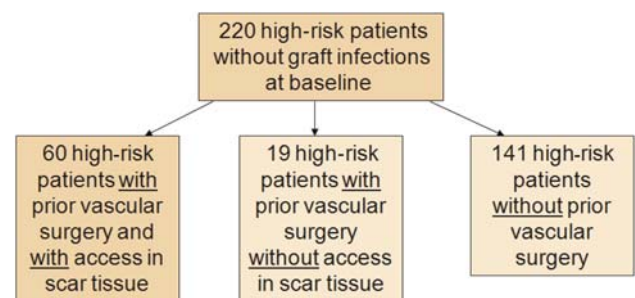
Reconstructions with access in scar tissue were documented at baseline. The majority of patients did not have any prior vascular surgery 64.1% (141/220). However, 60 patients had prior vascular reconstructions and had vascular access in scar tissue 27.3% (60/220). Figure 1 illustrates the distributions relative to this surgical risk factor.

## Results

### Revisions

In-hospital revisions were done in 15.5% of all patients (34/220 patients). There were six early deaths during the first week of hospitalization. In all, 84.8% (180/220) patients did not require additional in-hospital revisions to correct the course of the healing process (see Figure 2).

Figure 2 shows the frequency of revisions prior to discharge where several revisions per patient could be specified. The most commonly practised revision was a wound revision at the external vascular access site (30.2%, 13/43). Vacuum therapy to enhance healing was applied in 7.0%



**Figure 1** Patient groups without graft infection at baseline relative to the risk factors 'scar tissue access and prior vascular surgery'

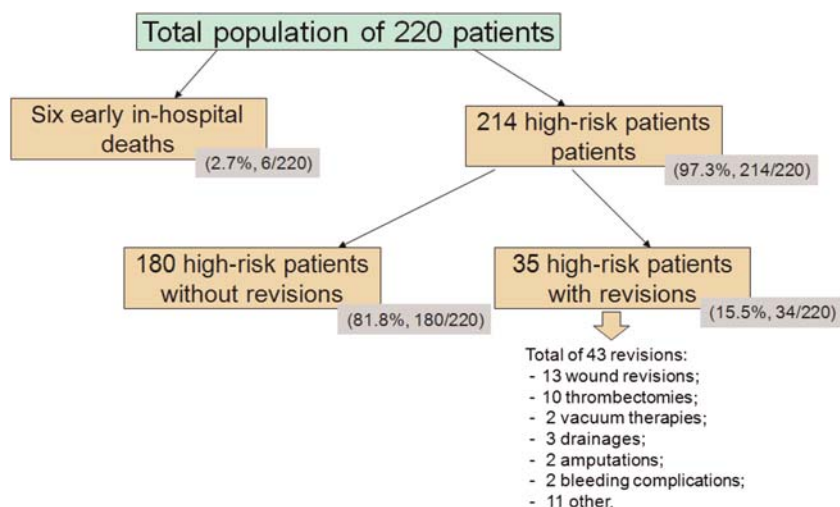


Figure 2 Revisions prior to patients' discharge

during hospitalization (3/43) while thrombectomies for graft patency were indicated in 23.3% (10/43) of all cases.

At the 12-month follow-up, 84.4% of all available patients (151/179) did not have any additional revisions since discharge. Five patients had revisions prior to their death.

The most frequent revision were thrombectomies (35.1%, 13/37) followed by wound revisions (24.3%, 9/37) (Figure 3).

### Mortality

The Kaplan–Meier curve for absence of all-cause death revealed a 15.5% mortality rate at one year (34/220 patients) in the patient subset without graft infection at baseline (Figure 4). There were three deaths in the 10 patients who had a graft infection at baseline. Two of the three deceased patients had infected peripheral reconstructions at baseline (iliaco-femoro, femoro-femoral) and one extra-anatomic graft infection (axillo-bifemoral).

In total, there were 41 reported deaths of patients during the follow-up interval. Independent of their temporal documentation on the Kaplan–Meier curve, one can categorize their cause of death as shown in Table 3.

### Patency

The primary assisted patency rate at discharge, i.e. the flow-related graft function with optional interventions such as thrombectomy was 205 out of 214 patients or 95.8%. Six patients were lost due to early in-hospital deaths (see Figure 5). Nine patients (4.2%) underwent at least one thrombectomy to establish patency prior to discharge.

Secondary patency was assessed in all living patients at the long-term follow-up (Figure 6). In patients who passed away, the graft was assumed patent unless it was specified to be occluded and/or the potential cause of death may have had a relationship with a failed graft. At the follow-up of  $15.5 \pm 8.3$  months, there were 41 deaths. Two of these

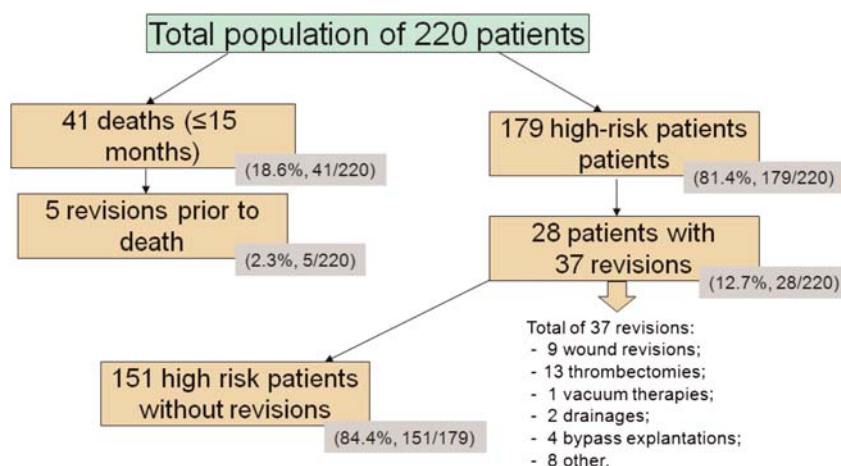
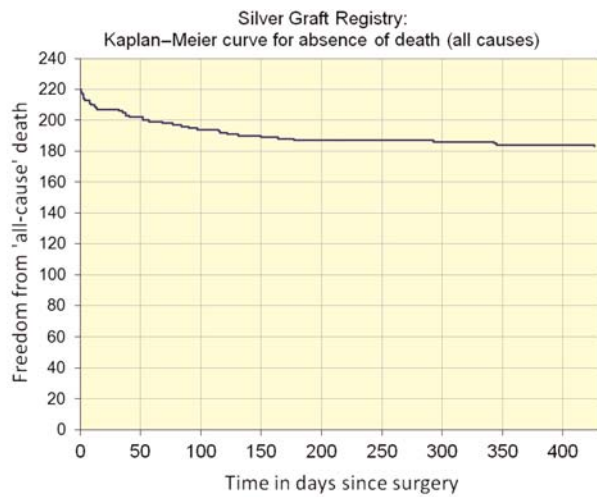


Figure 3 Revisions up to the long-term follow-up





Patients at risk

Days	0	50	100	150	200	250	300	350	400	450
Patients	220	202	194	189	187	187	186	186	184	183

**Figure 4** Long-term Kaplan–Meier Curve for Freedom from ‘all-cause death’ ( $N=220$ ) in the patient population without graft infection at baseline

**Table 3** Cause of mortality in the patient group without ‘graft infection’ at baseline, total number of deceased patients ( $n=41$ )

Cause of death	Frequency
Cardiac failure	26.8% (11/41)
Multiorgan failure	14.6% (6/41)
Sepsis	12.2% (5/41)
Respiratory failure	12.2% (5/41)
Other causes, e.g. UTI, intestinal infarction	9.8% (4/41)
Unknown	14.6% (6/41)
Unknown but not surgery-related according to their CRF	9.8% (4/41)

UTI, urinary tract infection; CRF, case report form

patients had a documented occluded graft. In the 179 living patients, 165 had patent grafts at the time of the follow-up. However, between the discharge and the long-term

follow-up, thrombectomies were performed in 13 patients and four patients had a graft explantation.

The long-term secondary patency rate at  $15.5 \pm 8.3$  months was 92.2% (165/179).

A subgroup analysis of secondary patency per type of reconstruction revealed a secondary patency in aortic reconstructions of 98.7% (75/76) and in peripheral reconstructions of 95.1% (iliaco-x, 39/41) and 83.9% (femoropopliteal, 26/31). In the patient group with extra-anatomic revascularizations the patency was 90.0% (54/60).

### Perigraft reactions and graft/tissue integration

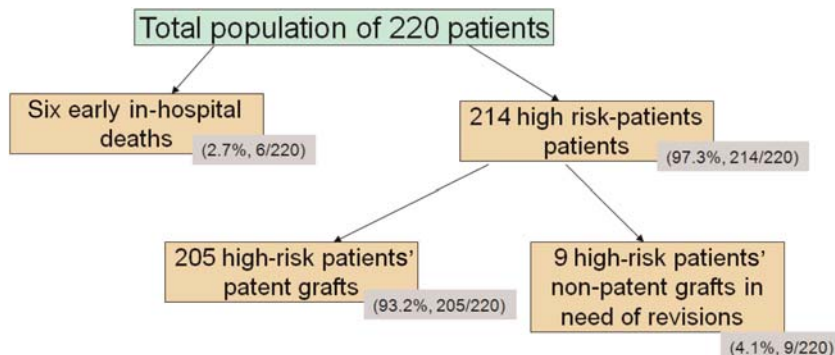
A pivotal marker for graft/tissue integration is the presence of perigraft fluid around the implanted vascular graft which can also be assessed during hospitalization for an early tendency. The results are given in Figure 7. In 92.1% (197/214) of all available patients, perigraft fluid could not be detected around SG. In 5.6% (12/214) of the implanted grafts, perigraft was observed in this high-risk patient group. In five patients, sonograms were not available.

At the long-term follow-up, there were eight patients with some detectable perigraft fluid layer in the entire patient population. Five of these had additional signs of infections whereas three patients had perigraft fluids without signs of infections. Among the eight patients, there were three who had a documented lymph fistula at the time of the follow-up. One of these patients with a lymph fistula had perigraft fluid with additional signs of infection (Figure 8).

In total, 95.5% of all living patients were perigraft free and 1.7% (3/179) had a detectable perigraft fluid layer without symptoms or complications.

### Infections

At discharge, 14 patients had certain signs of infections including pneumonia, urinary tract and wound infections as documented by, for example C-reactive protein or white blood cell count. Two of these 14 patients died of multiorgan



**Figure 5** In-hospital patency rates at discharge

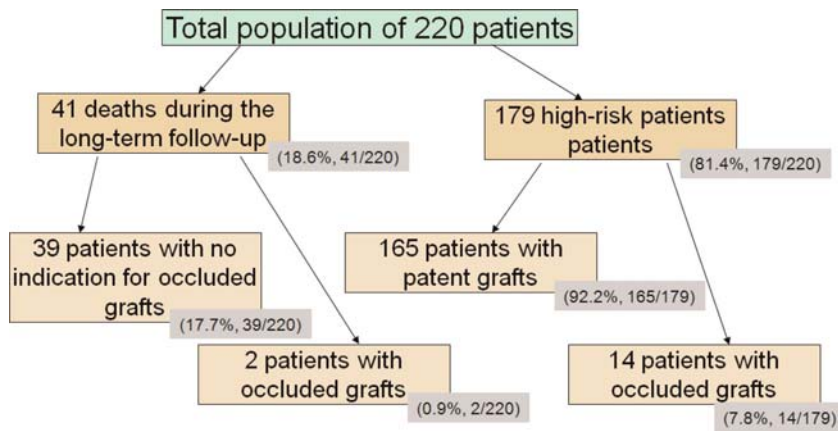


Figure 6 Secondary patency at the long-term follow-up of 15.5 ± 8.3 months

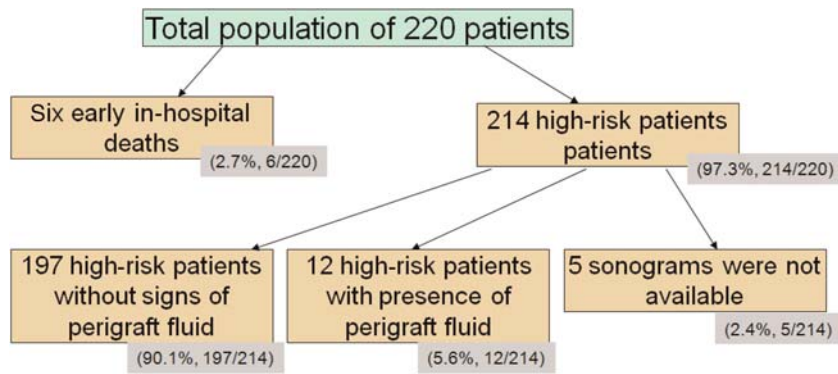


Figure 7 In-hospital perigraft fluid presence prior to discharge in the entire registry population

failure. A relationship between the vascular reconstruction and the source of the infection was excluded in six patients. In 55.7% (128/230) of the entire patient population, perisurgical β-lactamase inhibitors combined with ampicillin were given and 27.8% (64/230) received cephalosporin. In 16.5% (38/230) of all patients, other antibiotics were administered. As previously mentioned, *de novo* infections were documented according to their risk factors access in scar tissue and vascular exposure in the groin.

The patient risk groups without graft infections at baseline were divided in patients with and without access in scar

tissue (Figure 9). The group with scar tissue access showed an infection rate of 6.7% (4/60) while patients which were not preoperated, i.e. no scar tissue access had an infection rate of 3.1% (5/150). This difference, however, was not significant ( $p=0.238$ ).

Likewise, an analysis was done relative to vascular exposure in the groin which revealed a graft infection rate of 4.2% (7/167) in the high-risk group with vascular exposure in the groin and a 3.8% infection rate (2/53) without vascular exposure in the groin. The graft infection group in which a previously implanted graft was partially or

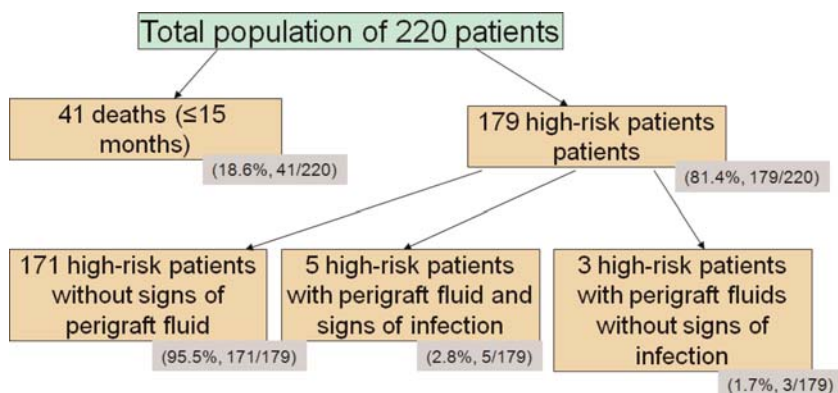
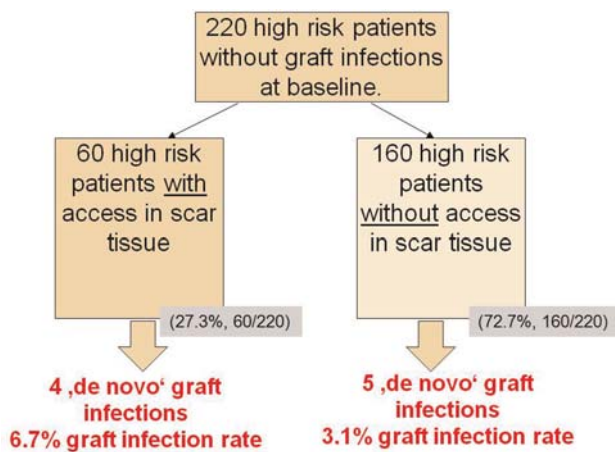


Figure 8 In-hospital perigraft fluid presence at the long-term follow-up



**Figure 9** Graft infections relative to access in scar tissue of the available 12-month follow-ups

entirely replaced by SG had one reinfection; however, distally of the original SG reconstruction.

Subgroup analyses of *de novo* infections relative to the type of reconstruction (Table 4) and Fontaine classifications (Table 5) are shown in the following tables.

The lowest infection rates were observed in reconstructions involving the aorta (2.6%). Higher infection rates were seen in iliac arteries (4.9%), femoropopliteal (6.5%) and crural bypasses (8.3%).

In all patients with Fontaine IIa, there were no *de novo* infections whereas the infection rates were higher as a

**Table 4** *De novo* graft infections per reconstruction

Type of reconstruction	De novo infections
Aorto-xxx	2.6% (2/76)
Iliaco-xxx	4.9% (2/41)
Femoropopliteal	6.5% (2/31)
xxx-crural	8.3% (1/12)
<b>Extra-anatomic</b>	3.3% (2/60)
Crossover with common femoral artery	0.0% (0/10)
Protheto-xxx	14.3% (1/7)
Other extra-anatomic	2.3% (1/43)
For example, axillo-xxx	

**Table 5** *De novo* graft infections per Fontaine class

Fontaine classification	De novo infection
IIa	0.0% (0/15)
IIb	3.0% (2/67)
III	7.5% (4/53)
IV	6.5% (2/31)

function of Fontaine classes with a peak in Fontaine III (7.5%) and IV (6.5%) (Table 5).

### Complications in the high-risk patient group with pre-existing graft infections at baseline

There were ten patients with pre-existing graft infections at baseline. Five of these infected grafts were completely replaced by SG and five grafts were partly explanted at baseline.

These 10 patients in the graft infection group (see right side in Figure 10) had the following complications at baseline:

- Six cases with detected pus around the prosthesis;
- None of the infected grafts were incorporated into the tissue (after previous reconstructions).

At the long-term follow-up this subgroup ( $N = 10$ ) had:

- Three deaths (non-graft-related);
- All grafts were patent (primary assisted patency);
- Three revisions;
- One partial explantation (one leg of bifurcation);
- One reinfection distal of the original revascularization.

### Analyses

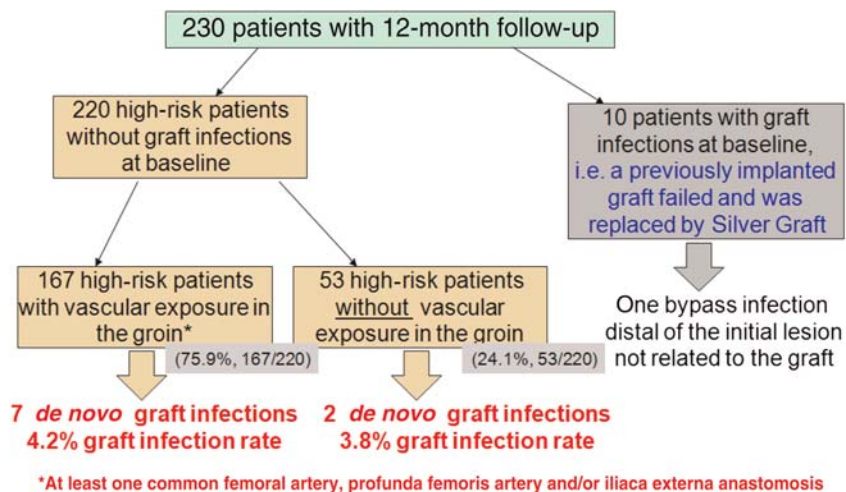
ORs were calculated based on contingency tables. Outcomes such as patency, *de novo* graft infections and mortality were analyzed relative to the following selected risk factors:

- Perigraft reaction at follow-up;
- Diabetes at baseline;
- Dialysis dependence at baseline;
- Chronic renal failure at baseline;
- Malignancy at baseline;
- Coronary artery disease;
- Chronic obstructive pulmonary disease (COPD);
- Fontaine III/IV.

The main risk factors for graft patency were perigraft reaction at follow-up ( $P < 0.001$ , OR = 0.0909; confidence interval [CI] 95% [0.0286–0.2885]) and Fontaine III/IV classification at baseline ( $P = 0.042$ , OR = 0.3488; CI 95% [0.1263–0.9637]).

Perigraft reaction at follow-up was the only risk factor for *de novo* graft infection ( $P < 0.0001$ , OR = 0.004; CI 95% [0.0015–0.0112]).





**Figure 10** Graft infections relative to vascular exposure in the groin of the available 12-month follow-ups

Mortality risk factors were as follows:

- Dialysis dependence at baseline ( $P < 0.001$ , OR = 0.0994; CI 95% [0.0299–0.3302]);
- Chronic renal failure at baseline ( $P = 0.019$ , OR = 0.4328; CI 95% [0.2147–0.8725]);
- Malignancy at baseline ( $P = 0.005$ , OR = 0.2784; CI 95% [0.1146–0.678]);
- Coronary artery disease (CAD) at baseline ( $P = 0.051$ , OR = 0.4684; CI 95% [0.2185–1.0043]).

Diabetes or COPD at baseline were not associated with higher risks for graft occlusion, *de novo* graft infections or increased mortality.

## Discussion

It is of paramount importance to point out that studies with the patient population of this registry and its associated co-morbidity (CAD 62.0%, Fontaine III/IV 39.7%) are not frequently described in the literature. Within the nature of any clinical activity, there is a direct and overpowering relationship between the complexity of the treated patients and their expected clinical outcomes. So-called ‘study patients’ to provide favorable data were expressively excluded from this ‘real world’ clinical registry. It is needless to say that patency rates, the frequency of vascular revisions and *de novo* infections, perigraft fluid presence and graft/tissue integration depend heavily on lesion-specific and patient-related risk factors. Consequently, any comparison to other clinical registries or studies<sup>5–7</sup> that do not primarily include high-risk patient groups can only be done with a maximum level of caution.

## Graft patency

Post *et al.*<sup>6</sup> reported secondary patency rates at three years for Dacron prosthesis in femoral popliteal reconstructions of 81%. Jensen *et al.*<sup>5</sup> observed a 76% secondary patency rate at two years; however, in femoral popliteal bypasses only. Assisted primary patency rates are available from Nicoloff *et al.*<sup>8</sup> in infrainguinal bypass grafting for limb salvage. Given that these patients are one of the ‘worst case’ risk subgroups, their six-month primary assisted patency rates were reported as 94.9%. It can be stated that the SG secondary patency rates at  $15.5 \pm 8.3$  months of 98.7% in aortic reconstructions and 83.9% in femoropopliteal revascularizations are in agreement with the relevant literature. In this registry, perigraft reactions at follow-up and Fontaine III/IV classification at baseline were indicative for graft patency. The lack of statistical significance for other risk factors such as diabetes is somewhat surprising but may be explained by an insufficient samples size or the dominance of other risk factors.

## Infections

Unfortunately, data on highly complex patient populations with, for example Fontaine III-IV accounting for over one-third of the overall patient population, are very scarce and are not frequently published. It seems that these challenging patients are not included in controlled clinical trials for a number of reasons.

As mentioned earlier, the comparison of meaningful to compare ‘interstudy’ infection rates as proposed by Ricco<sup>9</sup> must be done by adjusting for potent biases such as

- Presence of scar tissue;
- Vascular access in the groin;

- Extra-anatomic reconstructions;
- Co-morbidities, e.g. Fontaine III/IV.

*De novo* graft infections can range from 0.5 to 3% in reconstruction with a proximal aortic anastomosis and can be as high as 8.0% in extra-anatomic revascularizations (Table 6).<sup>10</sup>

In this registry, a strong tendency between frequency of graft infection and prior access in scar tissue was observed. In the patient group with prior scar tissue access, there were five *de novo* graft infections in 60 patients (8.3%). We observed a 6.5% infection rate in the femoropopliteal position which appears high but needs to be put into perspective by the findings of Brothers *et al.*<sup>11</sup> and Pounds *et al.*<sup>7</sup> Brothers *et al.*<sup>11</sup> reported a 18.0% infection rate in infrainguinal grafts mostly after major amputations. Pounds *et al.* found in their retrospective study a three-year infection rate of 29.3% in infrainguinal reconstructions.<sup>5</sup> In lower-limb grafts, Bandyk<sup>12</sup> provided a 10–20% range of infections. Therefore, our observation of 6.5% seems quite reasonable given the profound co-morbidities of our patient population. Vascular exposure in the groin does not seem to be associated with the incidence of graft infection (groin exposure 4.2 versus 3.8% non-groin exposure). Extra-anatomic reconstructions accounted for 27.1% (60/220). It is noteworthy that in this subgroup, there were only two *de novo* infections (3.3%, 2/60). Higher rates were observed in smaller lumen reconstructions such as femoropopliteal or crural reconstructions with infection rates of 6.5% (2/31) and 8.3% (1/12). A properly powered analysis could not be done due to the limited number of cases per group. The remarkable efforts undertaken by Larena-Avellaneda *et al.*<sup>13</sup> to retrospectively study the prophylactic use of silver acetate-coated versus uncoated polyester grafts did not show a significant effect on the prevention on graft infections. Their patient population consisted of 430 patients receiving silver acetate-coated grafts and 483 treated with standard grafts. Vascular reconstructions were also quite diverse, thereby adequately reflecting the plethora of possible lesions sites in this patient target group.

**Table 6** Incidence of prosthetic vascular graft infection relative to implant site<sup>9</sup>

Graft implant site	Incidence
Aorto-iliac	0.7–3.0%
Aorto-femoral	0.5–3.0%
Femoro-femoral	1.3–3.6%
Axillo-femoral	5.0–8.0%
Femoropopliteal	0.9–4.6%

The important challenge to truly determine the efficacy of silver may have been overshadowed by other bias introducing risk factors. From a statistical point of view, a true randomized trial to show a 50% reduction based on a 3% infection rate would require 1534 patients per treatment arm (power 80%,  $\alpha=0.05$ , two-sided based on nQuery® Advisor version 7.0; Statistical Solutions). Also, polyester grafts independent of their chemical composition (silver acetate versus metallic silver) may not be the best choice for below the knee vascular reconstructions where autologous grafts were reported to be superior.<sup>7</sup>

### Mortality

Engelhardt *et al.*<sup>14</sup> studied the quality of life in patients undergoing infra-geniculate bypass surgery for limb salvage. Their studied cohort included severe co-morbidities such as coronary artery bypass grafting (12%), myocardial infarction (MI) (20%) and diabetics (60%). Patients' survival at 12 months was 77% which corresponds well with our observed 12-month survival rate of 84.5%. At 24 months, this research group reported a 35% mortality rate. Our subgroup analysis revealed that CAD, chronic renal failure, dialysis dependence and malignancy had ORs predictive of mortality. Arvela *et al.*<sup>15</sup> found a strong relationship between the glomerular filtration rate and mortality in patients with infrainguinal bypasses and critical limb ischemia. Their study population included 60% of patients with Fontaine IV classification. Their survival rates in terms of glomerular filtration rates ranged from 47.9 to 78.6%, which are slightly lower than the survival rates our registry population. Also, in the German getABI trial,<sup>16</sup> patients underwent routinely ABI measurements to predict their cardiovascular risk and mortality. There were several groups of patients depending on their status (symptomatic versus asymptomatic) and their ABI classifications with cut-off values at 0.5, 0.7, 0.9, 1.1 and 1.5. In the symptomatic patient group, the event-free survival consisting of MI, coronary target lesion revascularization, carotid artery stenting/carotid endarterectomy and peripheral revascularization or amputation was 80% at two years.<sup>17</sup>

All of the abovementioned rather high event rates in these reports are in agreement with our findings, notably the overall mortality rate of 15.5% at 12 months or 18.6% at 15.5 ± 8.3 months in the overall population on varying time points of the corresponding Kaplan–Meier curve.

### Perigraft fluid

Since perigraft seromas could be indicators for adverse events,<sup>17,18</sup> they were assessed during the routine sonograms to determine patency.

A perigraft reaction review of Vollmar *et al.*<sup>19</sup> revealed that among retrospectively studied vascular reconstructions using polytetrafluoroethylene (PTFE) and polyester grafts in over 2200 patients, perigraft fluid accumulation occurred in 0.7% (polyester) and 1.0% (PTFE) of all reconstructions. These perigraft fluid incidences were observed between postsurgical months 1 and 26.

Vollmar *et al.*<sup>19</sup> explained the observed perigraft fluid reactions with either physical-chemical irritation of the surrounding tissue, mechanical trauma (continuous graft movement in the tissue bed) and latent or manifest renal insufficiency.

The available long-term ultrasound follow-ups showed in 3.6% (8/220) of all patients. In these eight patients, three lymph fistulas were detected. The presence of perigraft fluid seems to be related not only to the graft but also to the anatomic proximity to lymphatic pathways. More importantly, the presence of perigraft fluids at the long-term follow-up is strongly predictive of graft infections ( $P < 0.0001$ , CI: 0.0015; 0.112). The notion that perigraft fluid is a good surrogate marker for poor graft/tissue integration or healing seems to be overshadowed by its importance to predict graft infection. We sense that perigraft fluid at a later follow-up interval is rather a 'red flag' for graft infection.

## Revisions

Relative to surgical revisions prior to discharge and during the long-term observational period, no unexpected outcomes or deviations from relevant literature reports can be stated. Wound revisions were done in 6.1% of all available patients which are within the wound healing complication range reported by Chung *et al.*,<sup>20</sup> who found that 25% of all patients did not have completely healed wounds at one year.

The most frequent revision in this cohort was surgical thrombectomy to re-establish patency. This finding is also in agreement with other findings by Jensen *et al.*<sup>5</sup> who found that 51% of all revisions were thrombectomies. To conclude this discussion on revisions, it should be stressed again that the Silver Graft International Registry included 'high-risk' patients to 'mirror image' the 'real world' clinical challenges that are encountered by the vascular surgeon. This is also reflected in the significant numbers of revisions in a total of 28 patients, i.e. 28/179 or 12.7%.

## Final conclusions

- The secondary patency rates in aortic and peripheral reconstructions compare favorably to other published data;
- *De novo* graft infections depend heavily on patients' risk factors. Fontaine III/IV classification at baseline and

perigraft fluid at follow-up are risk factors for *de novo* graft infections. We observed a 6.5% infection rate in the femoropopliteal position which appears high at first glance only but is put into perspective by the recent findings of Bandyk,<sup>11</sup> i.e. (10–20%) and in the context of our high-risk patients;

- The freedom from perigraft fluid was 96.4% at the time of the long-term follow-up. Perigraft fluid at this late time point is highly predictive of *de novo* graft infections;
- The 12-month all cause mortality rate of 15.5% was high but agrees with comparable literature in high-risk patients;
- A prophylactic efficacy of silver-coated grafts is not obviously detectable. Trends in efficacy could be observed in extra-anatomic reconstructions (3.3%) for which higher rates were reported in the literature;
- In graft infection patients at baseline, there were no re-graft infections of the original vascular reconstruction. A universal conclusion for treatment with silver-coated graft cannot be manifested but needs to be seen in concert with additional patient care such as the combination with other measures such as local antibiotics and the application of vacuum therapy;
- Silver Graft® was safe and effective to maintain patency during the observation period of 15 months.

## Outlook

Due to the statistical constraints of detecting small incremental differences in adverse events, it seems promising to study cost-effectiveness of silver-coated grafts as proposed by Bisdas *et al.*<sup>21</sup> They found that cryopreserved arterial homografts are three times as costly compared with silver-coated grafts with comparable efficacy.

## Limitations

The Silver Graft Registry is not a randomized trial and the frequency of adverse events could have been underestimated. All efforts were made to perform source data verifications by an independent contract research organization for adverse events. Nevertheless, the risk of graft occlusion or other serious adverse events does not end after our mean observation period of  $15.5 \pm 8.3$  months. It can also not be assumed that patients return to their primary care provider so that complete data on potential revisions may not be complete. Within a registry, however, it is commonly accepted that there is a risk of event under reporting in exchange for real world data in the routine clinical setting.<sup>21</sup>

## Declarations

**Conflicts of interest:** MW is a full time employee of B.Braun Melsungen AG.

**Contributorship:** MZ and GG were involved in conception and design of the study and analysis and interpretation; MZ, GG and MW wrote the article; and MZ, GG and Ralf Degenhardt (HKZ Rotenburg) carried out statistical analysis. All authors were involved in data collection, final approval of the article, critical revision of the article and obtained funding. MZ took overall responsibility.

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