NATIONAL REGISTRY

Editor's Choice — Outcome of Radical Surgical Treatment of Abdominal Aortic Graft and Endograft Infections Comparing Extra-anatomic Bypass with *In Situ* Reconstruction: A Nationwide Multicentre Study

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WHAT THIS PAPER ADDS

The current data regarding optimal treatment of aortic graft infection (AGI) are scarce and there are no randomised controlled trials comparing the two main surgical strategies: extra-anatomic bypass (EAB) and *in situ* repair (ISR). Some evidence derived mainly from small single centre studies suggests that ISR, and allogenic vein grafts (neo-aorto-iliac systems) in particular, appear to be more durable and re-infection resistant, which is reflected in the current AGI guidelines. This paper adds data from a nationwide, multicentre setting comparing the real life outcomes of a large abdominal AGI cohort treated by EAB or ISR.

Objective: Abdominal aortic graft and endograft infection (AGI) is primarily treated by resection of the infected graft and restoration of distal perfusion through extra-anatomic bypass (EAB) or *in situ* reconstruction/repair (ISR). The aim of this study was to compare these surgical strategies in a nationwide multicentre retrospective cohort study.

Methods: The Swedish Vascular Registry (Swedvasc) was used to identify surgically treated abdominal AGIs in Sweden between January 1995 and May 2017. The primary aim was to compare short and long term survival, as well as complications for EAB and ISR.

Results: Some 126 radically surgically treated AGI patients were identified — 102 graft infections and 24 endograft infections — treated by EAB: 71 and ISR: 55 (23 neo-aorto-iliac systems, NAISs). No differences in early 30 day (EAB 81.7% *vs.* ISR 76.4%, $p = .46$), or long term five year survival (48.2% *vs.* 49.9%, $p = .87$) were identified. There was no survival difference comparing NAIS to other ISR strategies. The frequency of recurrent graft infection during follow up was similar: EAB 20.3% *vs.* ISR 17.0% ($p = .56$). Survival and re-infection rates of the new conduit did not differ between NAIS and other ISR strategies. Age ≥ 75 years (odds ratio [OR] 4.0, confidence interval [CI] 1.1 — 14.8), coronary artery disease (OR 4.2, CI 1.2 — 15.1) and post-operative circulatory complications (OR 5.2, CI 1.2 — 22.5) were associated with early death. Prolonged antimicrobial therapy (> 3 months) was associated with reduced long term mortality (HR 0.3, CI 0.1 — 0.9).

Conclusion: In this nationwide multicentre study comparing outcomes of radically treated AGI, no differences in survival or re-infection rate could be identified comparing EAB and ISR.

Keywords: Aortic graft infection, *In situ* repair, Extra-anatomical bypass, NAIS, Multicentre, Nationwide

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INTRODUCTION

Aortic graft and endograft infections (AGIs) are rare and serious complications after aortic surgery. The frequency of these events has been reported to range from 0.3 to 4%.[1–4] Due to the lack of larger cohort and population based studies, as well as a heterogeneous definition, the true incidence is difficult to determine.

The diagnosis of AGI is based on a combined assessment of clinical, radiological, and microbiological information.[3,5,6] Recently the Management of Aortic Graft Infection Collaboration (MAGIC) proposed a criteria oriented scoring system for a more homogeneous definition.[7]

Different surgical methods have been developed to treat AGI, such as complete extirpation of the infected graft and debridement followed by either extra-anatomic bypass (EAB) or *in situ* reconstruction/repair (ISR).[8–13] EAB by means of an axillobifemoral bypass was previously considered to be the gold standard for radical surgical treatment. However, studies showing the feasibility of *in situ* repair with silver or antibiotic soaked grafts as well as the emerging use of cryopreserved allografts and femoropopliteal vein grafts as neo-aorto-iliac systems (NAISs) has changed this.[8,12,14,15] Recent meta-analyses suggest a trend towards lower re-infection and overall mortality rates using ISR compared with EAB[12,15,16] and the recently published European Society for Vascular Surgery (ESVS) AGI guidelines recommend ISR, preferably NAISs when feasible, as first line of treatment.[17] However, the data are mostly derived from small retrospective single centre studies subject to publication, selection, and time bias.

This study was designed with the purpose of researching AGI in a nationwide setting with minimal selection bias and "real life" outcomes. The primary aim was to compare the outcome of EAB and ISR in terms of survival and complication rates. Secondary aims were to identify possible surgical time trends, identify risk factors for peri-operative and long term mortality following AGI repair and investigate the frequency of recurrent graft infections.

MATERIALS AND METHODS

Design and study population

Patients undergoing surgical treatment for an abdominal AGI between January 1995 and May 2017 were identified using the Swedish Vascular registry (Swedvasc), a prospective registry with national coverage including all vascular surgery procedures with high internal and external validity for vascular surgery.[18] All vascular centres in Sweden with at least one potential AGI repair identified were asked to provide detailed data on each case. Fig. 1 shows the flowchart of patient identification and selection for the study. The MAGIC criteria for AGI were used to define an AGI (Table 1).[7] Patients fulfilling the criteria for a diagnosed AGI were included (Fig. 1). Only patients who underwent an attempt at radical surgical treatment with removal of the infected graft and either EAB or ISR were included. Both infected aortic grafts and stent grafts were included.
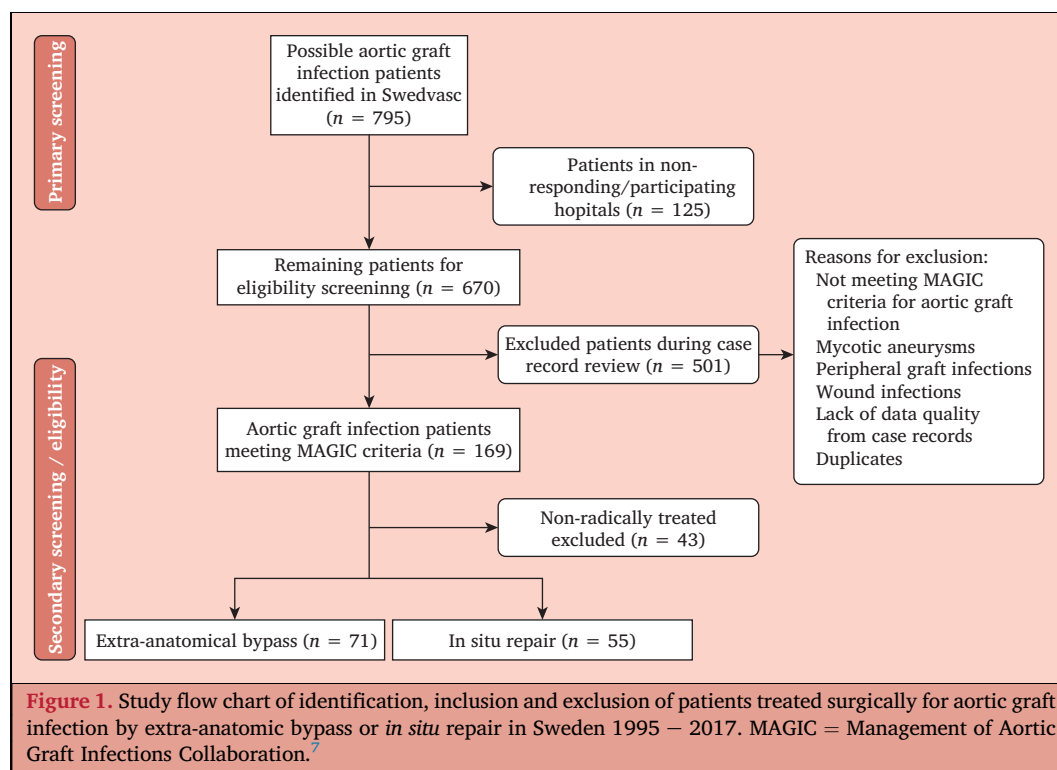
Data acquisition and definitions

Pre-, peri-, and post-operative data as well as data on microbiology were extracted from the case records using a predetermined protocol (Supplementary Table S1 shows the definition of pre-operative comorbidities). The perioperative American Society of Anaesthesiologists Physical Status Classification System score (ASA score) was retrieved. A "high" ASA score was defined as ASA score ≥4. Incomplete graft excision was defined as any residual graft material of the primary infected aortic graft left *in situ* due to either the extent of the infection, anatomic, or technical reasons. Graft enteric fistula (GEF) was defined when a perioperative finding of a bowel erosion with connection between the intestinal tract and the graft/stent graft fabric, with or without an aorto-enteric fistula with communication with the aortic lumen, was confirmed.

Early AGI was defined as development of graft infection within the first four months after the primary aortic repair, and late AGI defined as development of graft infection after four months after the primary aortic repair.

Post-operative complications were divided into circulatory/haemodynamic instability (>24 hours of vasopressor treatment), respiratory (>24 hours of invasive ventilation), acute kidney injury (dialysis requirement), amputation (above the ankle), multi-organ dysfunction syndrome (progressive organ dysfunction in two or more major organs as well as the documented diagnosis from a critical care physician), myocardial infarction (elevated troponins and chest pain or ischaemic electrocardiogram changes), abdominal compartment syndrome (intra-abdominal pressure >20 mmHg and associated organ dysfunction), sepsis (systemic inflammatory response syndrome due to suspected infection), lower extremity compartment syndrome (need for fasciotomy), stroke (suspected cerebrovascular event with neurological deficit lasting >24 hours), mesenteric ischaemia (clinical diagnosis and/or need for bowel resection), and pulmonary embolism (radiological evidence of pulmonary embolism). Treatment resistant or recurrent graft infection are not defined by the MAGIC criteria. As such, this phenomenon was defined as a persistent or renewed infection in the new conduit used to treat the AGI, as determined at the discretion of the clinician reviewing the case records.

Survival outcomes were assessed through cross matching of unique patient identifiers with Swedish population registry, ensuring a 100% survival follow up index (FUI) for Swedish residents.[19] Short and long term survival was

Figure 1. Study flow chart of identification, inclusion and exclusion of patients treated surgically for aortic graft infection by extra-anatomic bypass or *in situ* repair in Sweden 1995 − 2017. MAGIC = Management of Aortic Graft Infections Collaboration.[7]

defined as 30 days and five years of post-operative survival, respectively. Unless otherwise specifically stated, no events were excluded from the survival analyses performed.

Microbiology

For data on microbiology, possible contaminants were defined as normal skin flora according to the MAGIC criteria (e.g., Coagulase negative staphylococci, *Cutibacterium acnes*, etc.). Polymicrobial growth was defined as three or more species. Data on antimicrobial therapy were gathered. For the feasibility of retrospective data collection, only treatments used after hospital discharge, 30 days post-operatively, were included.

Statistical analysis

Data were assessed for normality using histograms, the Shapiro—Wilk test and Q-Q plots. Dichotomous variables were compared using the chi squared test of homogeneity and continuous variables using one way analysis of variance (ANOVA) if the assumptions of normal distribution, lack of outliers and equal variance mere met. Fisher's exact test and Mann—Whitney U test were used when appropriate. Overall survival was assessed using Kaplan—Meier (KM) survival curves with truncation if the standard error or numbers at risk reached >10% or $n \leq 5$, respectively. Differences in survival were analysed using the log rank test if the assumptions of independence of censoring, lack of

secular trends and similar amount of censorship between groups were met.

Factors associated with short and long term mortality after AGI repair were analysed in binary logistic regression and Cox regression models respectively. Binary logistic regression was used for 90 day survival due to the follow up being restricted to the same period with a dichotomous outcome without any censored events. Four different regression models were used:

(1) When determining the impact of choice of operative method (EAB *vs.* non-NAIS ISR *vs.* NAIS) on overall survival, a Cox regression was used adjusting only for pre-operative confounders.
(2) For assessment of factors associated with peri-operative mortality, deaths within 90 days of the operation were included. Peri- and post-operative factors were included.
(3) When assessing overall factors associated with long term mortality (five years), deaths occurring within 90 days were excluded. Peri- and post-operative factors were included.
(4) The effect of prolonged antimicrobial treatment was analysed in a Cox regression model excluding deaths occurring within 90 days to eliminate immortal time bias. Duration of antimicrobial treatment was dichotomised into short *vs.* prolonged (>3 months). Effect size was measured by odds ratio (OR) or

Table 1. Management of Aortic Graft Infection Collaboration (MAGIC) criteria for aortic graft infection (AGI) diagnosis

Criterion	Clinical/surgical	Radiology	Laboratory
Major	Pus (confirmed by microscopy) around graft or in aneurysm sac at surgery	Peri-graft fluid on CT scan ≥3 months after insertion	Organisms recovered from an explanted graft
	Open wound with exposed graft or communicating sinus	Peri-graft gas on CT scan ≥7 weeks after insertion	Organism recovered from an intra-operative specimen
	Fistula development, e.g., aorto-enteric or aorto-bronchial	Increase in peri-graft gas volume demonstrated on serial imaging	Organisms recovered from a percutaneous, radiologically guided aspirate of peri-graft fluid
	Graft insertion in an infected site, e.g., fistula, mycotic aneurysm or infected pseudoaneurysm		
Minor	Localised clinical features of AGI, e.g., erythema, warmth, swelling, purulent discharge, pain	Other, e.g., suspicious peri-graft gas/fluid/ soft tissue inflammation; aneurysm expansion; pseudoaneurysm formation; focal bowel wall thickening; discitis/ osteomyelitis; suspicious metabolic activity on FDG-PET/CT; radiolabelled leucocyte uptake	Blood culture(s) positive and no apparent source except AGI
	Fever ≥38°C with AGI as most likely cause		Abnormally elevated inflammatory markers with AGI as most likely cause, e.g., ESR, CRP, white cell count

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CT = computed tomography; FDG-PET/CT = ^{18}F-fluoro-D-deoxyglucose positron emission tomography/computed tomography; ESR = erythrocyte sedimentation rate; CRP= C reactive protein.

hazard ratio (HR) with 95% confidence interval (CI) reported.

In Cox regression models, date of AGI intervention was used as baseline, and participants accrued follow up time until date of death, or 31 May 2017, whichever occurred first. Factors included in multivariable models were pre-specified according to clinical reasoning and an attempt was made to limit the number of factors to one per five events analysed to reduce the risk of overfitting.[20] Assumptions regarding independence of observations, sample size, linear relationship, as well as lack of multicollinearity were checked *a priori*.

A *p* value <.050 was considered statistically significant, SPSS software package version 22.0 and 23.0 (IBM, Armonk, NY, USA) was used for data processing and statistical analysis.

The study was approved by the regional ethics committee in Uppsala, Sweden.

RESULTS

Study population and time trends

A total of 126 patients (102 graft infections and 24 endograft infections) who met the MAGIC criteria and underwent radical surgical treatment for AGI by EAB (*n* = 71) or ISR (*n* = 55) were included (Fig. 1). Among the endograft infections, 10 were treated by EAB and 14 by ISR.

There was a significant decline in the use of EAB during the study period and a corresponding increase in ISR.

Dividing the study period into an early (1995 – 2008) and late (2009 – 2017) period (including roughly 50% of the patients in each time period), there was a decline in EAB (63.9% to 48.4%) and a corresponding increase in ISR (36.1% to 51.6%). A total of 83 (65.9%) of the identified cases were treated at the six tertiary referral vascular centres participating in this study. Treatment heterogeneity among these centres was significant, with EAB being performed in 0 – 91% of cases depending on centre. Overall,

Table 2. Comparison of pre-operative baseline characteristics among 126 patients treated surgically for aortic graft infection by extra-anatomic bypass or *in situ* repair in Sweden 1995–2017

Baseline characteristics	Extra-anatomic bypass (*n* = 71)	*In situ* repair (*n* = 55)	*p*
Age – y	69.8 ± 7.3	70.4 ± 8.6	.68
Male sex	60 (85)	44 (80)	.51
Hypertension	46 (70)	33 (60)	.27
Smoking	30 (45)	18 (33)	.15
Chronic kidney disease	6 (9)	7 (13)	.52
Diabetes	5 (8)	5 (9)	.76
Heart failure	6 (9)	3 (5)	.45
Coronary artery disease	25 (38)	12 (22)	.056
Lung disease	9 (14)	4 (7)	.26
Circulatory shock	5 (7.5)	6 (10.9)	.51
ASA score >3	16 (24)	17 (31)	.41
Graft enteric fistulae	34 (50)	28 (51)	.92

Data are presented as *n* (%) or mean ± standard deviation. ASA = American Society of Anaesthesiologists Physical Status Classification System score.

Table 3. Comparison of post-operative 30 day outcomes between among 126 patients treated by extra-anatomic bypass and *in situ* repair for aortic graft infections

Post-operative complications	Extra-anatomic bypass (*n* = 71)	*In situ* repair (*n* = 55)	*p* value
Mesenteric ischaemia	6 (9)	3 (6)	.73
Acute limb ischaemia	4 (6)	6 (10)	.50
Multi-organ dysfunction syndrome	16 (25)	9 (18)	.37
Dialysis	13 (20)	4 (8)	.067
Respiratory	21 (33)	11 (22)	.18
Circulatory	17 (27)	11 (22)	.57
Myocardial infarction	4 (6)	3 (6)	1.0
Abdominal compartment syndrome	1 (2)	2 (4)	.58
Sepsis	11 (17)	4 (8)	.16
Lower extremity compartment syndrome	2 (3)	2 (4)	1.0
Stroke	2 (3)	0 (0)	.50
Pulmonary embolism	1 (2)	2 (4)	.58
Median intensive care unit stay (IQR) — h	41 (133)	72 (62)	.48
Median in hospital stay (IQR) — d	24 (24)	24 (23)	.61
30 day survival (95% CI) — %	81.7 (72.7–90.7)	76.4 (65.2–87.6)	.46

Data are presented as *n* (%) unless stated otherwise. IQR = interquartile range; CI = confidence interval.

Table 4. Comparison of crude long term complication rates among 126 patients during clinical follow up after radical surgical repair for aortic graft infection using extra-anatomic bypass vs. *in situ* repair

Long term complications	Extra-anatomic bypass (*n* = 71)	*In situ* repair (*n* = 55)	*p* value*
Median follow up (IQR) — y[†]	5.5 (8.1)	3.1 (4.1)	.039
Recurrent graft infection	13 (21)	9 (17)	.56
Stump blowout	6 (10)	0 (0)	.029
Anastomotic dehiscence	1 (2)	5 (9)	.095
Amputation above the ankle	3 (5)	2 (4)	1.0
Re-intervention	18 (28)	13 (25)	.70

Data are presented as n (%) unless stated otherwise. IQR = interquartile range.
* *p* < .050 considered statistically significant.
[†] Median clinical follow up among survivors.

the ISR cohort consisted of 24 (43.6%) NAIS, 10 (18.2%) silver impregnated grafts, 10 (18.2%) rifampicin soaked antibiotic grafts, four (7.3%) arterial autografts, and seven (12.7%) miscellaneous (mainly untreated standard grafts).

Total operative volume per centre during the 22 year study period was low: range 1 – 32. The median volume per quintile was 1 (Q$_1$), 2 (Q$_2$), 5 (Q$_3$), 8 (Q$_4$), 23 (Q$_5$). Overall, 69 (54.8%) of the total surgical AGI volume was performed at three centres in Q5.

Baseline characteristics

Baseline characteristics at the time of AGI repair as well as symptoms and biochemistry are shown in Table 2, Supplementary Table S2, and Supplementary Table S3, respectively. Some 77 (81.0%) were treated with an open repair, and in the total cohort 25.4% had a history of ruptured AAA as the primary pathology at the index surgery preceding AGI repair. There was no significant difference in pre-operative comorbidities, including frequency of high ASA score or presence of GEF between the EAB and the ISR cohorts.

Comparing clinical presentation at the time of AGI repair in the total cohort among patients with a diagnosed GEF *vs*. no GEF, presence of a gastrointestinal bleeding

(48% *vs*. 12%) and circulatory shock (15% *vs*. 3%) was significantly higher among patients with a GEF, while groin infections (8% *vs*. 25%) were more common in patients without a GEF. The median time from primary aortic repair to surgical treatment for AGI was 28.8 months (range 0.4 – 420 months). In the total cohort 20% presented with an early AGI and 34% of the cohort were diagnosed within one year of the primary aortic surgery (Supplementary Fig. S1). Patients presenting with a GEF (*vs*. no GEF) had a significantly longer duration between primary repair and AGI treatment (median time: 3.86 years *vs*. 1.35 years, *p* = .035).

Outcome of surgical treatment by EAB and ISR

The 30 day post-operative complications were similar between the two surgical cohorts. There was a non-significant trend of increased need for dialysis after EAB: 20.3% *vs*. ISR: 8.0% (*p* = .067). The intensive care unit and in hospital length of stay after AGI repair did not differ significantly between the two cohorts (Table 3).

The crude frequency of long term complications during clinical follow up are shown in Table 4. The median duration of clinical follow up among survivors was significantly longer in the EAB cohort *vs*. the ISR cohort. The overall rate of recurrent graft infection was 20.3% for EAB after a median follow up of 5.5 years and 17.0% for ISR after a median follow up of 3.1 years (*p* = .56). The rate of aortic stump blow out after EAB and anastomosis dehiscence after ISR during the total follow up period was the same at 9.8%. While there were no data on the time of the diagnosed long term complications, four of six patients with EAB stump blow out and three of five patients with an ISR anastomosis dehiscence died within 30 days of the primary AGI surgery.

Table 5. Overall survival after aortic graft infection repair among 126 patients comparing extra-anatomic bypass and *in situ* repair

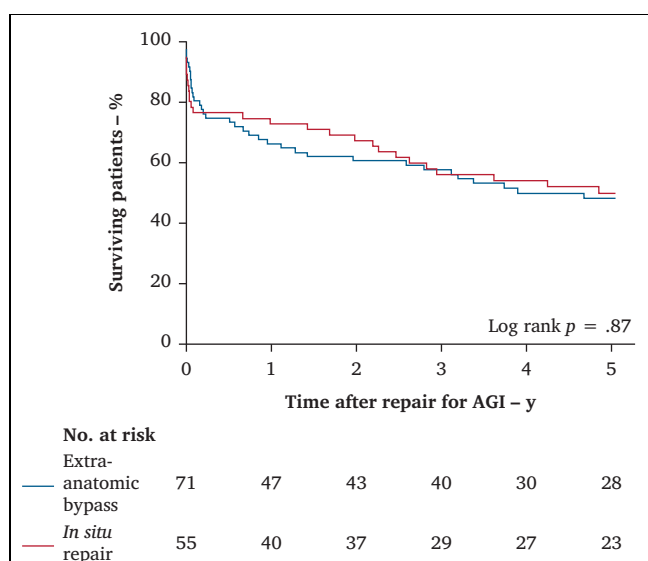| Survival	Extra-anatomic bypass (*n* = 71)	*In situ* repair (*n* = 51)	*p* value
90 day survival	74.6 (64.4−84.8)	76.4 (65.2−87.6)	.82
One year survival	66.2 (55.2−77.2)	72.7 (60.9−84.5)	.43
Five year survival*	48.2 (36.2−60.2)	49.9 (36.4−63.4)	.87

Data presented as % with (95% confidence intervals).
* Unadjusted Kaplan−Meier estimation for five year survival.

A subgroup analysis on long term complications was performed comparing NAIS repairs *vs.* the other repairs in the ISR cohort (Supplementary Table S4). There was no statistical difference in median clinical follow up (NAIS: 2.3 years *vs.* other ISR: 3.1 years, *p* = .71). There were no significant differences comparing rates of anastomotic dehiscence, amputation, or re-intervention.

Survival

Uncensored survival data up to one year were available for all patients. No short or overall long term differences in survival was identified after AGI repair comparing EAB *vs.* ISR (Table 5 and Fig. 2). No overall survival difference was seen comparing patients developing early *vs.* late AGI.

There was no difference in short term survival in patients with GEF *vs.* those without a GEF (30 days − GEF: 72.6%, no GEF: 85.2%; *p* = .085). Long term survival was also similar (five year KM estimated survival − GEF: 41.2%, no GEF: 56.6% GEF, log rank *p* = .12) (Supplementary Fig. S2). There

Figure 2. Cumulative Kaplan−Meier estimate on 126 patients with aortic graft infection (AGI), comparing unadjusted overall long term five year survival for extra-anatomic bypass *vs. in situ* repair. No survival difference was identified using log rank test (*p* = .87).

Table 6. Multivariable Cox regression on 126 patients identifying impact of operative method on overall five year mortality after radical surgical repair for an aortic graft infection adjusting for pre-defined confounders

Factors	Hazard ratio (95% CI)	*p* value*
Age ≥75 years	2.7 (1.6−4.6)	< .001*
Coronary artery disease	0.9 (0.5−1.6)	.69
Chronic kidney disease	2.1 (1.0−4.0)	.064
Pulmonary disease	0.5 (0.2−1.3)	.16
Extra-anatomic bypass *vs. in situ* repair excluding vein grafts†	0.7 (0.4−1.2)	.18
Extra-anatomic bypass *vs.* neo-aorto-iliac systems (NAIS/vein grafts)†	1.1 (0.6−2.3)	.72
Graft enteric fistulae	1.4 (0.8−2.3)	.23
Shock	2.6 (0.9−7.6)	.085

CI = confidence interval.
* *p* < .050 considered statistically significant.
† Extra-anatomic bypass used as index comparator.

was no difference in short or long term survival outcome between NAIS *vs.* other ISR repairs (*p* = .51, Supplementary Fig. S3). Additionally, there was no difference in overall survival comparing graft AGI *vs.* endograft AGI (*p* = .89, Supplementary Fig. S4).

While adjusting for pre-defined peri-operative confounders, choice of operative method with EAB as comparator did not impact overall five year mortality: non-NAIS ISR (HR 0.7, CI 0.4 − 1.2) and NAIS (HR 1.1, CI 0.6 − 2.3) (Table 6).

In a binary logistic regression analysis, advanced age defined as ≥ 75 years (OR 4.0, CI 1.1 − 14.8), coronary artery disease (OR 4.2, CI 1.2 − 15.1), and post-operative circulatory complications (OR 5.2, CI 1.2 − 22.5) were independently associated with 90 day mortality. Operative method (EAB *vs.* ISR) did not impact 90 day mortality (OR 1.4, CI 0.4 − 4.9, *p* = .60) (Table 7).

In a multivariable Cox regression analysis, excluding 90 day death, advanced age defined as ≥75 years (HR 2.9, CI 1.1 − 7.7), chronic kidney disease (HR 7.0, CI 2.4 − 20.4), and coronary artery disease (HR 3.7, CI 1.1 − 12.7) were independently associated with five year overall mortality. Once again, no association between long term mortality and EAB *vs.* ISR could be identified (Table 8).

Microbiology, antimicrobial treatment, and recurrent infections

Data on microbiological work up was available in 117/126 patients (92.9%). Median number of species (excluding contaminants) identified on blood, peri-graft, or graft cultures per patient was one (range 0 − 6) (Supplementary Fig. S5). Gram negative and Gram positive bacteria were identified in 51.3% and 47.0% of the cases respectively, while a polymicrobial growth was present in 24.1% of the total cohort. Polymicrobial growth was, as expected, more common among patients with a GEF (37.1%) *vs.* without a GEF (8.8%) (*p* < .001). A more detailed mircobiological etiology is shown in Supplementary Table S5.

Table 7. Multivariable binary logistic regression on 126 patients identifying factors associated with 90 day mortality after radical surgical repair for an aortic graft infection

Factors	Odds ratio (95% CI)	p value*
Pre-operative		
Age ≥ 75 years	4.0 (1.1–14.8)	.020
Coronary artery disease	4.2 (1.2–15.1)	.025
Chronic kidney disease	0.6 (0.1–3.5)	.53
Pulmonary disease	0.2 (0.0–2.0)	.17
Rupture	9.4 (0.3–22.7)	.19
Peri-operative		
Shock	3.5 (0.3–37.6)	.31
Extra-anatomic bypass *vs. in situ* repair[†]	1.4 (0.4–4.9)	.60
Graft enteric fistulae	1.2 (0.3–4.3)	.78
Incomplete graft excision	0.5 (0.1–2.2)	.36
Post-operative		
Circulatory complications	5.2 (1.2–22.5)	.025
Respiratory complications	2.7 (0.6–12.4)	.20
Dialysis	1.5 (0.3–8.5)	.63
Time period, early *vs.* late[‡]	1.5 (0.4–6.0)	.55

CI = confidence interval.
* p < .050 considered statistically significant.
[†] Extra-anatomic bypass used as index comparator.
[‡] Time period 1995–2006 *vs.* 2007–2017.

Table 8. Multivariable Cox regression on 91 patients, with 90 day mortality excluded, identifying factors associated with five year mortality after radical surgical repair for an aortic graft infection

Factors	Hazard ratio (95% CI)	p value*
Pre-operative		
Age ≥ 75 years	2.9 (1.1–7.7)	.017
Coronary artery disease	3.7 (1.1–12.7)	.045
Chronic kidney disease	7.0 (2.4–20.4)	.006
Pulmonary disease	0.8 (0.2–3.3)	.77
Rupture[†]	–	–
Peri-operative		
Shock	5.1 (1.1–24.2)	.045
Extra-anatomic bypass *vs. in situ* repair[‡]	0.5 (0.2–1.3)	.15
Graft enteric fistula	0.9 (0.4–2.2)	.88
Incomplete graft excision	0.5 (0.2–1.5)	.24
Post-operative		
Circulatory complications	1.6 (0.6–4.6)	.39
Respiratory complications	0.4 (0.1–1.2)	.13
Dialysis	1.9 (0.6–6.1)	.31
Time period, early *vs.* late[§]	0.7 (0.3–1.9)	.47

CI = confidence interval.
* p < .050 considered statistically significant
[†] Only one case occurred.
[‡] Extra-anatomic bypass used as index comparator.
[§] Time period 1995–2006 *vs.* 2007–2017.

A total of 20.5% had a positive *Candida albicans* blood, peri-graft, or graft culture. The frequency of *Candida* was significantly higher in the cohort with a GEF (30.5%) *vs.* without a GEF (10.3%) (*p* < .001).

Some 101 patients survived to hospital discharge and were eligible for data collection on long term antimicrobial therapy. Data were retrievable for 75/101 (74.3%) patients. Some 12/75 (16.0%) of the patients were treated with continuous antimicrobial therapy (life long or until end of follow up) — ISR: 6/36 (16.7%), EAB: 6/39 (15.4%). Of the patients with a finite treatment period, the median duration was three months (range 1 – 39 months). There was no difference in antimicrobial treatment duration between EAB *vs.* ISR.

The impact of prolonged antimicrobial therapy (>3 months) was determined in a Cox regression analysis. Fifty-nine patients met the pre-determined criteria and had complete data available (Supplementary Table S6). Prolonged antimicrobial therapy, while adjusting for EAB *vs.* ISR, was associated with reduced long term mortality (HR 0.3, CI 0.1 – 0.9).

Recurrent graft infection occurred in 19.3% of patients. No factor (including EAB *vs.* NAIS *vs.* other ISR or prolonged antimicrobial treatment) was found to be associated with recurrent graft infection in a binary logistic regression (Supplementary Table S7).

DISCUSSION

This large nationwide multicentre study compared the outcomes after treatment with EAB *vs.* ISR for abdominal AGIs. The observed short and long term survival rates are comparable with contemporary studies.[16] While subject to a potential lack of statistical power, this is an important finding that highlights the difference between meta-analyses based on selected retrospective single centre publications, susceptible to publication and selection bias, *vs.* prospectively collected population based data. This finding challenges the current prevailing preference for ISR over EAB in most situations.[17]

Rates of EAB stump blow out and ISR anastomosis dehiscence were similar (9.8% *vs.* 9.4%). While the available data on early EAB blow outs and ISR anastomosis dehiscence within 30 days of the AGI repair showed similar mortality rates (4/6 *vs.* 3/5), no statistical comparisons can be made due to the low number of events. The intra-ISR comparisons are probably affected by the small sample size introducing risk of type II statistical error. Regardless, while non-significant, the numerically higher crude rates of anastomosis dehiscence for NAIS repairs during follow up raises concerns regarding the durability of the repair (NAIS: 17.4% *vs.* other ISR: 3.3%, *p* = .15) (Supplementary Table S4). On the other hand, the trend towards a reduction in recurrent graft infections (NAIS: 11.1%, non-NAIS ISR: 20.0% and EAB: 21.3%, *p* = .65), is in line with the notion that vein grafts are more resilient against re-infection.[12] In the literature, a more recent systematic review by Niaz *et al.*, analysing studies comparing ISR *vs.* EAB including some 302 patients, did not demonstrate any survival benefit of either strategy (OR 0.93, CI 0.36 – 2.36).[21] Additionally, Janko *et al.* showed similar survival outcomes comparing EAB and ISR in AGI patients with GEF in a retrospective, international, multicentre setting.[22] Importantly, allografts

and bovine pericardial tubes are used infrequently in Sweden for abdominal AGI, and consequently no conclusions can be drawn regarding these strategies.

Surgical method for AGI treatment was heterogeneous in the tertiary referral hospitals and ranged from a clear EAB preference to an ISR only approach. While there were no data on the reasoning behind the choice of EAB vs. ISR, the preference for ISR or EAB remained stable over time in most centres during the entire study period. Also, the frequency of high ASA score was similar between the two cohorts. This probably reflects a level of centre preference as part of the decision making. Due to the small sample size, no comparison between "high volume" and "low volume" centres could be performed. Reports from high volume centres of excellence suggest that complex vascular graft infection surgery including NAIS can be performed with improved results under certain conditions.[14]

In the multivariable analysis, advanced age, presence of coronary artery disease, and post-operative circulatory complications were associated with early death. Meanwhile, advanced age, presence of coronary artery disease, circulatory shock at presentation, coronary artery disease, chronic kidney disease, and duration of antimicrobial treatment were factors associated with long term survival. While several studies have shown an association between the presence of a GEF and poor outcome, this was not statistically significant in the current cohort. However, the large numerical difference in 90 day survival, GEF 55.8% vs. no GEF 75.5% indicates that this probably represents a type II statistical error. Additionally, the broader definition of a GEF including erosions explains the high frequency of GEF in this study population, possibly diluting the contribution to short term mortality due to less bleeding. Due to the retrospective and multicentre aspect of the data retrieval, for feasibility reasons, more detailed data could not be acquired on aspects of the AGI procedure such as anatomical position of the GEF, NAIS vein graft anatomy, staging of EAB procedure, or degree of local contamination.

Incomplete graft excision could not be identified to be a risk factor associated with short or long term mortality. One explanation is that it is likely to be a factor in the decision to prolong post-operative antimicrobial treatment ultimately ameliorating the impact.

Patient selection, post-operative care and microbiological work up as well as treatment are factors to likely improve over time. The long study period of 22 years was required to obtain a large enough study sample but introduces the possibility of time bias. However, adjusting for treatment period in the Cox regression did not affect the results or conclusions.

A significant weakness of this study is its partly retrospective design. While Swedvasc is a prospective registry with excellent coverage, the bulk of the data was retrieved through retrospective case record studies. As Swedvasc only covers surgically treated graft infections, the true incidence of AGI in Sweden cannot be assessed with these data, as patients treated with antimicrobial therapy and non-surgical drainage alone could not be identified. While attempting to adjust for common risk factors such as peri-operative risk factors and peri-operative parameters such as presence of shock and GEF in regression analyses, residual confounders are likely to be present and removing all the impact of selection bias in terms of treatment method in a retrospective observational study without randomisation is not possible. To expose potential systematic errors in the antimicrobial treatment data, validation analyses were performed showing a high probability of correct antibiotic coverage of the isolated cultures on patient level data indicating correct data entry.

A survival benefit associated with a prolonged antimicrobial strategy of more than three months was identified, while adjusting for survivorship bias. However, an association between prolonged antimicrobial treatment and the reduced risk of recurrent graft infection could not be shown, making the mechanism behind the survival benefit elusive. One possible explanation is the reduced mortality caused by infection related aortic stump blowout, anastomosis dehiscence or septic shock before the diagnosis of recurrent graft infection could be made. Also, the total number of recurrent graft infection events was limited, making a type II statistical error possible, as made evident by the large CIs. Furthermore, the impact of prolonged antimicrobial treatment on renewed graft infection, lacking intention to treat data, is probably severely affected by residual confounders. For instance, patients with a higher baseline risk or an actual diagnosis of renewed graft infection are probably more likely to receive prolonged or indefinite antimicrobial treatment. Another shortcoming is the lack of data on adverse events associated with prolonged antimicrobial exposure.

The bacteria associated biofilm is a known factor that contributes to the difficulty in treating vascular graft infections.[23,24] Partly, the biofilm acts as a physical barrier, reducing the penetrability of leucocytes, reducing opsonisation, and local antibiotic concentrations, but the bacteria also transform into a non-planktonic state with lowered metabolism where their susceptibility to antimicrobial treatment is greatly reduced.[25] Antibiotic agents with a known biofilm activity on Gram positive bacteria, such as rifampicin and daptomycin, have previously been shown to be associated with a survival benefit and reduced frequency of recurrent infections. As only 10 patients were treated with rifampicin in this study cohort, no further analyses could be made. About one third of patients with GEF were culture positive for Candida albicans, which is in line with other AGI case series.[11,13] Untreated, a Candida albicans infection threatens to compromise the new repair, increasing the risk of graft degeneration/pseudoaneurysm formation and anastomosis dehiscence (Supplementary Fig. S6). In light of these data, it is not unreasonable to apply an ex juvantibus echinocandin (anti-fungal) treatment strategy, due to its superior effect in biofilm compared with fluconazole, when a GEF is identified.[25]

Finally the complexity of this disease and the disastrous consequences of erroneous treatment further highlights the need for a multidisciplinary approach with the involvement of infectious disease specialists.[25]

Conclusion

In this nationwide multicentre study analysing the outcomes after AGI repair, no differences in terms of re-infection rate or overall survival could be identified comparing EAB *vs.* ISR. There was a decrease in the use of EAB over time. Prolonged antimicrobial treatment was associated with improved long term survival. These findings question the current perception that ISR is always preferable to EAB. Instead, an individualised approach in the choice of surgical technique is advocated.

CONFLICT OF INTEREST AND FUNDING

APPENDIX A. SUPPLEMENTARY DATA

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