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A systematic review of preclinical data regarding Commercial Silver coated Vascular grafts.

Short title: Preclinical data of commercial silver grafts.

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Abstract

Objective: Vascular graft infection (VGI) is a serious complication with a high mortality and morbidity rate. Several measures could be taken to reduce the risk. One of them are silver containing vascular grafts. However, to date, no clinical advantages have been reported. This study reviews the outcome of preclinical studies focusing on the role of commercially available silver coated grafts in the prevention of VGI.

Methods: A systematic review was performed with a focus on the preclinical role of commercially available silver coated vascular grafts in the prevention and treatment of VGI. A comprehensive search was conducted in Medline, Embase and Web of Science.

Results: Nine *in vitro* and five *in vivo* studies were included. Two commercial grafts were used (INTERGARD SILVER™ and Silver Graft™). *In vitro* studies used both gram-positive and gram-negative strains. A positive antimicrobial effect was observed in seven out of nine studies (77.8%). A delayed antifungal effect against *Candida* species was observed *in vitro* but disappeared when adding serum proteins. *In vivo* studies witnessed a microbicidal effect in two out of five studies (40%), but only tested a single causative pathogen *(i.e. Staphylococcus aureus).*

Conclusion: Both *in vitro* and *in vivo* studies demonstrated conflicting and mixed results concerning the antimicrobial efficacy of commercially available silver containing grafts in the prevention of VGI. In general, the study set-up was heterogeneous in the different papers. Given the lack of convincing preclinical evidence and their poor performance in clinical studies, more data are needed at this time to guide the appropriate use of silver grafts in the future.

Keywords: Intergard Silver, Silver graft, infection, prevention, *in vitro*, *in vivo*

Conflicts of interest: The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abbreviation:

CFU: colony Forming Unit

E. Faecalis: Enterococcus faecalis

ESBL: extended spectrum beta lactamase

expanded Polytetrafluoroethylene: ePTFE

IGS: Intergard Silver

MRSA: methicillin resistant Staphylococcus aureus

SG Silver Graft

VGI: Vascular Graft Infection

Introduction

Vascular graft infection (VGI) is a serious complication. The incidence ranges from 0.6 to 6%, depending on the anatomical localization. (1, 2) Today, the clinical evidence regarding vascular graft coatings (e.g. antibiotic, silver) being protective against VGI remains scarce. (3)

The antimicrobial properties of silver have been described for many centuries. (5) Before the discovery of antibiotics, its use was wide-spread, especially due to its broad spectrum efficacy against both gram-positive and gram-negative strains. (5, 6) The antimicrobial properties of silver have been attributed to its oxidized form (Ag^{+}) and act through multiple pathways: 1) disruption of bacterial cell membrane function; 2) interference with metabolic proteins/ enzymes and displacement of other metal ions (Zn^{+}, Ca^{2+}) that are essential to cell survival; 3) blockage of adenosine triphosphate (ATP) synthesis; and 4) inhibition of mRNA transcription through disruption of ribosomes. (7, 8)

As silver coatings potentially have less problems with resistance and clinical studies showed promising results in other domains (i.e. orthopaedic device-related infections), their use could be of interest for vascular grafts as well. (4) Silver coated grafts are commercially available in two forms: 1) Silver graft™ (SG) (B. Braun Melsungen AG, Vascular systems, Berlin, Germany), a polyester prosthesis impregnated with absorbable modified bovine gelatin (Polygelin) and coated with elemental silver; and 2) INTERGARD SILVER™ (IGS) (Maquet, Getinge group, NJ USA), a knitted or woven polyester graft cross-linked with type I bovine collagen and silver acetate. In addition, Maquet also introduced a combination of silver acetate with triclosan to increase the antibacterial properties (INTERGARD SYNERGY, Maquet, Getinge group, NJ USA). No clinical data are available on the use of this latter in the prevention of VGI.

Although these silver coated grafts are commercially available, data on clinical outcome seems contradictory (**table 1**). (2, 9-11) Ideally, these kind of studies should focus on patients at risk where a higher incidence of VGI is seen. A multicenter prospective study showed that IGS is safe and effective, resulting in a VGI rate of 1.3% (N=2/149) and 0% (N=0/140) in case of aortobifemoral bypass and aortoiliac bypass surgery, respectively. (9) However, a retrospective study comparing results of a IGS with non-silver grafts could not show any significant benefit for the silver coated grafts. (2) In case of femorodistal bypass surgery, studies showed an even higher infection rate of 9.4% for these grafts compared to 5.9% in the non-silver group (p=0.11). (2) (**Table 1**) Therefore, to date, the clinical efficacy of silver coated grafts has not been proven. The aim of this study was to summarize and discuss the currently available preclinical *in vitro* and *in vivo* studies focusing on the antimicrobial efficacy of commercially available silver coated grafts (IGS or SG).

Material and methods

A systematic search focusing on the role of vascular graft coatings in the prevention of VGI was conducted according to the PRISMA extension for scoping reviews guidelines. (12) A complete search without language restrictions in MEDLINE , Web of Science, and Embase was performed on May 20th, 2020. For each database, specific search sequences were created with the help of a biomedical information specialist. (**Addendum 1**). With the search strategy, papers focusing both on the treatment and prevention of VGI could be included. The abstracts were screened by two reviewers (HM and JVDE). In case no consensus could be reached, a third investigator (IF) was consulted. If further disagreement or doubt remained, the article was included for full text review.

Inclusion criteria were: (1) an i*n vivo* or *in vitro* model, (2) presence of a vascular graft coating on a synthetic vascular graft, and (3) local or systemic inoculation of the graft with a pathogen. All human studies were excluded.

For full text reading, only English papers were included. Based on this search, articles including commercially available silver coated grafts (SG or IGS) were reviewed. The primary outcome was to define antibacterial properties of silver coated grafts.

Results

A total of 4667 studies were identified. Of these, 1177 duplicates were excluded. Abstracts of 3490 studies were screened, of which 223 were judged as potentially eligible. Reasons for exclusion are summarized in **Figure 1**. Finally 16 studies used a commercially available silver coated graft in their protocol (9 *in vitro* and 7 *in vivo* studies). A positive antibacterial effect was defined when the silver graft revealed (statistical significant) better results compared to a control graft (13-16) or to a later timepoint. (17) Three studies mentioned the presence of bactericidal activity as a >3 $\log_{10}$ reduction factor. (18-20)

*In vitro studies **(Table 2)***

Nine *in vitro* studies used a silver coated graft in their protocol. Efficacy was tested against a variety of bacterial strains. *S. aureus* was the most frequently used strain (13, 14, 16, 18, 19, 21, 22). Depending on the study, different outcome results were observed. In seven studies (N=7/9, 77.8%) a promising antibacterial or antifungal effect was seen. (13, 14, 16, 18-20, 23)

Ricco et al. investigated the bactericidal effect of the IGS against methicillin resistant Staphylococcus aureus (*MRSA)* up to 24 hours. Grafts were placed on Petri dishes, inoculated with 0.1ml 1.0 x 10^7 colony forming units (CFU) and evaluated at different time intervals. Only

at 24 hours, a significantly lower mean CFU-count was observed compared to a collagen coated grafts (1.04×10^4 vs. 6.47×10^5; p=0.031). This effect was reached faster compared to collagen coated grafts and observed 4h after inoculation in case of IGS. (20)

This bactericidal effect was also confirmed in other studies. Berard et al. investigated the anti-infectious properties of IGS during the first 24 hours and after seven days against *S. epidermidis*, *MRSA*, *E. coli* producing extended spectrum beta-lactamase (*ESBL-E coli*) and *C. albicans*. Grafts were immersed in a solution containing the microorganisms and sonicated at different time points. Compared to a non-antibacterial coated collagen polyester graft, a significant reduction ($p<0.05$) in viable counts was observed at 4, 8, 24 and 168 hours for all bacterial strains. This was not the case, however, for *C. albicans* at 4 hours; here, a delayed efficacy was visible. Bactericidal activity was considered to be present in case of a Log_{10} reduction factor > 3. This factor varied for all strains. At 169 hours, a variation of 3.34-4.85 was seen. (18, 19) No silver resistance could be detected at seven days. (18)

The inhibitory potential of silver on *Candida* was also investigated by Tammer et al. A strong inhibitory effect on the attachment and biofilm formation was seen in serum-free media. In the presence of serum, however, a significantly higher adherence ($p<0.005$) was seen compared to collagen coated grafts at 90 minutes, 24 hours and 72 hours. Moreover, the metabolic activity was significantly higher at all time points. The authors suggested that this paradoxical effect might be explained in two ways: firstly, by the binding of silver ions by serum proteins, thereby reducing the amount of silver ions that can act on *Candida* cell structures. Secondly, silver nitrate in sublethal concentrations induces biofilm formation.(23)

Strathmann et al. investigated the potential of SG in damaging bacterial cells (*S. aureus*) by means of a bacterial cell viability assay that makes use of an oxonol dye. Visualization of

membrane damage is an indication of the proportion of depolarized cells as a measure of the cells which lost their viability. After 12, 24 and 48 hours, a significant reduction of biofilm volume on silver coated grafts of 62%, 43%, and 55% was seen respectively, compared to uncoated grafts ($p < 0.005$). Membrane damage of *S. aureus* cells was higher in the silver coated group (91.4%, 82.5%, and 72% after 12, 24 and 48 hours) compared to the uncoated group (3.9%, 5.6%, and 5.7%, $p<0.005$). (14) Finally, Obermeier et al investigated the efficacy of new gentamycin fatty acid salt coatings on gelatin sealed expanded polytetrafluoroethylene (ePTFE) . Both IGS and gelatin sealed ePTFE could completely eradicate different concentrations of *S. epidermidis* (1000, 5000, 10 000 CFU/ml) when in direct contact with a bacterial solution for 18 hours. (16)

Not all studies (N=2/9, 22.2%) could confirm this beneficial antibacterial effect of silver coated grafts. (21, 22) Osińska-Jaroszuk et al. demonstrated that IGS was not able to inhibit bacterial growth against *E coli*, *S. aureus* and *P. aeruginosa*. Testing was performed up to 30 days. When grown on an agar plates (solid medium), inhibition was only observed beneath the graft. In liquid media containing 10^5 CFU/ml, IGS revealed scarce antibacterial activity against *E. coli*, *ESBL P. aeruginosa*, *S. aureus*, *S. epidermidis* and *MRSA*, mainly limited to the first day of the experiment. Grafts were incubated in the bacterial solution during the whole period. (21) In a study by Hardman et al., the same phenomenon was witnessed with absence of a zone of inhibition for any of the tested organisms on agar plates. However, in a second protocol, grafts were first placed in a liquid bacterial solution for 15 minutes, then incubated for one hour in a humid atmosphere and finally incubated on agar plates. IGS could resist *MRSA* and *E. faecalis* growth until day three, *E. coli* and *S. epidermidis* until day five whereas no resistance was observed in gelatin impregnated grafts. (13)

Wozniak et al. used comparable microorganisms but different strains in a liquid solution (*S. aureus*, *S. epidermidis*, *P. aeruginosa* and *E. faecalis*) for 24 hours. The grafts were washed and sonicated to investigate attached bacteria. Compared to an uncoated polyester graft, no difference in implant associated infections was observed. (22)

In vivo studies ***(Table 3)***

Seven articles studied a commercially available silver coated graft in an animal model. (8, 15, 17, 24-27) In this group, two studies added rifampicin soaking onto the silver coated graft. This combination resulted in an augmented antibacterial activity and a prolonged release of antibiotic and silver in the perigraft site. (8, 25) These studies were excluded as the focus of this study was to review the antibacterial effect of silver coated grafts exclusively. In dogs, a graft was sutured at the level of the infrarenal aorta; in rat and mice a subcutaneous pocket was created. In this latter, the effect of blood flow not mimicked. In one study, bacterial challenge was performed by intravenous infusion two days after implantation. (26) All other studies used topical inoculation. In all studies, *S. aureus* was used to test the antibacterial properties. No clinical evidence of silver related adverse events were mentioned.

Different results were obtained. In the study of Artini et al. (24), IGS could prevent infection at 21 days if a low bacterial load (10^5 CFU/ml) was used, but not when a high bacterial load was applied (10^8 CFU/ml). This effect disappeared when no systemic antibiotics (levofloxacin intraperitoneally for seven days) were given. This was in contrast with the rifampicin soaked graft where infection could be prevented even with a high bacterial load (10^8 CFU/ml).

These findings have been confirmed in two other studies. Firstly, Goëau-Brissonnière et al. found that IGS could not prevent infection, with infection rates of 83.3% (5/6 animals) five days

after bacterial challenge (10^9 CFU/ml, 48 hours after implantation). In contrast, almost no (N=1/6, 16.7%) infection was observed in the rifampicin coated grafts. (26) Secondly, in the study by Hernàndez-Richter et al., all silver coated grafts (N=6/6, 100%), both IGS and the non-commercial silver/gelatin-coated graft, had been infected 14 days after local contamination of the implanted graft with a bacterial load of 10^7 CFU/ml, while only 1/6 (16.7%) of the rifampicin impregnated grafts had been contaminated. (27)

Only two *in vivo* studies mentioned a positive antibacterial result: Schmacht et al. investigated antibacterial properties of IGS at three, seven and 14 days after graft placement in dogs. At day three, grafts had a significantly higher resistance to MRSA colonization compared to day 7 and 14 (5.34×10^1 - 10^3 versus $3.27 \times 10^5 – 10^7$ and $4.78 \times 10^3 – 10^7$ respectively; $p < 0.05$). Compared to the rifampicin impregnated graft, IGS and the perigraft fluid were more susceptible to *MRSA* infection at each interval (3,7, 14 days) (5.34×10^1 - 10^3,$3.27 \times 10^5 – 10^7$ and $4.78 \times 10^3 – 10^7$ versus 0, $4.4 \times 10^{1-3}$, 0.37×10^5 respectively; $p < 0.05$). (17) In contrast, no or only minimal (N=2/7, 29%) graft contamination was seen in silver coated grafts (IGS and SG respectively) at five days in the study of Lorenz et al. This was significantly better when compared to polyester terephthalate (N=5/7, 71%), ePTFE (N=5/7, 71%) and bovine pericardium (N=7/7, 100%) grafts. Important here to mention is that a mouse model and *S. aureus* instead of *MRSA* were used (15)

Discussion

To date, no convincing clinical data are available regarding the efficacy of silver in the prevention of VGI. (**Table 1**) Two possible explanations for this phenomenon: 1) the incidence of VGI is low and larger studies are mandatory to generate sufficient statistical power. (9) 2) variable risk factors create an additional bias for interstudy comparisons of VGI rates and

increase infections rates. (9, 11) Using commercial grafts in the preclinical setting has the advantage that variations in available active coating substance can be deleted (e.g. method of binding, sterilization technique, and one would expect uniform results. However, our systematic review shows that also in preclinical studies, conflicting data have been reported. In the included studies, results varied from no antibacterial effect to complete prevention of graft infections up to 21 days after bacterial inoculation. Brochures used for both SG and IGS only referred to papers with a positive antibacterial effect. (14, 19, 20) In the *in vitro* studies a positive antimicrobial effect was observed in seven out of nine studies (77.8%). (13, 14, 16, 18-20, 23) *In vivo*, a positive effect was witnessed in only two out of five studies (40%). (15, 17)

In vitro functionality of silver coated grafts was proven up to seven days, studies with a longer duration could not demonstrate an added value of a silver coating beyond this timeframe.(18, 21) This antibacterial efficacy was shorter in animal studies, where in general a significant effect was seen during the first three to five days postoperatively. *In vitro*, a positive effect was demonstrated against both gram-positive (*S. aureus*, *S. epidermidis*) and gram-negative strains (*E. Coli*, *E. faecalis*). Interestingly, multidrug resistant strains such as *MRSA* and *ESBL-E. coli* were also susceptible to silver. No development of resistance against silver could be proven after testing multiple strains. (18) The duration of microbial exposure had an impact on outcome results *in vitro*. After short exposure of the graft during 15 minutes, IGS could resist *MRSA* or *E. coli* infection up to three days, whereas longer exposure (24 hours) limited the efficacy to the first day. (13, 21) On the other hand, both early (90 minutes) and delayed (7 days) efficacy against *Candida* species was described. (18, 23) To our knowledge, no *in vivo* testing concerning the efficacy of a commercial silver coated graft against *Candida* has been performed.

In vivo, *S. aureus* was the only species tested. Comparable to published clinical data, no adverse effects related to silver release were observed. (2) Concerning antibacterial efficacy, varying data have been reported. Animal and type of implantation seem to play a role. In two studies, the infrarenal aorta of dogs was investigated as the implantation site. In both studies, infection was not prevented. (17, 26) In two studies, mice were used and the graft was implanted subcutaneously. (15, 27) Here different results were obtained: in the study by Lorenz et al., no infection was seen at five days with the IGS. In the study by Hernàndez-Richter et al., all grafts were infected at 14 days. (15, 27) An observation that can be expected as silver is an active release coating and our *in vitro* studies could not demonstrate efficacy of silver coatings longer than seven days. (7) In a study of a subcutaneous implantation model in rats, a positive effect was observed only with a low inoculum (10^5 CFU/ml) and in the presence of systemic antibiotics. (24) Possible reasons for these conflicting *in vivo* results are the fact that different animal species were studied – all with their inherent different immune systems – and the extent to which the graft is exposed to bacteria and physiological conditions such as shear stress and serum components (i.e. bloodstream).

With regard to *in vitro* testing, Wozniak et al. could not demonstrate any benefit against *S. aureus*, *S. epidermidis*, *P. aeruginosa* or *E. faecalis* at 24 hours when compared to an uncoated polyester graft. Here, the initial bacterial load was not recorded. (22) On the other hand, Berard et al. investigated the anti-infectious properties against *S. epidermidis*, *MRSA* and *ESBL-E. coli* and found a significant reduction in viable counts at 4,8, 24 hours and 7 days when compared to a collagen polyester graft. In contrast to the previous study, other bacterial strains were used. (18, 19) A discrepancy was seen between testing on agar plates and testing in liquid media. Hardman et al. proposed that there could be two possible explanations for the inability of silver to inhibit

bacterial growth on agar plates: either 1) silver cations are unable to diffuse in the Iso-sensitest agar, and 2) silver cations are able to diffuse through the agar, but are immediately bound and inactivated by anions that are present in the agar plates. The authors therefore stressed that *in vitro* testing should be done in liquid medium rather than on agar plates (13). However, a study by Lee et al. showed that it was feasible to demonstrate the antimicrobial activity of silver particles on agar plates if the plates were highly hydrated and a disc diffusion test was performed. Overall, it appears that testing in liquid medium remains recommended to ensure proper silver release from the graft.

Similarly, it has been demonstrated that serum proteins can reduce the concentration of silver ions delivered from the surface of vascular grafts to subinhibitory levels, which may result in a stimulation of biofilm formation. (23) It should therefore be taken into account at any time, that the finding of *in vitro* efficacy cannot be translated directly into *in vivo* success. Part of the discrepancies between *in vitro* and *in vivo* studies of vascular graft infection might therefore be explained by the influence of physiological conditions on graft pharmacokinetics and/or pharmacodynamics.

Finally, some limitations to this review need to be highlighted: 1/ Not all studies were designed to primarily investigate the antimicrobial efficacy of silver grafts compared to control grafts. 2/ Due to the heterogenicity of the study set-ups and variables used, it was not possible to make a complete and clear overview of the outcome results. 3/ Polymicrobial infections and the synergic effect of different bacterial strains, which is more common nowadays, were not tested.

In conclusion, the antibacterial efficacy of commercially available silver containing vascular grafts silver containing grafts has been tested preclinically and both *in vitro* and *in vivo* studies have demonstrated varying results. Candida species were only used *in vitro* and a delayed

efficacy was observed. In general, the study set-up was heterogeneous in the different papers. Given the lack of sound preclinical evidence (i.e. both *in vitro* and *in vivo* positive results in > 50% of studies) and their poor performance in clinical studies, more data are needed at this time to guide the appropriate use of silver grafts in the future.

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Figure Legend:

Figure 1: PRISMA diagram

Table Legend:

Table 1: Overview of clinical studies including commercial available silver coated grafts in the preventive setting

Table 2: *In vitro* studies with commercial silver grafts

Table 3: *In vivo* studies with commercial silver grafts

Table 1: Overview of clinical studies including commercial available silver coated grafts in the preventive setting

Study	Patients (N)	Type Graft	Preoperative Risk factors for infection	Aortic aneurysm disease N (%)	Aortic occlusive disease N (%)	Peripheral surgery N (%)	VGI Aortic N (%)	VGI peripheral N (%)	Follow-up time (months+/- SD)
Ricco et al, 2006 (5)	289	IGS	Diabetes (N=42,14.5%) Obesity (N=34, 11.8%) Redo aortic surgery (N=4, 1.4%) Iliofemoral bypass (N=5, 1.7%) Lower limb bypass (N=8, 2.8%)	160 (55.4%)	129 (44.6%)	/	4 (1.4%)	/	55 +/- 10
Larena-avellaneda et al, 2009 (2)	430	IGS	Tissue loss (N=135, 31.4%) Bypass in groin (N=82, 19.1%) Thrombendarterectomy (N=34, 7.9%)	/	93 (21.6%)	-Total: 337 (78.4%) -FP1: 119 (27.7%) -FP3:48 (11.2%) -Crural bypass: 142 (33%) -Multilevel: 28 (6.5%)	/	Total: 32 (4.7%) -Aortic: 1 (1.1%) -FP1: 7 (5.9%) -FP3: 8 (16.7%) -Crural bypass: 14 (9.9%) -Multilevel: 2 (7.1%	56.7 +/-1.6
Zegelman et al, 2009 (6)	50	SG	Diabetes (N=13, 26%) Tissue loss (N=8, 16%) Previous surgery at operation site (N=8, 16%)	/	/	-Femorofemoral crossover 15 (30%) -FP1: 27 (54%) -FP2 & 3: 4 (8%) -Iliacofemoral 1 (2%) -Iliacoexterna/profunda: 1 (2%) -Iliacopopliteal: 1 (2%) -Femoroprofundal: 1 (2%)	/	2/50 (4%)	18
Zegelman et al, 2013 (7)	220	SG	Diabetes (N=46,21%) Tissue loss (31, 14.6%) Revision operation (N=36, 16.5%)	76 (34.5%)		Total: 144 (65.5%) -Iliaco-xxx: 41 (18.6%) -FP: 31 (14.1%) -xxx-crural: 12 (5.5%) -Extra-anatomic: 60 (27.3%)	2 (2.6%)	Total: 9/220 (4.1%) -Iliaco-xxx: 2/41 (4.9%) -FP: 2/31 (6.5%) -xxx-crural: 1/12 (8.3%) -Extra-anatomic: 2/60 (3.3%)	15.5 +/-8.3

IGS: INTERGARD SILVER™; FP: femoropopliteal; FP1: femoropopliteal bypass above knee; FP2: femoropopliteal bypass on P2 segment; FP3: femoropopliteal bypass below the knee; VGI: vascular graft infection; SG: Silver graft™; SD: standard deviation

Table 2: *In vitro* studies with commercial silver grafts

Year	author	country	graft	Control group	Tested organism	efficacy	Statistical analysis
2004	Strahtmann et al (14)	Duisburg, Germany	SG	Protegraft® DV 1900	*S. Aureus*	confocal laser scanning microsope for biofilm evaluation after staining with SYTO62	Significant less intact biofilm on IGS compared to control graft.
2004	Hardman et al. (13)	Leicester, UK	IGS	Gelsoft Plus® rifampicin soaked Gelsoft Plus® (60mg/ml)	*S. aureus; MRSA* *S. Epidermidis; E. Coli; E. faecalis*	zone of inhibition on agar	Rifampicin grafts inhibit better ($p< 0.001$)growth of gram positive strains at d2 & 3 compared to IGS IGS more effective ($p < 0.001$) against gram negative strains until day 4
2009	Osinska-Jaroszuk et al. (21)	Lublin – Rzeszów, Poland	IGS	Hemashield Gold™; Wovex™; Gelsoft® Uni-graft®; Uni-graft® + amikacin (250mg/ml) or + gentamicin (40mg/ml); Tricogel®	*S. Aureus; E. Coli Pseudomonas aeruginosa; S. Epidermidis*	zone of inhibition on agar CFU count	NR
2012	Ricco et al. (20)	Poitiers, France & Vienna, Austria	IGS	Intergard Synergy™; Intergard™	*MRSA*	CFU count	IGS was more effective ($p<0.05$) compared to Intergard™ at 24 hours.
2012	Obermeier et al. (16)	Munich, Germany	IGS	Alpha graft® PTFE +/-coated with gentamicin salts (gentamicin-palmitate, gentamicin-SDS and gentamicin-laurate) (16.6mg/ml) SEALPTFE™ +/- coated with rifampicin (40mg/ml)	*S. Epidermidis*	CFU count	NR
2014	Tammer et al. (23)	Magdeburg, Germany	IGS	Intergard™ + various concentrations of $AgNO_3$	*Candida albicans*	CFU count (with CTT reduction assay)	At all timepoints significantly more ($p<0.005$) biofilm formation and attachment compared to collagen-only grafts.
2016	Berard et al. (19)	Bordeaux, France	IGS	Intergard Synergy™ Intergard™	*S. Epidermidis; MRSA* *E. coli; Candida Albicans*	CFU count	At 24h significant better results compared to Intergard™ against all strains
2017	Wozniak et al. (22)	Warsaw, Poland	SG	Dallon H®; Impra®; Viabahn®; Fluency Plus® Zenith Flex®; NO-REACT patch; Omniflow II	*S. Aureus; S. epidermidis;* *Pseudomonas Aeruginosa* *E. faecalis*	CFU count	After 24h, sginificantly more ($p< 0.001$) bacteria were recovered on SG compared to Impra®, Viabahn®, Fluency Plus®, No-React patch®. Significant better result compared to Omniflow II® ($p<0.001$)
2019	Berard et al.(18)	Bordeaux, France	SIG	Intergard™; Rifampicin soaked Intergard® (5mg/ml) Intergard Synergy™	*S. Epidermidis; MRSA* *E. Coli; Candida Albicans*	CFU count	Bactericidal efficacy at 7 days against all strains.

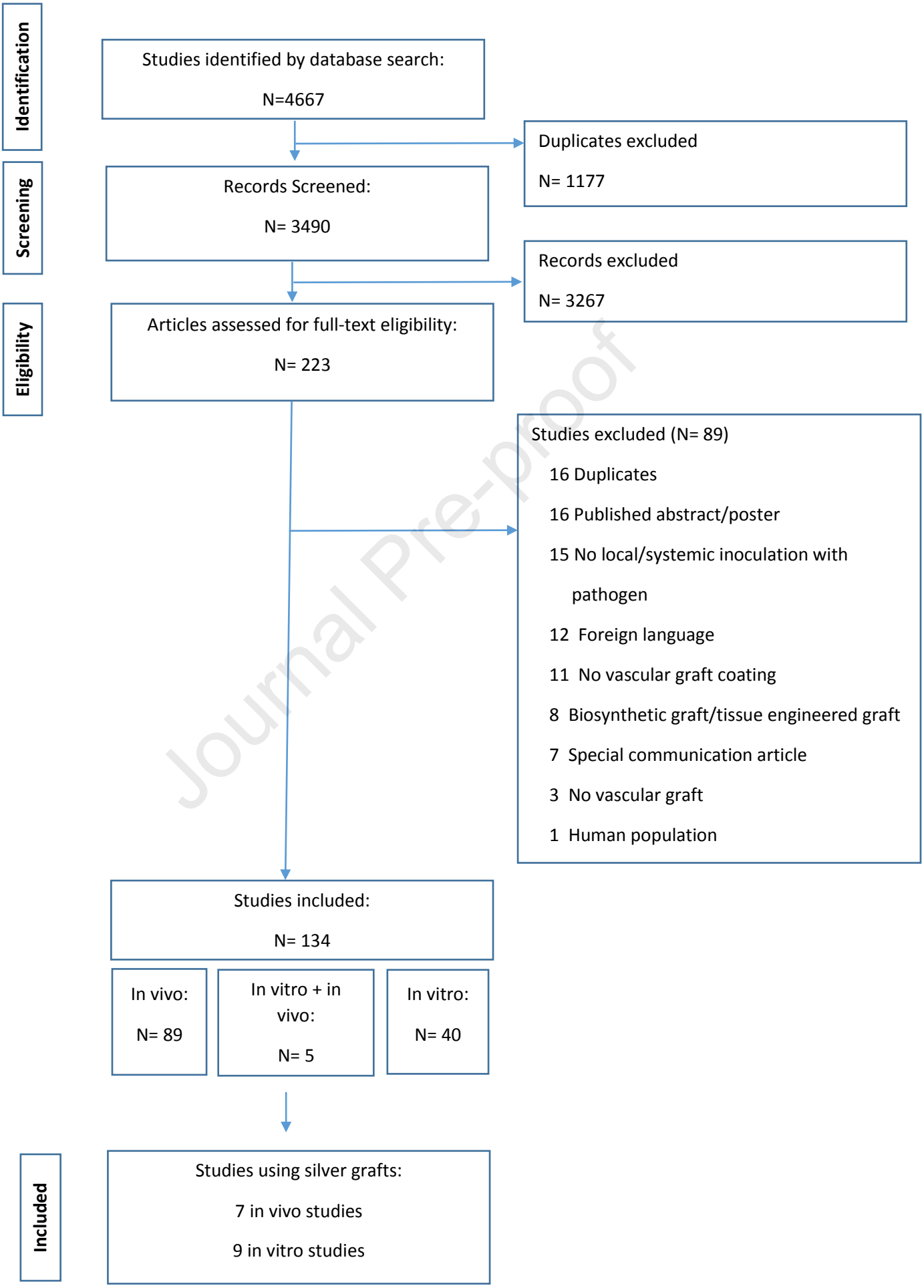
SG: Silver Graft™; IGS: Intergard Silver™; CFU: colony forming unit; NR: not recorded; Gelsoft Plus®, Sulzer Vascutek, Inchinnan, Renfrewshire, Scotland; Intergard™, Intervascular, La Ciotat, France; Uni-graft® DV, Braun Melsungen AG, Melsungen, Germany; Impra®, Bard, Tempe, AZ, USA; Alpha graft® PTFE, Alpha Research, Berlin, Germany; SEALPTFE™, Vascutek, Hamburg, Germany; Intergard Synergy, Intervascular, La Ciotat, France; Hemashield Gold™, Boston Scientific, MA, USA; Wovex™, Bard, Cardial, Saint-Etienne, France; Protegraft® DV 1900, B/Braun, Melsungen, Germany; Tricogel®, Tricomed, Lodz, Poland; Dallon H, Tricomed Lodz, Poland; Viabahn®, WL Gore, Flagstaff, AZ, USA; Fluency Plus®, Bard, Tempe, AZ, USA; Zenith Flex®, Cook, Bloomington, IN, USA; NO-REACT patch®, BioIntegral Surgical, Mississauga, Canada; Omniflow II®, Bio Nova International Pty Ltd, Melbourne Australia.

Table 3: *In vivo* studies with commercial silver grafts

Year	author	country	graft	Control group (antibiotic concentration in mg/ml)	Animal	Tested organism	efficacy	Statistical analysis
2002	Goëau-Brissonière et al.(26)	Boulogne-Billancourt, Paris, France	SIG	-Intergard ™ -Gelsoft Plus® -Rifampicin soaked Gelsoft Plus® (0.06mg/ml)	dog	*MRSA*	CFU count clinical	P<0.05 versus gelatin -sealed rifampicin bonded grafts
2003	Hernández-Richter et al. (27)	Munich, Germany	SIG	-Uni-graft ® -Intergard ™ -Silver/gelatin sealed (not commercial) -Rifampicin-soaked Uni-Graft® (60mg/ml) -Triclosan coated Intergard™	mouse	*S. Aureus*	CFU count clinical histology	p>0.05 versus Uni-Graft®
2005	Schmacht et al. (17)	Tampa, FL, USA	SIG	-Rifampicin soaked Gelsoft® (30mg/ml)	dog	*MRSA*	CFU count clinical blood sample	Significant increase (p< 0.05) in Rifampicin group perigraft fluid and graft resistance to MRSA colonization compared to SIG at day 3, 7, 14
2010	Artini et al. (24)	Rome, Italy	SIG	-Rifampicin-soaked Gelsoft Plus® (12mg/ml)	rat	*S. Aureus*	CFU count clinical	NR
2011	Lorenz et al. (15)	Wuerzburg, Germany	SG& SIG	- Intergard™ - Impra® - VascuGuard®	mouse	*S. Aureus xen29*	CFU count clinical biophotonic imaging	Day 5: SG & SIG: p<0.05 versus Intergard®, Impra®, Vascugard®

SG: Silver Graft™; IGS: Intergard Synergy™; CFU: colony forming unit; NR: not recorded; Gelsoft Plus®, Sulzer Vascutek, Inchinnan, Renfrewshire, Scotland; Intergard™, Intervascular, La Ciotat, France.

Uni-graft® DV, Braun Melsungen AG, Melsungen, Germany; Impra®, Bard, Tempe, AZ, USA; Vascugard®, Synovis, Minnesota, USA



Pubmed

Concept 1: vascular graft

"Vascular Grafting"[Mesh:NoExp] OR vascular-graft*[tiab] OR blood-vessel-graft*[tiab] OR vascular-prosthes*[tiab] OR "Blood Vessel Prosthesis Implantation"[Mesh] OR blood-vessel-prosthes*[tiab] OR "Blood Vessel Prosthesis"[Mesh] OR vascular-patch-graft*[tiab] OR artery-graft*[tiab] OR aortic-graft*[tiab] OR aortic-prosthes*[tiab] OR artery-prosthes*[tiab]

Concept 2: Antibiotic properties

"Prosthesis-Related Infections"[Mesh] OR infection*[tiab] OR "Infection"[Mesh] OR "Biofilms"[Mesh] OR biofilm*[tiab] OR EPS-matri*[tiab] OR extracellular-polymeric-substance*[tiab] OR exopolymer*[tiab] OR

Concept 3: preclinical (NOT)

("humans"[Mesh]) NOT (“animals”[Mesh:NoExp] OR "Models, Animal"[Mesh] OR "In Vitro Techniques"[Mesh])

Embase

Concept 1: vascular graft

‘blood vessel graft’/de OR ‘blood vessel graft*’:ti,ab,kw OR ‘vascular graft*’:ti,ab,kw OR ‘vascular patch graft*’:ti,ab,kw OR ‘artery graft’/exp OR ‘artery graft*’:ti,ab,kw OR ‘aortic graft’/exp OR ‘aortic graft*’:ti,ab,kw OR ‘blood vessel prosthesis’/de OR ‘blood vessel prosthes*’:ti,ab,kw OR ‘aortic prosthes*’:ti,ab,kw OR ‘artery prosthes*’:ti,ab,kw OR ‘prosthesis implantation'/exp OR ‘vascular prosthes*’:ti,ab,kw

Concept 2: antibiotic properties

‘infection'/exp OR ‘infection*’:ti,ab,kw OR ‘graft infection’/exp OR ‘biofilm'/exp OR ‘biofilm*’:ti,ab,kw OR ‘extracellular polymeric substance'/exp OR ‘EPS matr*’:ti,ab,kw OR ‘exopolymer*’:ti,ab,kw OR ‘extracellular polymeric substance*’:ti,ab,kw

Concept 3: preclinical (NOT)

('human'/exp) NOT ('animal'/de OR 'animal model'/exp OR 'in vitro study'/exp)

WoS

Concept 1: vascular graft

“Vascular graft*” OR “blood vessel graft*” OR “vascular prosthes*” OR “blood vessel prosthes*” OR “vascular patch graft*” OR “artery graft*” OR “aortic graft*” OR “aortic prosthes*” OR “artery prosthes*”

Concept 2: Antibiotic properties

infection* OR biofilm* OR “EPS matri*” OR “extracellular polymeric substance*” OR exopolymer*