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On Complications After Aortic Surgery

*With A Focus On Aortic Graft and Endograft
Infections*

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Abstract

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Aortic surgery has transformed with the widespread adoption of endovascular repair, reducing perioperative morbidity and mortality, particularly in older and frail patients, but introducing new complications and long-term challenges. This thesis investigated outcomes following complications of aortic surgery, focusing on critical care requirements after abdominal aortic aneurysm (AAA) repair and the epidemiology, management, and outcomes of aortic graft and endograft infections (AGI).

Study I analysed a single-centre retrospective cohort of 707 AAA repairs between 1999 and 2013. Prolonged intensive care unit length of stay (ICU LOS) decreased over time while the frequency of endovascular repair increased. Open repair and rupture were the strongest predictors of prolonged ICU stay. Prolonged ICU LOS was associated with increased short-term mortality, but long-term survival among 90-day survivors was comparable.

Study II compared extra-anatomical bypass (EAB) and in situ reconstruction (ISR) following radical surgical treatment of abdominal AGI in a nationwide Swedish cohort of 126 patients between 1995 and 2017. No differences were observed in short- or long-term survival or reinfection rates between EAB and ISR. Prolonged antimicrobial therapy (>3 months) was independently associated with improved long-term survival.

Study III evaluated semi-conservative (SC) strategies versus radical surgery (RS) for abdominal AGI in 169 patients in the same nationwide cohort. Short-term survival was similar between groups, but SC was associated with a higher risk of recurrent infection, particularly in graft-enteric fistulae. Differences in long-term survival were attenuated after adjustment for comorbidities.

Study IV analysed aortic endograft infections (AeGI) after complex endovascular aortic repair (cEVAR) between 2010 and 2024 in a single center setting. AeGI incidence was higher than after standard EVAR. Infectious index pathology and late aortic reinterventions were independently associated with AeGI. Outcomes were acceptable without secondary fistulae but poor when fistulae were present.

In conclusion, while endovascular repair has reduced early postoperative complications and critical care requirement after aortic surgery, AGI remains a major challenge. AGI outcomes in the studied cohorts were driven less by surgical techniques alone and more by patient and anatomical factors, underscoring the need for individualised, multidisciplinary decision-making.

Keywords: Aorta, Complications, Graft infection, aortic graft infection, endograft infection, vascular prosthetic infection

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*To my amazing family and friends,
we're making it out of the hood with this one!*

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. Reprints were made with permission from the respective publishers.

- I. **Gavali** H, Mani K, Tegler G, Kawati R, Covaciu L, and Wanhainen A. Editor's Choice - Prolonged ICU Length of Stay after AAA Repair: Analysis of Time Trends and Long-term Outcome. *Eur J Vasc Endovasc Surg.* 2017;54:157-163.
- II. **Gavali** H, Mani K, Furebring M, Olsson KW, Lindström D, Söreljus K, Sigvant B, Gidlund KD, Torstensson G, Andersson M, Forsell C, Åstrand H, Lundström T, Khan S, Sonesson B, Stackelberg O, Gillgren P, Isaksson J, Kragsterman B, Horer T, Sadeghi M, and Wanhainen A. Outcome of Radical Surgical Treatment of Abdominal Aortic Graft and Endograft Infections Comparing Extra-anatomic Bypass with In Situ Reconstruction: A Nationwide Multicentre Study. *Eur J Vasc Endovasc Surg.* 2021;62:918-926.
- III. **Gavali** H, Mani K, Furebring M, Olsson KW, Lindström D, Söreljus K, Sigvant B, Gidlund KD, Torstensson G, Andersson M, Forsell C, Åstrand H, Lundström T, Khan S, Sonesson B, Stackelberg O, Gillgren P, Isaksson J, Kragsterman B, Horer T, Sadeghi M, and Wanhainen A. Semi-conservative treatment versus radical surgery in abdominal aortic graft and endograft infections. *Eur J Vasc Endovasc Surg.* 2023;66(3), 397-406.
- IV. **Gavali** H, Mani K, Furebring M, Wanhainen A. Endograft Infections After Complex Endovascular Aortic Repair. 2025. *Under review.*

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Abbreviations

AAA	Abdominal aortic aneurysm
AEF	Aorto-enteric fistula
AeGI	Aortic endograft infection
AGI	Aortic graft infection
ANOVA	One way analysis of variance
ASA	American Society of Anesthesiologists
BEVAR	Branched endovascular aortic repair
CI95	95% confidence interval
CIF	Cumulative incidence function
CoNS	Coagulase-negative <i>Staphylococci</i>
CT(-A)	Computed tomography (angiography)
EAB	Extra-anatomical bypass
EVAR	Endovascular aortic repair
[18F]FDG PET	18-fluorodeoxyglucose positron emission tomography
FEVAR	Fenestrated endovascular aneurysm repair
GEF	Graft-enteric fistula
HR	Hazard ratio
ICU	Intensive care unit
IGR	Infected graft removal
IQR	Interquartile range
ISR	In-situ repair
KM	Kaplan-Meier
LOS	Length of stay
MAA	Mycotic aortic aneurysm
MAGIC	Management of aortic graft infection collaboration
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
NAIS	Neo-aorto iliac system
NPV	Negative predictive value
OR	Odds ratio
OR*	Open repair
PCR	Polymerase chain reaction

RCT	Randomised controlled trial
rRNA	Ribosomal ribonucleic acid
RS	Radical surgery
SAEF	Secondary aorto-enteric fistula
SC	Semi conservative
SOFA	Sequential organ failure assessment
SPECT(/CT)	Single-photon emission computed tomography(/computed tomography)
SSI	Surgical site infection
SUV(max)	(maximum) Standardised uptake value
TEVAR	Thoracic endovascular aneurysm repair
VGEI	Vascular graft and endograft infection
VGI	Vascular graft infection
WBCS	White blood cell scintigraphy

Introduction and rationale

Aortic surgery has changed dramatically over the past decades with the introduction of endovascular repair (Parodi, 1991; Volodos, 1987). In the open surgical era, vascular surgery, and aortic surgery particularly, was associated with extensive and resource-demanding postoperative critical care (Cunneen, 1998). The modernisation of aortic surgery through minimally invasive endografting under local anaesthesia (Eefting, 2013), advancements in medical imaging including preoperative computed tomography angiography (CT-A) and hybrid C-arm suites, improved medical management of comorbidities (Golledge, 2011; Zhang, 2015), advances in critical care, and the introduction of abdominal aortic aneurysm (AAA) screening (Scott, 1995; Scott, 2002; Wanhainen, 2016) has fundamentally reshaped the global landscape of aortic repair. These developments have improved overall mortality after aortic surgery and enabled treatment of older and more frail patients (Bahia, 2015; O’Hara, 1995; Timmers, 2013; Yei 2022).

Despite these advances, postoperative complications and the associated “failure to rescue” - usually defined as mortality among patients who develop postoperative complications, reflecting a healthcare system’s ability to recognize and effectively manage such events - remain the primary drivers of critical care utilization (Scali, 2022; Waits, 2014). Additionally, changes in prolonged critical care requirements, and their impact on early and long-term mortality in the endovascular era, remain poorly understood.

One of the most complex and resource-intensive complications is aortic graft or endograft infection (AGI), with a reported lifetime incidence of 0.5–3.0% following aortic surgery; however, estimates vary depending on definitions used, study period, and underlying pathology or treatment modality (Berger, 2015; Hobbs, 2010; Laohapensang, 2017; Swain, 2004). Notably, reliable contemporary incidence data remain limited.

The gold-standard treatment for AGI remains complete surgical explantation of the infected aortic prosthesis, debridement of infected tissue, and restoration of distal perfusion either by extra-anatomical bypass (EAB), such as axillobifemoral bypass, or in-situ repair (ISR) (Chakfé, 2020). Partial or complete graft preservation (conservative therapy) is an alternative, traditionally reserved for patients unfit for radical surgery. Antimicrobial therapy is

essential, guided by microbiological findings, with treatment durations ranging from weeks to lifelong.

Although ISR is generally considered superior (Colacchio 2023), the evidence base consists largely of small case series with substantial selection and publication bias as well case-mix heterogeneity. Outcomes for AGI remain poor, with early postoperative mortality of 10–50% depending on cohort and treatment type, and reinfection rates of 10–20% (Chakfé, 2020; Colacchio 2023).

There is a clear lack of population-based AGI studies to improve data quality and define real-world mortality and reinfection outcomes after EAB and ISR. The role and outcomes of semi-conservative, partial graft-preserving strategies in the emerging era of (complex) endograft infections also remain uncertain.

The aim of this thesis was to examine the evolution of modern aortic surgery in Sweden, focusing on changes in complications and critical care requirements. Particular emphasis was placed on AGI, with the objectives of comparing outcomes of different surgical treatments, mapping causative pathogens, analysing antimicrobial strategies, identifying risk factors for mortality and recurrent infection, and investigating the risk factors and outcomes of complex branched or fenestrated aortic endograft infections.

Background

AAA – definitions, epidemiology and outcomes

Definitions

The abdominal aorta is the section of the aorta that starts caudal of the diaphragm and extends all the way to the iliac bifurcation (Figure 1). An AAA is defined as a local dilatation of the abdominal aorta. A true aneurysm, defined as dilation involving all layers of the aortic wall, is distinguished from pseudoaneurysms caused by trauma or infection. Different specific definitions have been used over time for AAA, but the most common ones include:

- i) A diameter that is 50% larger than the expected aortic diameter at that specific aortic segment, taking age and gender into account (Johnston, 1991).
- ii) A ratio between the infrarenal- and suprarenal aorta of greater than 1.5 (Sterpetti, 1987).
- iii) An absolute diameter of any segment of the infrarenal aorta greater than 30mm, which is the most common clinical definition (McGregor, 1975).

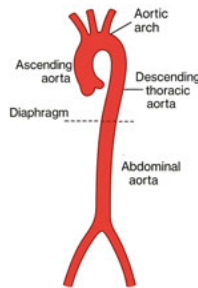


Figure 1. Schematic illustration of the aorta and the different anatomical segments.

While variably defined, complex aneurysms typically refer to abdominal and thoracoabdominal aortic aneurysms requiring suprarenal clamping or treatment with branched or fenestrated endografts at time of repair (Meuli, 2026).

Risk factors and pathophysiology

The pathophysiology underlying AAA development remains incompletely understood. In Western populations, more than 90% of infrarenal AAAs are true aneurysms (Wanhainen, 2024). A hallmark of true AAA formation is progressive degeneration of the aortic media, characterised by apoptosis of vascular smooth muscle cells and fragmentation of elastin fibres and collagen (Björck, 2013; Lu, 2021; McCormick, 2007).

Several traditional atherosclerotic risk factors are strongly associated with AAA, including male sex, advanced age, hypertension, hypercholesterolaemia, and particularly smoking. Smoking has historically been estimated to account for up to 70% of AAA cases (Smelser, 2014; Zhang, 2025). The presence of other peripheral aneurysms also increases risk; for example, up to 30% of patients with a popliteal artery aneurysm have a concomitant AAA (Dawson, 1997; van Laarhoven, 2021).

Genetic susceptibility further contributes to disease development. In a twin study, Wahlgren et al. reported a 71-fold increased risk of AAA in the monozygotic twin of an affected individual compared with the monozygotic twin of an unaffected individual (Joergensen, 2016; Klarin, 2020; Wahlgren, 2013).

In contrast, diabetes mellitus appears to be inversely associated with AAA risk. Experimental and observational data suggest that exposure to antidiabetic agents, particularly metformin, may partly explain this protective effect (Vasamsetti, 2015), and several ongoing clinical trials are currently investigating this hypothesis (Dalman, 2021; Golledge, 2021; Wanhainen, 2021; Wanhainen, 2025).

Epidemiology

The prevalence of AAA has varied over time and between regions, largely reflecting differences in population risk profiles. Early randomised AAA screening trials, such as the MASS study, reported a prevalence of approximately 4–5% among men aged over 65 years in the United Kingdom in the late 1990s (Scott, 2002). More contemporary screening cohorts from Sweden and the United Kingdom demonstrate a substantially lower prevalence, closer to 1–2% in the same demographic group (Jacomelli, 2016; Söderberg, 2025; Wanhainen, 2016; Wanhainen*, 2024). This decline is probably primarily attributed to the reduction in smoking rates (Svensjö, 2011), but improved cardiovascular risk management including blood pressure control and widespread statin use are also considered contributing factors (Fattahi, 2024; Persson, 2017).

Rupture risk and surgical repair

The natural history of untreated AAA is characterised by continuous expansion, and rupture risk rises as diameter increases. Several factors influence growth rate and rupture risk, including female sex, hypertension, current smoking, and aneurysm size; the latter being the most influential known predictor (Gokani, 2015; Parkinson, 2015; Prendes, 2024). The rationale for elective AAA repair has been to identify a diameter threshold at which rupture risk outweighs the morbidity and mortality of surgical repair. Meta-analyses of older randomised controlled trials (RCT) (UKSAT, CESAR, PIVOTAL, ADAM) support a minimal 55-mm threshold for men, with no benefit of earlier intervention (Filardo, 2015; Wanhainen, 2024). New data suggest that contemporary rupture risk is lower than previously assessed indicating that larger thresholds for elective AAA repair in men could be equally safe (Wanhainen*, 2025). However, data quality regarding thresholds for elective AAA repair in women remains poor and with the observed increased rupture risk at smaller diameters in this cohort, the ongoing WARRIORS RCT is attempting to answer the question if reduced AAA diameter thresholds for repair in women is superior to current strategies (Bertrand, 2025).

Elective repair and outcomes

Traditionally, large AAAs have been repaired through open surgical repair (OR), where the aneurysm is exposed through an abdominal incision and a dissection to the retroperitoneal space, followed by an exclusion of the aneurysm from the circulation through incorporation of a prosthetic graft that is sutured to the healthy aorta proximally and distally of the aneurysm (Dubost, 1952). The minimally invasive endovascular aneurysm repair (EVAR) instead relies on the deployment of a vascular prosthesis (covered stentgraft) via femoral arterial access under X-ray fluoroscopic guidance, to exclude the aneurysm from the circulation (Volodos, 1986). In the contemporary context, this is usually achieved under local anesthesia with the patient fully awake.

The minimally invasive EVAR, with lower 30-day mortality (EVAR: ~1–2% vs OR: ~3–5%) and reduced perioperative morbidity, has expanded the pool of patients eligible for AAA repair and enabled treatment of older and more comorbid individuals with acceptable early outcomes (Cherian, 2024; Greenhalgh, 2004; Mani, 2009; Pirinen, 2024; Veličković, 2023; Yei, 2022). However, late complications such as stentgraft migration and kinking requiring reinterventions, as well as endoleaks associated with late rupture during long-term follow-up, remain important concerns and continue to question the very long-term durability of EVAR (Katzen, 2006; Marrewijk, 2002; Veličković, 2023; Yei, 2022). These issues likely explain why long-term

overall and aneurysm-related survival are similar between EVAR and OR in randomised trials and contemporary meta-analyses of patients fit for either repair strategy (Cherian, 2024; Lederle, 2012; Patel, 2016; Veličković, 2023).

Regarding early postoperative complications, most studies still tend to favour EVAR over OR for elective AAA repair in terms of intensive care unit length of stay (ICU LOS) (EVAR: median 0–1 days vs OR: median 2–3 days), as well as overall cardiac complications such as acute coronary syndrome or decompensated heart failure (EVAR: 5–10% vs OR: 10–20%), abdominal compartment syndrome (EVAR: ~0.5% vs OR: ~1.5%) and pulmonary complications such as pneumonia or hypoxic/hypercapnic respiratory insufficiency (EVAR: 2–7% vs OR: 10–15%) (Cherian, 2024; De La Motte, 2013; Elkouri, 2004; Ersryd, 2016; Pirinen, 2024). In the retrospective study by De La Motte et al. of over 1,000 elective AAA repairs in Denmark treated with either EVAR or OR, the frequency of prolonged ICU LOS, defined as >3 days, was less than 1% for patients treated with EVAR (De La Motte, 2013). More recent population-based and registry studies confirm that perioperative mortality after intact AAA repair is now low in both modalities, and that temporal trends, centre expertise and patient selection for EVAR significantly influence the observed range of perioperative complications (Cherian, 2024; Pirinen, 2024; Veličković, 2023). In line with these data, the ESVS AAA guidelines recommend EVAR as the preferred treatment in most patients with suitable anatomy, reserving open repair primarily for selected patients with long life expectancy and acceptable operative risk (Wanhainen, 2024).

Ruptured repair and outcomes

A ruptured abdominal aortic aneurysm (rAAA) constitutes a surgical emergency. Earlier autopsy and population-based studies estimated an incidence of approximately 5–20 per 100 000 person-years and an overall mortality rate—including those who never reach hospital—of around 80–90% (Bengtsson, 1993; Gunnarsson, 2021; Johansson, 1986). Contemporary registry analyses highlight that, while rAAA outcomes have improved over time, it remains associated with high early overall mortality (Gunnarsson, 2021). Among patients who survive the initial rupture and are eligible for emergency repair, the most recent randomised controlled trials comparing EVAR and OR have shown similar 30-day mortality rates of approximately 25–35% (Desgranges, 2015; IMPROVE Trial Investigators, 2014; Reimerink, 2013). Notably, the IMPROVE trial demonstrated a three-year mortality benefit favouring EVAR (48% vs 56%) together with higher quality-adjusted life-years as well as increased frequency of independent life (IMPROVE Trial Investigators, 2017). Additional post-hoc analyses of the same cohort have indicated a survival

benefit of ruptured AAA EVAR under local anaesthesia as compared to general anaesthesia (Hazard ratio [HR]: 0.62) (Mouton, 2019).

Because many patients present in profound haemorrhagic shock, the incidence of early postoperative organ dysfunction among survivors is substantial. In a retrospective cohort of more than 1,000 rAAA cases, Ali et al. reported lower rates of postoperative cardiac complications (EVAR: 29% vs OR: 38%), respiratory complications (EVAR: 28% vs OR: 46%), and bowel ischaemia (EVAR: 3.9% vs OR: 10%) in favour of EVAR (Ali, 2015). The median intensive care unit length of stay (ICU LOS) was likewise significantly shorter for EVAR (2 days) compared to OR (6 days) (Ali, 2015). Large contemporary observational analyses have similarly shown reduced in-hospital mortality, less organ dysfunction including acute kidney injury, as well as shorter ICU and hospital stays following EVAR for rAAA (Alsusa, 2022). Given this cumulative data, the ESVS AAA guidelines issue a strong recommendation for EVAR under local anaesthesia as first line strategy for ruptured AAA patients with suitable anatomy (Wanhainen, 2024).

AGI – definitions and risk factors

Definitions

The definition of AGI has varied over time in the literature, ranging from broad clinical judgement to strict microbiological pathogen verification on an explanted aortic prosthesis. In several earlier studies, aortic and peripheral vascular graft infections as well as primary infected/mycotic aortic aneurysms (INAA/MAA) were at times combined with pure AGI cohorts, contributing to heterogeneity and limited comparability across reports (Teebken, 2012). The Management of Aortic Graft Infection Collaboration (MAGIC) sought to standardise terminology and diagnostic criteria in 2016, proposing a structured definition based on major and minor findings across surgical, radiological, and microbiological domains (Lyons, 2016) (Figure 2). The MAGIC criteria have since been prospectively validated, demonstrating high sensitivity (>90%) and moderate specificity (approximately 40–60%) for diagnosing intracavitary AGI (Anagnostopoulos, 2021). In brief, a confirmed AGI according to MAGIC requires at least one major criterion plus a major or minor criterion in another domain.

	CLINICAL / SURGICAL	RADIOLOGY	LABORATORY
MAJOR CRITERIA	<ul style="list-style-type: none"> • Pus (confirmed by microscopy) around graft or in aneurysm sac at surgery • Open wound with exposed graft or communicating sinus • Fistula development e.g. aorto-enteric or aorto-bronchial • Graft insertion in an infected site e.g. fistula, mycotic aneurysm or infected pseudoaneurysm 	<ul style="list-style-type: none"> • Peri-graft fluid on CT scan \geq 3 months after insertion • Peri-graft gas on CT scan \geq 7 weeks after insertion • Increase in peri-graft gas volume demonstrated on serial imaging 	<ul style="list-style-type: none"> • Organisms recovered from an explanted graft • Organisms recovered from an intra-operative specimen • Organisms recovered from a percutaneous, radiologically-guided aspirate of peri-graft fluid
MINOR CRITERIA	<ul style="list-style-type: none"> • Localized clinical features of AGI e.g. erythema, warmth, swelling, purulent discharge, pain • Fever \geq38°C with AGI as most likely cause 	<ul style="list-style-type: none"> • 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 leukocyte uptake 	<ul style="list-style-type: none"> • Blood culture(s) positive and no apparent source except AGI • Abnormally elevated inflammatory markers with AGI as most likely cause e.g. ESR, CRP, white cell count

Figure 2. Management of Aortic Graft Infection Collaboration (MAGIC) criteria for aortic graft infection diagnosis. Reproduced with the permission from Lyons OT et al (Lyons, 2016).

Moving from a strict definition including confirmation of a pathogen from an explanted aortic prosthesis towards a criterion-based definition has two major benefits:

- i) Culture-negative AGI; among patients with a sufficiently high clinical suspicion of AGI to warrant explantation and antimicrobial therapy, culture positivity is reported in only 60–80% (Capoccia, 2016; Janko, 2021; Ljungquist, 2021; Gavali, 2023;), meaning that a substantial proportion of clinically treated AGIs would be excluded by a purely microbiological definition
- ii) Improved clinical utility; The MAGIC criteria provide pragmatic diagnostic support, guiding imaging, microbiological work-up, and pre-test probability assessment, and thus offer greater real-world value in diagnostic decision-making.

Beyond diagnostic criteria, several systems have been proposed to classify AGIs anatomically and guide management. Szilagy et al. first introduced a staging system describing the extent of infectious involvement of the graft, anastomosis, and associated complications (Szilagy, 1972). This was later adapted into the Samson staging system, which incorporates recommendations for imaging work-up and definitive treatment strategies (Table 1) (Samson, 1988).

Table 1. Staging of vascular graft infections according to Szilagyi et al. and Samson et al. respectively.

Stage	Szilagyi	Samson
I	Superficial infection above the graft limited to the dermis.	Superficial infection above the graft limited to the dermis.
II	Infection above the graft involving the subcutaneous tissue without extension to the vascular graft.	Infection above the graft involving the subcutaneous tissue without extension to the vascular graft.
III	Deep infection involving the graft body or graft-artery anastomosis.	Deep infection involving limited to the graft body but without affection of the graft-anastomoses.
IV		Deep infection involving the graft-anastomoses without complications such as sepsis or dehiscence/bleeding.
V		Deep infection involving the graft-anastomoses with complications such as sepsis or dehiscence/bleeding.

Fistulation from an infected graft or stent graft may occur, most commonly to adjacent bowel. Terminology in the literature varies and includes secondary aorto-enteric fistulae (SAEF) or graft-enteric fistulae (GEF), which are used interchangeably to differentiate from primary aorto-enteric fistulae (AEF) occurring in the absence of an aortic prosthesis. Some authors further distinguish between true SAEF versus paraprosthetic SAEF, and GEF versus graft-enteric erosion (GEE); the former indicating direct involvement of the graft–aortic anastomosis with a corresponding risk of major haemorrhage, and the latter describing fistulation or erosion without direct communication with aortic flow. It is estimated that this level of stratification is applied in only around 50% of published cases (Kakkos, 2016), likely reflecting the difficulty in reliably determining the level of fistulation in retrospective record reviews.

Risk factors

Risk factors for the development of an aortic graft infection (AGI) after aortic surgery can broadly be divided into three categories:

- i) perioperative factors at the time of the primary repair,
- ii) patient-level factors, and
- iii) factors associated with late complications.

Perioperative risk factors and prophylaxis

The perioperative risk-factor spectrum mainly consists of treatment-strategy decisions and immediate perioperative complications following the primary aortic repair.

One of the most extensively studied perioperative factors is the use of systemic prophylactic antimicrobial therapy. Randomized trials and meta-analyses of RCTs have demonstrated that perioperative antibiotics reduce the risk of surgical-site infection (SSI) and likely decrease the frequency of peripheral vascular graft and endograft infections (VGEI), with relative risks of 0.25 and 0.31, respectively, compared with placebo (Hasselgren, 1984; Satzmann, 1983; Stewart, 2006). Demonstrating a specific reduction in AGI, however, is challenging due to the rarity of the event and limited statistical power. Nevertheless, perioperative systemic antibiotics, selected according to patient characteristics and local resistance patterns, remain the accepted standard of care (Wanhainen, 2024).

Historical experimental and animal models have shown that the susceptibility of newly implanted grafts or stent grafts to bacterial colonisation diminishes over the first months following implantation, likely due to endothelialisation/intraluminal biological coating and anastomotic healing (Malone, 1975; Sauvage, 1975; Welch, 1992). These observations raised interest in local prophylactic strategies, including antimicrobial-impregnated grafts. In early work, Malassiné and Goëau-Brissonnière demonstrated that protein- or gelatin-sealed grafts could absorb rifampicin, release it over several days, and protect against *S. aureus* AGI in canine models (Goëau-Brissonnière, 1991; Malassiné, 1996). However, subsequent human studies have not been able to reproduce meaningful preventive benefit from rifampicin-soaked grafts or stent grafts (Mufty, 2022; Stewart, 2006). Potential explanations include sub-therapeutic antibiotic concentrations at the graft–tissue interface, limited antimicrobial spectrum, and a lack of additive benefit beyond systemic prophylaxis (Mufty, 2022).

Aortobifemoral bypass procedures, whether performed for aneurysmal or aorto-iliac occlusive disease, also appear to increase AGI risk (Legout, 2012; Zarrintan, 2025). Groin incisions carry an SSI rate of 5–10%, contributing to elevated graft infection risk (Antonios, 2006). Proposed mechanisms include the high density of lymphatic vessels, proximity to gram-negative intestinal flora, and mechanical stress affecting wound healing (Pejkić, 2014; Zarrintan 2025).

Patients undergoing emergency aortic repair, often for ruptured AAA, appear to be at increased risk of subsequent AGI. In a contemporary cohort, emergency aortic repair was an independent predictor for the development of

AGI (HR: 3.6, CI95: 1.1-11.6) (Shirae, 2019). This is probably multifactorial, involving increased risk of intestinal contamination due to non-occlusive mesenteric ischaemia and higher rates of systemic infection associated with critical illness and prolonged intensive care (Vogel, 2008). Other population-based series have reported similar overall AGI incidence after emergency and elective repair, indicating that emergency status is not the sole determinant of risk (Pettersson, 2017)

INAA/MAA are also associated with a markedly increased risk of infectious complications and subsequent AGI in the implanted graft or stent graft. This is reflected in the MAGIC criteria, where MAA constitutes a major diagnostic criterion. Sörelius et al. reported that severe infectious complications occurred in 20% of MAA patients (n=132), while AGI developed in 6.5% and 5.7% following open and endovascular repair, respectively (Sörelius, 2016). These rates are potentially underestimated, as patients dying from septic shock or aorto-enteric fistulas were categorised separately.

Patient-level risk factors

Immunocompromised states and significant comorbidity burdens are empirically accepted as AGI risk factors. In a national inquiry, Fiorani et al. found that malignancy and immunosuppression were more common among patients who developed endograft infections (22%) compared with non-infected EVAR patients (Fiorani, 2003). Identifying host-specific predictors in multivariable analyses has been more challenging. Vogel et al. conducted one of the few population-based analyses in this area, comparing 61 AGI cases with a non-AGI cohort. In their multivariable logistic regression, only bacteraemia, defined as positive blood cultures, was independently associated with AGI (OR 4.2, CI95: 1.5–11.9) (Vogel, 2008). No additional host-specific predictors were identified. In a more recent analysis, Duarte et al. conducted a case-control study of patients treated with open aortic repair and identified alcohol use disorder (OR 42.4), prolonged hospital-stay (OR 1.05 per day), and malignancy (OR 5.82) as factors independently associated with AGI (Duarte, 2022). However, the small cohort sizes and the very limited number of EVAR-treated patients in these studies restrict the generalisability of these risk factors to contemporary aortic practice.

Late complications

One of the major late complications directly linked to AGI is the development of a GEF/SAEF. These fistulae allow direct communication between the enteric microbiome and the graft or stent graft, promoting polymicrobial AGI. In published AGI case series, GEF occurs in approximately 20–50% of patients, with similar frequencies between open grafts and stent grafts in the

abdominal aorta (Antonopoulos, 2019; O'Connor, 2006; Smeds, 2016). The underlying mechanism is believed to predominantly be mechanical erosion into adjacent bowel, usually the duodenum. However, the temporal relationship between AGI and GEF is often unclear, and it remains uncertain whether fistulation is a cause or consequence of AGI.



Figure 3. Patient with an exposed stentgraft with a graft-enteric fistulae and an erosion into the duodenum visualised during a gastroduodenoscopy (Söreljus, 2014). Reprinted by permission of SAGE Publications, Ltd.

Late disseminated systemic infections are also implicated in late AGI development. The proposed mechanism involves microbial adherence to the prosthesis following episodes of transient or sustained bacteraemia. As noted, bacteraemia has been shown to be an independent risk factor for AGI (Vogel, 2008). The influence of focal non-SSI infections, such as pneumonia, urinary tract infections, and gastrointestinal infections, on AGI risk is not well defined, though it is plausible that intermittent bacteraemia from such infections contributes to AGI pathogenesis.

With respect to prophylactic antimicrobial therapy before surgical and dental procedures, the European AAA guidelines recommend prophylaxis for interventions with a high risk of infectious complications, including gingival or mucosal manipulation and abscess drainage (Wanhainen, 2024). The evidence base is largely empirical and extrapolated from guidelines for prosthetic valve endocarditis (Wanhainen 2024; Wilson, 2021).

AGI – diagnosis

The diagnosis of AGI is multimodal, a principle reflected in the MAGIC criteria, and always begins with a high index of clinical suspicion (Lyons, 2016). Any patient with an aortic prosthesis who presents with a new onset airway-/gastro-intestinal bleeding or an infection with unclear focus should undergo a structured evaluation to exclude AGI (Wilson, 2016). Clinical presentation varies depending on the anatomical location of the prosthesis, the extent of infection, and the presence of local complications such as fistulation or anastomotic disruption (Wouthuyzen-Bakker, 2023).

In one of the largest published series of infected aortic stent grafts (n = 206; EVAR = 180), Smeds et al. reported that approximately 66% of patients presented with pain (most commonly abdominal or back pain), 66% with fever or chills, and 11% with rupture at the time of AGI diagnosis (Smeds, 2016). These findings must be interpreted with caution given the retrospective methodology and potential recall and documentation bias.

The presence of a secondary aorto-enteric fistulae (SAEF) alters the symptom profile. In the abdominal aorta, GEF may present with a spectrum of bleeding symptoms ranging from anaemia or melena to massive gastrointestinal bleeding with haematochezia and haemorrhagic shock, depending on the location and size of the fistula (Kahlberg, 2016). Thoracic graft or stent graft fistulation may present with haematemesis or haemoptysis due to esophageal or bronchial/airway lesions respectively (Kahlberg, 2019; Rey, 2025).

The largest review of SAEF/GEF to date, performed by Kakkos et al., analysed 823 cases derived from case reports and case series (Kakkos, 2016). Bleeding of any type occurred in 71.7%, haemorrhagic shock in 33.1%, and sepsis in 39.7% of cases. Among cases with specified anatomy, 77.6% involved the duodenum and 15.5% involved small bowel segments. Approximately half of all cases were stratified into true SAEF/GEF versus paraprothetic SAEF/graft-enteric erosion (GEE); of these, 57.2% represented true fistulae involving a direct connection between the graft–aortic anastomosis and the gastrointestinal lumen.

These distributions likely underestimate the true anatomical variability and symptom heterogeneity due to the reliance on case-based sources and inconsistent reporting across the included literature.

Radiology

Radiological assessment remains central to the diagnostic work-up of suspected AGI. Bedside duplex ultrasonography offers practical value owing to its broad availability and non-invasiveness, but its diagnostic performance in

intracavitary AGI is limited by low sensitivity and therefore a low negative predictive value (NPV) in this context (Erba, 2014; Lauri, 2022).

CT-A has historically been the first-line imaging modality for suspected graft infections (Chakfé, 2020). More recently, nuclear medicine imaging strategies, including technetium-99m or indium-111-labelled white blood cell scintigraphy (WBCS) and 18F-fluorodeoxyglucose positron emission tomography ([18F]FDG PET), particularly when combined with single-photon emission computed tomography/computed tomography (SPECT/CT) and CT respectively, have demonstrated higher diagnostic accuracy, with improved NPV and positive predictive value in selected cohorts (Folmer, 2020; Mahmoodi, 2022; Mergen, 2019; Shahidi, 2007).

CT-A

The presence of late periprosthetic gas on CT-A is regarded as a highly specific marker for AGI and may reflect ongoing bacterial metabolic activity or the presence of a GEF. Classic studies by O'Hara et al. and Qvarfordt et al., examining small cohorts of 29 AGI patients and 26 controls respectively, demonstrated that periprosthetic gas is detectable in roughly 60% of CT scans within the first postoperative week, but is exceedingly uncommon beyond eight weeks after open aortic repair (O'Hara, 1984; Qvarfordt, 1985). Similar findings have been reported after endovascular aortic repair, where early gas within the aneurysm sac is common but typically diminishes over time (Saltepsis, 2018). Although some of these findings were derived from earlier, lower-resolution CT technology, the principle remains valid, and periprosthetic gas seen ≥ 7 weeks after repair is considered a major diagnostic criterion in the MAGIC framework (Lyons, 2016).

Fluid collections surrounding the graft or stent graft are common in the early postoperative period and typically represent haematoma or seroma within or adjacent to the aneurysm sac. Persistent periprosthetic fluid beyond approximately 12 weeks is unusual and should raise the suspicion of AGI (Lyons, 2016; Qvarfordt, 1985).

A pseudoaneurysm in the setting of suspected AGI may reflect infection-related weakening of the aortic wall or early anastomotic breakdown. While concerning, this finding alone lacks sufficient sensitivity to confirm AGI (Saleem, 2015).

Associated periprosthetic complications increase the likelihood of infection. These include deep groin or retroperitoneal abscesses, psoas abscesses, and evidence of osteomyelitis or discitis. Bowel-to-graft adherence with associated mural thickening further heightens suspicion for a GEF (Gulati, 2021; Saleem, 2015).

Nuclear medicine imaging – WBCS-SPECT/CT and [18F]FDG PET/CT

The integration of nuclear medicine imaging with standard CT-A enhances diagnostic accuracy by combining metabolic or inflammatory activity with detailed anatomic assessment. Previous systematic reviews report sensitivities of approximately 90–95% for [18F]FDG PET/CT in detecting vascular graft infections, depending on SUV_max thresholds and visual scoring criteria used to define a positive scan (Folmer, 2020; Kim, 2019; Mahmoodi, 2022; Mergen, 2019; Spacek, 2009).

Despite high sensitivity, [18F]FDG PET/CT results may be confounded by diffuse, low-grade uptake along non-infected grafts or stent grafts, which can persist for months or even years post-implantation and reduce specificity (Manta, 2023; Saleem, 2015). Contemporary data generally report specificity values between 70-80% (Folmer, 2020; Kim, 2019; Mahmoodi 2022).

WBCS-SPECT/CT has demonstrated similar, and in some studies slightly superior, diagnostic performance compared with [18F]FDG PET/CT (Folmer, 2018; Lauri, 2023; Puges, 2019), particularly in early postoperative imaging where background inflammatory uptake can limit PET interpretation. However, WBCS is constrained by its technical complexity, prolonged imaging protocol, and limited availability.

As with all diagnostic modalities, reported sensitivity and specificity vary across studies due to differences in case mix and disease spectrum rather than disease prevalence itself. Many published series of nuclear medicine imaging include highly selected populations in which the prevalence of true AGI exceeds 50%, increasing pre-test probability and potentially inflating performance estimates, thereby limiting generalizability to lower-prevalence clinical settings. In contrast, positive and negative predictive values are directly dependent on disease prevalence and will vary substantially depending on high- vs low-prevalence populations, as well as threshold values for SUV_max or semi-quantitative assessments selected to define test positivity.

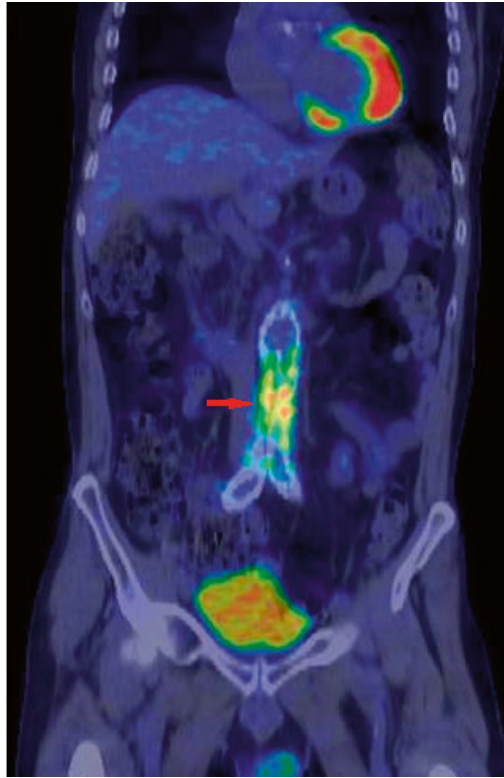


Figure 4. A patient with a previous endovascular repair for a mycotic aortic aneurysm presenting with an abdominal aortic endograft infection. 18-fludeoxyglucose positron emission tomography – computed tomography (18-FDG-PET-CT) showing pathological tracer uptake (red arrow) in the old stentgraft.

Microbiology

The microbiological work-up in suspected aortic graft infection (AGI) serves two essential purposes: (i) to increase the diagnostic likelihood and (ii) to guide optimal antimicrobial therapy. Obtaining appropriate blood cultures, perigraft cultures and, where possible, cultures from the explanted graft remains fundamental to achieve this. The literature supports culture positivity in approximately 60–90% of AGI cases (Braams, 2023; Fiorani, 2003; Erb, 2014; Gavali, 2023; Janko, 2021; Legout, 2012; Ljungquist, 2023; Smeds, 2016). Negative cultures are often attributable to prior antimicrobial exposure and biofilm-associated organisms, which may reduce the probability of identifying viable bacteria. Withholding antimicrobial therapy before deep tissue samples have been secured, in non-septic patients, have been shown to increase the microbiological yield in patients with prosthetic joint infections (Shahi, 2015; Trampuz, 2007). There is currently a lack of consensus regarding if this strategy can be applied to AGI cohorts accounting for the risk of

clinical or vascular deterioration (Wouthuyzen-Bakker, 2023). Furthermore, delayed operative intervention following prolonged antimicrobial therapy has been associated with improved outcomes in INAA/MAA (Söreljus, 2016), although this may be influenced by selection bias and extrapolation of these findings to an AGI cohort has yet to be confirmed.

Empirical antimicrobial treatment

Once peripheral blood and, when possible, deep tissue or graft samples have been obtained, empirical antimicrobial treatment is typically initiated according to local resistance patterns, taking the prevalence of MRSA, ESBL-producing organisms, and other multidrug-resistant pathogens into consideration. Revest et al. provided one of the first structured and comprehensive recommendation sets for empirical antimicrobial therapy across varying clinical and microbiological scenarios (Revest, 2015). These recommendations have since been expanded and refined by Wouthuyzen-Bakker et al. and, more recently, by Kouijzer et al. (Kouijzer, 2025; Wouthuyzen-Bakker, 2023).

Microbiological etiology

The distribution of pathogens in AGI varies across studies and is influenced by culture strategy, sample number, definitions of graft infection and contaminants, time period, repair method (open vs endovascular), and prevalence of intracavitary vs extra-cavitary AGI. Surgical site infection (SSI) is a recognised risk factor, and groin incisions, particularly in aortobifemoral bypasses, are associated with higher rates of gram-positive pathogens such as *Staphylococcus aureus* and CoNS. Older series with many aortobifemoral bypasses therefore frequently report gram-positive dominance (50–60%) (Erb, 2014). Similar pathogen profile with a high gram-positive prevalence approaching 30–50% is still reported for thoracic AGI (Kouijzer, 2022; Sandhu, 2021). In contrast, Smeds et al.'s series of 204 intraavitary, mainly abdominal, infected endografts reported gram-positive pathogens in only 22% of cases, suggesting a shift toward gram-negative or polymicrobial profiles in contemporary abdominal endograft infections (Gavali, 2023; Janko, 2021; Monnier, 2024; Smeds, 2016).

Polymicrobial infection, commonly defined as ≥ 2 –3 species isolated from graft or deep tissue samples, is reported in approximately 10–30% of AGI cases (Couture, 2021; Gavali, 2023; Janko, 2021; Monnier, 2024). This pattern is especially prevalent in the presence of SAEF/GEF, where *Candida* species are identified in 20–40% of cases, compared with 5–10% in non-GEF cohorts (Couture, 2021; Gavali, 2021; Janko, 2021; Monnier, 2024). The likely mechanism is direct contamination from the gastrointestinal tract where *Candida* species are commensals, combined with ecological shifts from

prolonged antibacterial therapy that favor fungal overgrowth (Lin, 2005; Pappas, 2018). Monnier et al. demonstrated in a multivariable analysis of a retrospective cohort of 148 patients with predominantly abdominal AGI that preoperative antimicrobial therapy ≥ 7 days was independently associated with fungal infection detected on blood or perioperative cultures (OR 2.9, CI95 1.1–7.4) (Monnier, 2024).

Microbiological work-up

Because AGI is rare and heterogeneous, data on optimal microbiological strategies remain limited. However, principles can be extrapolated from other foreign material infections such as prosthetic joint infections where fewer than three to five intraoperative samples reduce diagnostic sensitivity (Atkins, 1998; Peel, 2017; Wouthuyzen-Bakker, 2023). A similar rationale applies to AGI, where distinguishing true pathogens from contaminants is crucial. This is particularly relevant given the high prevalence of potential contaminants such as coagulase-negative staphylococci (CoNS) and *Cutibacterium acnes*, found in 10–30% of AGI samples (Gavali, 2021; Ljungquist, 2021; Ljungquist, 2023). These organisms are part of the normal skin flora, and single-sample growth may represent contamination (Larson, 2000). Additionally, treatment is complicated by the high prevalence of multidrug resistant phenotypes among CoNS isolates (Larson, 1986). Growth of the same pathogen across multiple spatially distinct samples significantly increases the likelihood of true infection.

Sonication, i.e. using high-frequency acoustic waves to detach bacteria from biofilm, has improved diagnostic yield in prosthetic joint infections in some studies (Trampuz, 2007). In AGI and peripheral VGEI, small studies support its utility. Ulcar et al. examined 22 patients (24 VGEI cases, including 12 AGI) and found that sonication and/or broad-range polymerase chain reaction (PCR) identified pathogens in 10 additional cases beyond standard cultures, with sonication fluid cultures alone yielding seven additional positives (Ulcar, 2018). Similarly, Puges et al. evaluated 39 VGEI patients (19 AGI) and found that combining sonication and PCR increased diagnostic sensitivity from 79% (CI95: 70–86%) to 97% (CI95: 92–99%) (Puges, 2018). More recent studies by Braams et al. and Puges et al. have reported similar findings, demonstrating that sonication in vascular graft infection increases pathogen detection and can meaningfully influence antimicrobial management in a subset of patients (Braams, 2023; Puges, 2024).

Prolonged incubation of blood and deep tissue cultures (beyond the routine five days) may further increase pathogen detection rate. Schäfer et al. demonstrated in a prosthetic joint infection cohort that pathogens continued to be

isolated up to day 13 of incubation, with late detections not solely attributable to identification of contaminants (Schäfer, 2008). Banzon et al. reported similar findings in a cohort of confirmed *Propionibacterium* spp. (now *Cutibacterium* spp.) prosthetic valve endocarditis, demonstrating that prolonged incubation of blood cultures (up to 14 days) substantially increased detection rates - 75% compared with 12.5% using standard incubation periods (Banzon, 2017).

Molecular diagnostic strategies including 16S ribosomal ribonucleic acid (rRNA) PCR and fungal deoxyribonucleic acid (DNA) PCR can identify minute quantities of microbial genetic material independent of culture viability. The utility of these techniques has been scarcely studied in the AGI literature; however, they may be particularly valuable when applied to deep tissue/graft specimens, or to sonication fluid samples, in patients who have received prior antimicrobial therapy (Basein, 2018; Puges, 2018; Rampini, 2011; Ulcar, 2018).

AGI – surgical- and microbiological treatment

Surgical treatment – general considerations

Surgical treatment remains the gold standard for managing AGI (Chakfé, 2020). Despite this, strict antimicrobial suppressive therapy is a readily applied treatment strategy in patients for whom surgical intervention is not feasible due to comorbidity burden or unfavourable graft anatomy. The prognosis of intracavitary AGI treated conservatively has historically been poor, with 1-year survival frequently below 50% (Li, 2018; Lin & Hsu, 2014). However, contemporary series focusing primarily on endograft infections, managed in centers with dedicated conservative treatment protocols, including comprehensive microbiological work-up, modern biofilm-active antimicrobial regimens, and adjunctive measures such as percutaneous drainage of the aneurysm sac or periprosthetic collections, have demonstrated markedly improved outcomes, with effective infection suppression and 1-year survival approaching 90% (Ljungquist, 2023).

Surgical strategies can broadly be categorised as:

- i) Complete resection of the infected vascular prosthesis with subsequent restoration of distal perfusion (radical surgery, [RS]), or
- ii) Total or partial graft preservation with debridement of infected paraprosthesis tissue (semi-conservative treatment, [SC]).

Among patients undergoing complete excision, restoration of distal perfusion can be achieved through:

- i) Aortic stump closure and extra-anatomical bypass (EAB), most commonly via an axillobifemoral conduit; or
- ii) In-situ repair (ISR), in which the resected aortic segment is reconstructed in-situ using an infection-resistant conduit.

A variety of conduits can be employed for ISR, with the most commonly reported including (Chafké, 2020; Jepsen, 2023):

- i) Neo-aortoiliac systems (NAIS) using autologous femoral veins
- ii) Xenogeneic grafts (non-human tissue)
- iii) Cryopreserved or fresh arterial/venous allografts
- iv) Silver(/triclosan)-coated or antibiotic-impregnated synthetic grafts (typically rifampicin-bonded)

ISR, and particularly NAIS, has increasingly become the preferred surgical strategy and is recommended as the primary mode of repair in surgically fit patients according to the European VGEI guidelines (Chafké, 2020). However, these recommendations are largely based on small, retrospective, single-center series that are highly susceptible to selection and publication bias. It is therefore reasonable to assume that outcomes achieved in centers of excellence with specific expertise in a given technique may not be fully generalisable. Consequently, the field of AGI research continues to lack robust, population-based comparative studies of different surgical strategies, limiting the overall quality of evidence and restricting evidence-based decision-making.

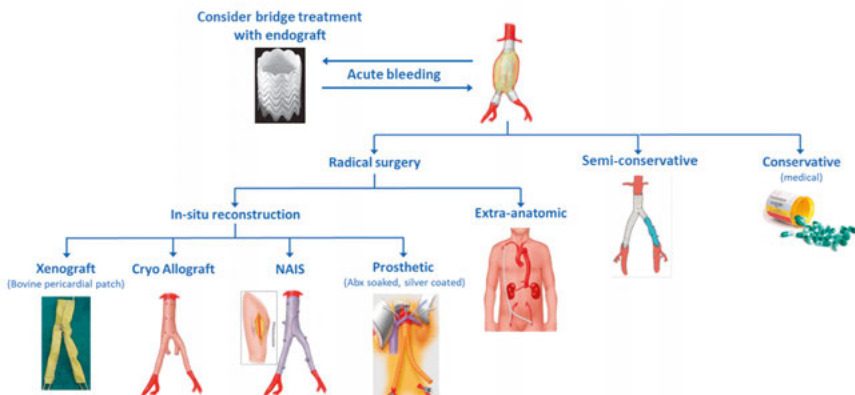


Figure 5. Flowchart illustrating the clinical decision steps and options in the treatment of aortic graft infections.

Extra-anatomical bypass

Historically, the main surgical reconstruction for abdominal AGI has been EAB. Typically, a midline abdominal incision is performed to obtain anterior access to the retroperitoneal space and the aortic prosthesis. After proximal and distal control is secured, the infected prosthesis and surrounding infected perigraft tissue are removed, and the proximal aortic and distal iliac or femoral stumps are closed. To restore lower-limb perfusion, bilateral femoral and uni- or bilateral axillary artery cut-downs are prepared. An axillobifemoral graft, usually ring-reinforced, is then tunnelled subcutaneously across the thorax and abdomen to the femoral arteries.

The procedural steps have historically been performed in different sequences. The empirically derived traditional consensus has been to remove the infected graft prior to constructing the extra-anatomic bypass, with the aim of reducing the risk of reinfection of the newly implanted conduit. Reilly et al. conducted a retrospective comparison in 1987 of three approaches: (i) infected graft removal (IGR) followed by immediate revascularisation (traditional), (ii) revascularisation followed by immediate IGR (sequential), and (iii) revascularisation followed by delayed IGR (delayed) (Reilly, 1987). In their cohort of 101 patients, revascularisation prior to IGR (sequential) significantly reduced the amputation rate (11%) compared with the traditional approach (43%), without increasing the rate of recurrent graft infection. There was also a non-significant trend toward improved overall survival in patients treated with either sequential or delayed strategies.

Reported postoperative 30-day mortality for EAB ranges from 10–30%, depending on factors such as haemorrhagic or septic shock at presentation, the presence of SAEF/GEF, and overall comorbidity burden (Reilly, 1987; Seeger, 2000). The major advantage of the extra-anatomic approach is the ability to revascularise the lower limbs outside the infected operative field, theoretically reducing the risk of reinfection of the new graft. In one of the largest meta-analyses, including approximately 459 EAB repairs, recurrent graft infection occurred in 6–7% of cases (O'Connor, 2006). However, the long length and extra-anatomic course of the prosthetic conduit increase the risk of graft thrombosis and acute limb ischaemia (ALI); major amputation rates of 10–20% have been reported during follow-up (O'Connor, 2006). In a more contemporary retrospective multicentre study by Janko et al., which included 69 AGI patients treated with EAB in the absence of SAE/GEF, EAB was shown to be inferior to ISR with respect to infection-free survival. One-year overall survival in the EAB cohort approached 60%, and the 1-year rate of reinfection or persistent infection was approximately 30% (Janko, 2022). In contrast, in a separate cohort studied by the same authors focusing on AGI

patients with concomitant SAEF/GEF, no significant differences in short- or long-term survival were observed when comparing EAB and ISR (Janko, 2021).

A treatment-specific and feared complication of EAB is aortic stump blow-out. The exact mechanism is not fully understood, but contributing factors likely include mechanical forces exerted on the blunt aortic stump, inherent aortic wall fragility, and persistent or residual infection at the suture line. Stump blow-out is estimated to occur in approximately 10% of patients following EAB and aortic stump closure for AGI, although the true incidence is likely underreported due to loss to follow-up (Kakkos, 2016; Moulton, 1986; Seeger, 2000).

In-situ repair

NAIS

Autologous deep femoral vein grafting for AGI was first described by Ehrenfeld et al. in 1979 (Ehrenfeld, 1979). Excision of the infected aortic prosthesis follows the same principles as previously outlined. Prior to, or concurrently with explantation, bilateral femoral vein harvesting is performed when feasible. The harvested veins are then spliced and configured into a “pantaloon” graft, or a suitable variant, forming the autologous neo-aortoiliac conduit, which is anastomosed in situ to replace the resected aortic segment. The reconstruction is typically reinforced with an omental flap or fascial coverage (Pallister, 2021).

A major advantage of NAIS is the complete removal of prosthetic material while restoring aortic continuity using an infection-resilient autologous conduit. Limitations include the requirement for adequate venous outflow of the lower limbs; patients with previous superficial venous harvesting or significant superficial venous insufficiency are generally unsuitable due to the heightened risk of postoperative morbidity, most notably severe oedema or venous compartment syndrome. Additionally, the harvested femoral veins must be of suitable calibre to avoid size mismatch at the proximal anastomosis and provide sufficient distal flow, and must exhibit acceptable wall integrity. Deep venous insufficiency, venous dilation, or a history of deep venous thrombosis increases the risk of later aneurysmal degeneration of the NAIS conduit (Ali, 2009; Pallister, 2021)

Because NAIS requires additional lower-extremity incisions and vein harvesting, unless performed simultaneously, the operative duration is prolonged and the physiological stress is greater compared with other techniques (Ali, 2009). Historically, this has likely influenced patient selection, with NAIS preferentially used in more fit patients. Reported perioperative mortality is

approximately 10-20%, while reinfection rates remain low at around 5-10% (Ali, 2009; Filiberto, 2021; Langenskiöld, 2021; O'Connor, 2006). Anastomotic disruption or graft failure occurs in 5–10% of cases over time, partly attributable to reinfection (Ali, 2009; Heinola, 2016). Long-term secondary patency of approximately 90% at 5 years has been reported (Chung, 2011; Heinola, 2016; Kryzaniak, 2024; Langenskiöld, 2021).

Xenogeneic grafts

Xenogeneic grafts constitute a subset of vascular conduits derived from tissues originating from non-human species. The most extensively studied xenogeneic materials in vascular surgery include bovine pericardial grafts and ovine hybrid grafts, which undergo chemical processing and decellularisation to reduce immunogenicity and minimise host immune responses (Czerny, 2011; El-Diaz, 2023). These grafts are biologically derived yet function as acellular scaffolds, preserving structural integrity while limiting immunogenicity. In the context of graft infection, xenogeneic grafts have attracted interest due to their potential resistance to infection, a property that is often attributed to the absence of synthetic polymer surfaces that facilitate bacterial adhesion and biofilm formation.

Bovine pericardial grafts, in particular, offer several practical and theoretical advantages in the management of AGI. In addition to their perceived infection resistance, they are readily available as off-the-shelf materials and allow considerable intraoperative flexibility. Ex-situ reconstruction is relatively straightforward, with the possibility of tailoring graft diameter, length, and configuration, including the construction of bifurcated grafts or branch vessels using conventional suturing techniques or vascular stapling devices (Weiss, 2017). Over the past decade, the use of bovine pericardial grafts for in situ reconstruction in AGI has increased, and early clinical series report reinfection rates comparable to those observed following neo-aortoiliac system (NAIS) reconstructions, typically around 10%, with short-term 30-day mortality following radical resection around 10-20%, along with acceptable mid- to long-term patency (Borghese, 2026; Li, 2026; Weiss, 2017; Glasgow, 2023; Weiss, 2024). Importantly, few cases of graft degeneration, pseudoaneurysm formation, or structural failure have been reported to date, although long-term durability data remain limited (Glasgow, 2023; Weiss, 2024).

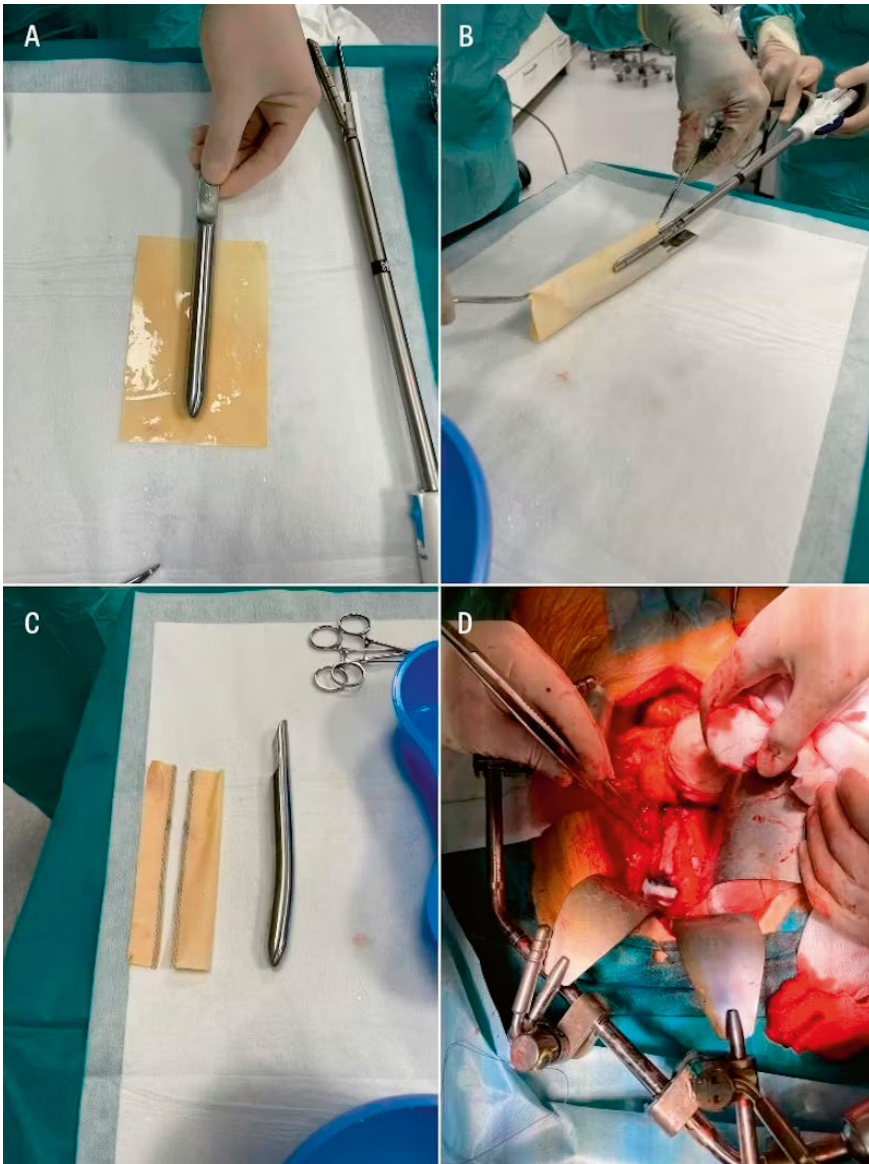


Figure 6. Intraoperative use of a bovine pericardium (A), and the ex-situ reconstruction to a tubular graft using vascular staples (B, C) and in-situ reconstruction after removal of the infected aortic graft (D). Reproduced with permission from *Läkartidningen*, 2025;122:24060, (Gavali, 2025).

Arterial- and venous allografts

Arterial and venous allografts, formerly termed “homografts” or “necrografts”, consist of vascular segments harvested from non – human leukocyte antigen (HLA)-matched donors, most commonly aortic or femoral arteries or veins. Their perceived advantages include:

- i) Improved resistance to infection compared with prosthetic materials;
- ii) Broader applicability due to the absence of patient-specific venous requirements; and
- iii) Avoidance of the physiological stress and morbidity associated with NAIS vein harvesting.

The use of arterial allografts dates back to the late 1940s (Swan, 1950), and the first successful aortic replacement for a non-infected AAA was performed using an aortic allograft by Dubost in 1951 (Dubost, 1951).

Early preservation methods involved refrigerated storage at 4°C in saline–plasma solutions. Histological studies demonstrated rapid degradation of smooth muscle cells and intimal architecture, with slower deterioration of medial fibrillin (Swan, 1950). Concerns about chronic rejection and late degeneration prompted development of cryopreservation, i.e. rapid cooling to –80° to –190°C with cryoprotectants to preserve structural integrity.

In one of the largest early series, Kieffer et al. analysed late outcomes in 179 AGI patients treated with allografts: 61% received fresh allografts and 39% cryopreserved ones. Graft complications occurred in 26% of patients, including occlusion and aneurysmal degeneration (Kieffer, 2004). Fresh allografts demonstrated significantly higher risk of degeneration. Similar findings favouring cryopreservation were reported in a cardiac valve allograft cohort (O’Brien, 1995).

Although cryopreservation may reduce the risk of late structural deterioration, modern series still describe substantial rates of occlusion and aneurysmal degeneration. In one of the largest contemporary cohorts of cryopreserved allografts (n = 220), Harlander-Locke et al. reported a cumulative 24% incidence of major graft-related complications, perioperative mortality of 9%, and explantation in 5% of patients at a median follow-up of 30 months (Harlander-Locke, 2014). Similar findings were reported by Couture et al. in a series of 200 patients with abdominal AGI treated using arterial allografts. In their cohort, 15 patients (7.5%) required graft-related surgical reintervention within 30 days, and a further 17 patients (8.5%) developed graft degradation with pseudoaneurysm formation or rupture within one year (Couture, 2021).

The mechanism of allograft degeneration remains incompletely understood. Mechanical trauma during harvesting, processing, or thawing may contribute, as may immunological reactions. Experimental models demonstrate activation of both cellular and humoral immune pathways, with adjunctive immunosuppressive therapy (Tacrolimus or Cyclosporin) reducing allograft degradation even when initiated one week after implantation (González-Gay, 2020; Matia, 2014; Schmitz-Rixen, 1988; Spunda, 2018).

In clinical practice, most vascular surgeons avoid routine immunosuppression due to concerns about infectious complications in the setting of active AGI. However, Pupka et al. reported reduced graft degradation in patients receiving long-term Cyclosporin compared with no immunosuppression, without increased infection rates (Pupka, 2011). The study was, however, small (~24 patients per arm). Decellularisation techniques may reduce graft immunogenicity and aneurysmal degeneration in animal models (Allaire, 1994), but clinical evidence remains limited. Cryopreservation itself appears to decrease immunogenicity, possibly reducing the marginal benefit of added immunosuppressive therapy (Hruby, 2020).

A recent meta-analysis by Antonopoulos et al. including 1377 patients treated with cryopreserved allografts reported 30-day mortality of ~15% (range 0–36%), reoperation rates of ~23%, stenotic/aneurysmal complications of ~15%, and overall follow-up mortality of ~20% (Antonopoulos, 2019). Outcomes remain heterogeneous, likely reflecting differences in graft preparation method, storage, thawing, operative indications (primary infection vs AGI; presence of GEF), and centre experience.

While several series have evaluated outcomes of allogeneic arterial reconstructions for AGI, the evidence supporting allogeneic venous conduits as ISR material remains limited. One of the few published reports is from Heinola et al., who described a cohort of 23 patients reconstructed with cryopreserved allogeneic venous grafts, predominantly femoral veins ($n = 21$), of whom 12 underwent repair for AGI. The 90-day mortality was 9%, and the rate of reintervention due to aneurysmal degeneration or reinfection was 13%, suggesting that venous allografts may offer outcomes comparable to those reported for arterial allografts (Heinola, 2019).

Antimicrobial coated synthetic grafts

Silver (in combination with triclosan)- and rifampicin-impregnated Dacron or polytetrafluoroethylene grafts have been developed and offer an off-the-shelf ISR solution with antimicrobial properties intended to reduce reinfection risk.

Silver-salts possess broad antimicrobial effects through reactive oxygen species generation, increased membrane permeability, and interference with bacterial respiratory pathways (Holt & Bard, 2005; Morones-Ramirez, 2013; Park, 2009). Graft silver content varies by preparation method, but animal studies have demonstrated silver concentrations above the minimal inhibitory concentration (MIC) for *Staphylococcus aureus* for 1–2 weeks post-implantation (Benvenisty, 1988). Increasing use of silver-containing medical devices raises concern about emerging silver- and antimicrobial cross-resistance (Mijnendonckx, 2013; Terzioğlu, 2023).

Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol), a broad-spectrum, non-ionic antimicrobial agent, has been widely incorporated into commercial products, including textiles and toothpaste, to inhibit microbial growth and biofilm formation. Its antibacterial activity is at least partially mediated through inhibition of the enoyl-acyl carrier protein reductase (FabI) enzyme, thereby blocking fatty acid synthesis, while higher concentrations disrupt bacterial membrane integrity (Alfhili, 2019; McMurry, 1998). Preclinical studies have showed an added bactericidal effect and biofilm inhibition comparing the addition of triclosan coating to silver impregnated synthetic grafts (Berard, 2016; Ricco, 2012; Tello-Díaz, 2023). Similar to ionic silver, concerns have been raised regarding triclosan-associated resistance, driven by *fabI* mutations, efflux pump upregulation, and cross-resistance to clinically relevant antibiotics, as well as potential human and environmental toxicity (Weatherly, 2017; Yazdankhah, 2006).

Rifampicin, a deoxyribonucleic acid (DNA)-dependent RNA polymerase inhibitor, is effective primarily against gram-positive bacteria (Goldstein, 2014). Although it bonds readily to gelatin-coated Dacron grafts, its durability of retention is limited, and activity against gram-negative organisms is suboptimal (Goëau-Brissonnière, 1991; Malassiney, 1996). Similar techniques for rifampicin-soaking of endografts have been described (Escobar, 2014).

Clinical outcomes for silver-, silver/triclosan-, or rifampicin-bonded grafts used for in-situ reconstruction (ISR) in abdominal AGI appear broadly comparable to those reported for other ISR strategies. Older series and meta-analyses describe reinfection rates of approximately 10–15% and overall mortality during follow-up in the range of 15–30% (Batt, 2018; O'Connor, 2006). More recent clinical data on rifampicin-bonded grafts in AGI remain limited; however, Vanbrugghe et al. reported an in-hospital mortality of 28% in a cohort of 18 abdominal AGI patients, with no documented recurrent infections during a median follow-up of 26 months among survivors (Vanbrugghe, 2020). For silver-based antimicrobial grafts, Caradu et al. presented outcomes from a larger mixed MAA/peripheral VGEI/AGI series of 86 patients treated with

silver–triclosan grafts, demonstrating a reinfection rate of approximately 7% at three years, with 1-year mortality ranging from 13% to 34% depending on the primary infectious pathology (Caradu, 2023).

Semi-conservative, conservative and hybrid solutions

Semi-conservative (SC) and conservative treatment strategies remain poorly defined in the literature. SC generally involves surgical debridement of infected aortic and peri-aortic tissue, with partial or no graft resection, thereby leaving selected components of the prosthetic graft or endograft in situ. Distal perfusion, if partial graft removal is performed, is typically restored via a partial ISR or EAB, such as a femoral–femoral crossover. These procedures may be combined with resection/repair of secondary fistulae when present, and, in selected cases, adjunctive endovascular techniques. The overarching objective is to minimise physiological stress and reduce aortic clamping time, while still removing overtly infected material and achieving adequate source control. In contrast, a true conservative treatment of AGI is usually defined as antimicrobial therapy without any open surgical interventions.

Because SC and conservative approaches are often reserved for either frail/anatomically complex patients who are poor candidates for radical excision or for cases where the infection is anatomically limited to a specific section of the aortic prosthesis, in combination with cohorts being mixed, outcomes reported in the literature are difficult to compare due to marked selection bias and heterogeneity.

Older studies have consistently reported poor outcomes for conservatively treated intracavitary AGI, with 1-year mortality and reinfection rates in the range of 30–50% (Moulakakis, 2014; Saleem, 2010). However, more recent data suggest that SC and conservative strategies may yield more favourable results in selected patients. In a retrospective international multicentre study including 114 AGI patients treated with SC, Janko et al. reported a 30-day mortality of 17.5%, a Kaplan–Meier median survival of 3.6 years, and a persistent or recurrent infection rate approaching 40% (Janko, 2021). In univariable analysis, the presence of a GEF, *Candida* infection, and the requirement for main-body resection were each associated with significantly worse survival.

Further supporting these findings, a network meta-analysis by Shu et al., including 852 abdominal AGI patients, demonstrated that SC treatment was associated with lower 1-year mortality (6.1%) compared with radical resection (23.8–41.4%), with reinfection rates remaining comparable across the different strategies (Shu, 2024). Similarly, recent work by Ljungquist et al. reported excellent outcomes in a cohort of 50 intracavitary AGI patients managed

primarily with conservative or SC approaches, including a 1-year mortality of 12% and a composite treatment-failure rate of 10% during follow-up (Ljungquist, 2023).

Advances in endovascular technology have also broadened the spectrum of hybrid options for AGI management. A key anatomical limitation of both ISR and EAB is the requirement for a suitable healthy aortic segment, or an adequate infrarenal aortic stump, for anastomosis, closure, or exclusion. To overcome this constraint, the branched endovascular aortic plug BEVAP was developed: a factory-modified Zenith t-Branch thoracoabdominal device in which the distal tubular portion is removed (Gavali, 2020). This innovation effectively expands the applicability of EAB to patients with hostile paravisceral aortic anatomy who would previously have been considered unsuitable for complete resection-based strategies.

SC repair and hybrid solutions are likely to be a part of the treatment arsenal for AGI patients in the future, but their definitive role remains unclear.

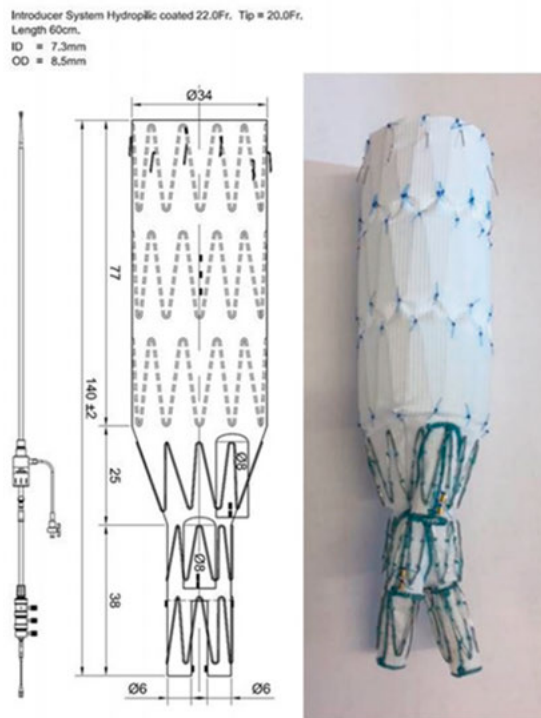


Figure 7. Schematics and real-life picture of the factory modified Zenith t-Branch thoracoabdominal endograft (branched endovascular aortic plug), with the distal tubular portion removed (Gavali, 2020).

Antimicrobial treatment

Following surgical treatment, a prolonged targeted antimicrobial strategy is often applied to reduce the risk of sepsis or recurrent graft infection and its associated complications, such as aortic stump blow-out or anastomotic dehiscence. In patients managed with fully conservative strategies, antimicrobial therapy is typically lifelong and suppressive in intent (Wouthuyzen-Bakker, 2023). The choice of antimicrobial regimen, depends on multiple case-specific factors, including the degree of local contamination, microbiological findings, presence of a SAEF/GEF, extent of graft excision, host factors such as immunosuppression, and the patient's clinical trajectory during hospitalisation and follow-up (Erb, 2014; Revest, 2015; Sixt, 2022; Wouthuyzen-Bakker, 2023). Local resistance patterns are also central to treatment selection. Ultimately, because therapeutic decisions are highly complex and often empirical, optimal management requires a multidisciplinary approach and close collaboration with infectious disease specialists experienced in vascular graft infections (Kouijzer, 2025; Sörelus, 2025).

Duration of antimicrobial therapy varies widely across published series, usually ranging from four weeks of targeted therapy to lifelong suppressive treatment (Legout, 2012; Revest, 2015; Smeds, 2016; Wouthuyzen-Bakker, 2023). To date, no prospective, intention-to-treat, head-to-head comparisons of different treatment durations exist within the AGI field. Retrospective data suggest a survival benefit associated with prolonged antimicrobial therapy (Janko, 2021).

A detailed discussion of antimicrobial strategies is beyond the scope of this literature review; however, some specific clinical contexts warrant further discussion:

Biofilm and gram-positive bacteria

Biofilm in the context of AGI represents a structured matrix of pathogen-derived glycoproteins that anchors microorganisms to the surface of the aortic prosthesis (Arciola, 2012). This matrix forms both a physical and biochemical barrier while creating a metabolically heterogeneous environment. Within the biofilm, bacteria can shift between an active, planktonic state and a dormant, non-planktonic phenotype. These transitions, combined with the protective extracellular layer, significantly diminish antimicrobial penetration and efficacy. Consequently, the antimicrobial minimum inhibitory concentration required to suppress or eradicate the pathogen is markedly increased, contributing to increased risk of treatment failure and persistence of infection (Høiby, 2010).

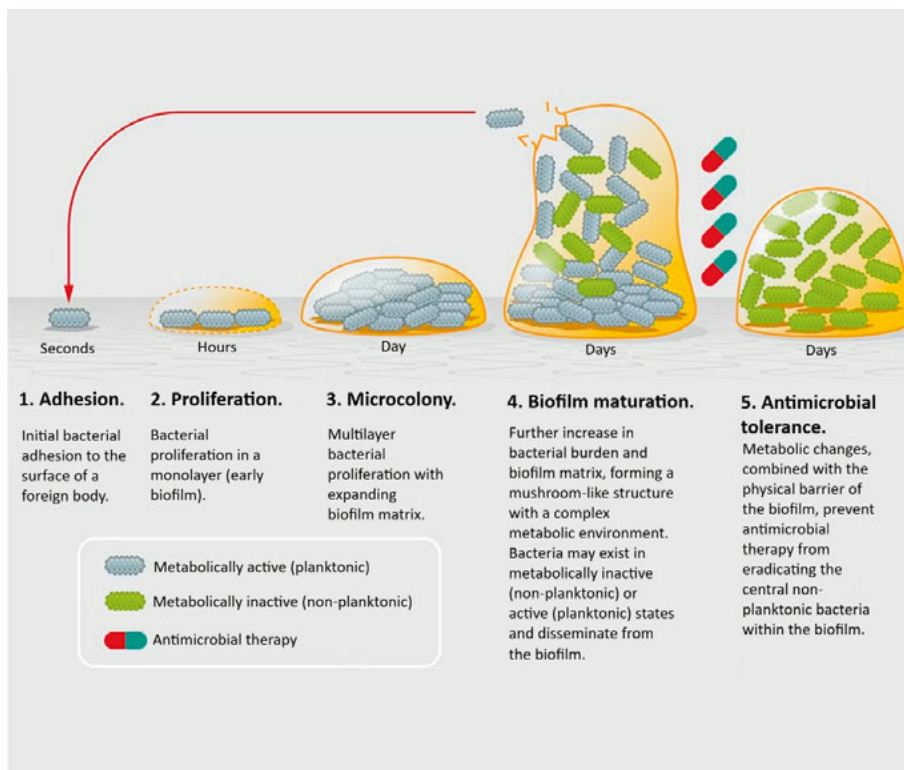


Figure 8. Schematic illustration of the maturation of a biofilm. Reproduced and adapted with permission from *Läkartidningen*, 2025;122:24060, (Gavali, 2025).

Historically, approximately 50% of pathogens associated with AGI have been gram-positive organisms, predominantly *Staphylococcal* species (Erba, 2014). These bacteria are well known for their capacity to form biofilm on prosthetic material (Otto, 2008). Given their prevalence in AGI, much of the research on adjunctive biofilm-active antimicrobial therapy has focused on rifampicin and daptomycin, antibiotics with well-documented in vitro synergistic effects against biofilm-associated gram-positive infections (Ciofu, 2017).

Rifampicin's pharmacodynamic properties have been discussed previously. Daptomycin, a cyclic lipopeptide, exerts its bactericidal activity by inserting into the bacterial cell membrane in a calcium-dependent manner, causing membrane depolarization and rapid inhibition of metabolic processes (Tedesco, 2004). Clinically, it is primarily used for infections caused by *Staphylococcus* spp. (including MRSA and CoNS), *Streptococcus* spp., and *Enterococcus* spp., particularly in the setting of prosthetic material infection (Vilhena, 2012).

Legout et al. conducted a prospective study of 84 patients with VGEI infected with *Staphylococcus aureus* or CoNS, comparing outcomes between

those receiving rifampicin (n = 45) and those who did not (n = 39). After adjustment for confounders, rifampicin therapy was independently associated with freedom from infection at one year (OR 0.32; CI95 0.10–0.96) (Legout, 2014). These findings align with the work of Zimmerli et al., who demonstrated superior outcomes when rifampicin was added to standard therapy in Staphylococcal prosthetic joint infection, both in their landmark RCT and subsequent confirmatory studies (Zimmerli, 1998; Zimmerli, 2019). In an international multicentre retrospective survey including 182 AGI patients with a GEF, Janko et al. reported that rifampicin use at discharge was independently associated with reduced mortality (HR 0.17; CI95 0.04–0.71) (Janko, 2021). Similar findings were reported by Coste et al., who analysed 112 patients with extra- or intracavitary VGEI and demonstrated that rifampicin exposure was independently associated with a reduced risk of treatment failure on multivariable analysis (OR 0.3; CI95 0.1–0.9) (Coste, 2021).

There are no prospective comparative studies evaluating daptomycin versus other antimicrobial strategies in VGI. In a small retrospective cohort of 15 VGEI patients treated with daptomycin, de la Revillas et al. reported that 67% achieved complete resolution of infection (De la Revillas, 2018). Although limited by sample size and heterogeneity, these data suggest potential utility. Supporting evidence can be drawn from related fields: in prosthetic valve endocarditis, Russo et al. demonstrated markedly lower mortality (6.5% vs 38%) among patients treated with daptomycin-containing regimens compared with non-daptomycin strategies in a cohort of 103 individuals (Russo, 2019).

Microbiological treatment considerations of secondary aorto-enteric fistula

SAEF-associated AGI significantly increases the risk of a polymicrobial infection by 2-3 fold (Couture, 2021; Janko, 2021). Accordingly, isolated culture results must be interpreted with caution, as they often capture only part of the pathogenic spectrum. Empirical regimens therefore commonly include extended gram-negative coverage, typically with a broad-spectrum β -lactam or a fluoroquinolone, until a full microbiological assessment is available.

Fungal infections, most frequently *Candida* spp., is likewise increased in the presence of SAEF, with 20–40% of cases showing positive blood or graft cultures, approximately tripling the prevalence observed in non-SAEF AGI (Gavali 2021; Janko, 2021; Puges, 2021). In view of this elevated risk, early empirical antifungal therapy, usually with an echinocandin, is often justified once a SAEF is identified, particularly in the perioperative period to protect any new aortic reconstructions.



Figure 9. Sagittal slice from a computed tomography angiography (CT-A) illustrating the abdominal aorta, including the coeliac trunk (A) and the superior mesenteric artery (B). A secondary aorto-enteric fistula (C) is demonstrated, appearing as a pseudoaneurysm extending toward the duodenum (D). Reproduced with permission from *Läkartidningen*, 2025;122:24060, (Gavali, 2025).

AGI – follow-up

Follow-up of AGI patients, whether treated with aortic graft explantation or conservatively, serves four principal objectives:

- i) Detection of graft-related complications, including pseudoaneurysm formation, critical inflow or outflow stenoses, and structural graft deterioration;
- ii) Identification of infectious complications, such as local abscess formation or recurrent conduit infection;
- iii) Overall assessment of treatment goals and revision of current treatment strategy; and
- iv) support of decision-making regarding the duration and intensity of long-term antimicrobial therapy.

Clinical assessment, serial blood-work including inflammatory markers, and imaging constitute the core components of follow-up (Chakfé, 2020; Kouijzer, 2025; Sörelus, 2025; Wouthuyzen-Bakker, 2023). There are no validated diagnostic criteria or single-modality thresholds for diagnosing recurrent graft infection. Consequently, isolated findings are rarely sufficient; current best practice relies on longitudinal trends and integrated interpretation of all available clinical, laboratory, and imaging data.

Historically, heterogeneity in outcome definitions has substantially limited comparisons between AGI treatment strategies. To address this, the 2025 VGEI Delphi consensus document proposed a standardised core outcome set to harmonise reporting across studies (Sörelus, 2025). The defined outcomes include:

- i) **Cure:** “Cure of VGEI, regardless of anatomical location, is defined as being achieved 1 year after cessation of antimicrobial therapy, without any signs of infection on follow up including: clinical evaluation, laboratory tests (white blood cell count and C reactive protein), and imaging with contrast enhanced computed tomography”;
- ii) **Disease in remission:** “Defined as suppressive antibiotic treatment for more than 1 year in a patient without deterioration of symptoms, and without any signs of infection on follow up including: clinical examination, laboratory tests (white blood cell count and C reactive protein), or imaging with contrast enhanced computed tomography; and
- iii) **Treatment failure:** “Defined as the failure to achieve cure or remission, but may develop at any time.”

Clinical assessment

Clinical follow-up focuses on early detection of complications or signs of treatment failure. Evaluation should include a detailed history and assessment targeting symptoms consistent with ongoing infection, such as recurrent unexplained fever, persistent malaise, or progressive weight loss. This is particularly important in early or indolent recurrences, where laboratory markers and imaging findings are often inconclusive (Sörelus, 2025).

Additional follow-up assessments should include evaluation of the tolerability of prolonged antimicrobial therapy and surveillance for drug-specific adverse effects, particularly in patients receiving long-term or suppressive treatment; clinically relevant examples include creatine kinase elevation and eosinophilic pneumonitis associated with daptomycin, bone marrow suppression and peripheral or optic neuropathy during extended linezolid therapy, and

hepatotoxicity as well as clinically significant drug-drug interactions related to rifampicin (Mohsen, 2020; Vilhena, 2012; Zimmerli, 2019).

Laboratory markers

Serial monitoring of inflammatory markers, including C-reactive protein (CRP), procalcitonin, white blood cell count, and erythrocyte sedimentation rate, is commonly used to assess treatment response and detect treatment failure. These markers are expected to be elevated in the immediate postoperative period due to surgical trauma and systemic inflammatory response. Accordingly, temporal trends are more informative than absolute values; a sustained plateau or secondary rise should prompt further evaluation. The literature does not provide validated cut-off values or predictive metrics (positive/negative predictive values), and laboratory data must therefore be interpreted within the broader clinical context.

Imaging

Computed tomography angiography (CTA) or magnetic resonance imaging angiography (MRI-A) constitutes standard imaging during early follow-up to assess graft integrity, aortic stump status, and local complications. Nuclear medicine imaging modalities, such as FDG PET/CT or WBCS-SPECT/CT, are increasingly utilised for surveillance after AGI repair. A recognised limitation is nonspecific tracer or leukocyte uptake during the first 3–6 postoperative months, even in the absence of active infection (Rojoa, 2019).

Certain PET imaging patterns, such as focal uptake or high-intensity uptake (e.g. SUVmax > 6), may increase suspicion of infection in the early postoperative period (Mitra, 2018), although specificity remains limited. When imaging findings are equivocal, early postoperative studies may serve as a baseline for longitudinal comparison. Despite limited supporting evidence, FDG PET/CT is increasingly used in clinical practice to support decisions regarding discontinuation of antimicrobial therapy based on stability or resolution of tracer uptake (Husmann, 2018).

Aims of the thesis

The overall aim of this thesis was to investigate outcomes following complications of aortic surgery including ICU requirement, with a particular focus on aortic graft infections. Emphasis was placed on identifying risk factors and comparing different treatment strategies. The specific aims of the included studies were:

- I. To analyse surgical time trends in AAA repair and the associated frequency of prolonged intensive care unit length of stay (ICU LOS) at a single tertiary vascular referral centre. Additional aims were to identify risk factors for, and outcomes associated with, prolonged ICU LOS following AAA surgery, for both open surgical and endovascular repair. (Study I)
- II. To compare survival and reinfection outcomes following radical surgical treatment of abdominal aortic graft infections, with particular emphasis on differences between extra-anatomic bypass and in situ reconstruction, in a nationwide population-based setting. (Study II)
- III. To compare radical surgical explantation with graft-preserving semi-conservative treatment for abdominal aortic graft infections, with a focus on survival and reinfection rates, in a nationwide population-based setting. (Study III)
- IV. To determine the incidence and risk factors of aortic endograft infection after complex endovascular aortic repair, and to describe management and outcomes, including survival and long-term infection control, in a single-center setting. (Study IV)

Material and methods

Study I-III, and parts of study IV used the Swedish Vascular Registry (Swedvasc) as the main data base for the identification of patients eligible for inclusion in the studies. Swedvasc is a prospective Swedish vascular surgical national registry database that was initially started at 1987 and reached national coverage in 1994 (Sigvant, 2019). The registry has been subjected to repeated validation studies which have shown excellent external and internal validity in the range of 95% for aortic procedures (Venermo, 2015).

Study I

Patient population

All patients undergoing surgery for infrarenal AAA, either intact or ruptured, at Uppsala University Hospital between January 1999 and December 2013 were identified for primary inclusion in the study ($n = 725$). Eligible patients were identified using Swedvasc. Indications for surgical repair of infrarenal abdominal aortic aneurysmal disease during the study period were primarily an anteroposterior maximum aneurysm diameter of ≥ 55 mm for both sexes, suspected symptomatic aneurysm, or aneurysm rupture.

Prolonged ICU LOS was defined as ≥ 48 hours, or the need for readmission to an ICU bed during the index hospital admission. This definition was based on local clinical practice, whereby an ICU bed was routinely reserved for 48 hours following open AAA repair, with longer stays indicating more severe postoperative complications. In addition, this threshold corresponded to the highest quintile of ICU LOS in the study population.

To avoid immortal time bias, only patients surviving ≥ 48 hours after AAA repair were included in survival analyses ($n = 707$). Patients were further stratified into three groups according to ICU LOS: (i) < 48 hours, (ii) 2–6 days, and (iii) ≥ 7 days.

Data collection

Data on patient characteristics, comorbidities, perioperative events, and postoperative complications were retrieved from Swedvasc, supplemented by

detailed case record review and hospital transfusion registries when required, according to a predefined study protocol. Survival data were obtained by cross-matching patients' personal identity numbers with the National Population Registry, thereby achieving complete (100%) follow-up for survival outcomes (Allmen, 2015).

Information on intensive care unit–equivalent length of stay was obtained from the hospital's internal ICU registry for the early study period and from the national ICU registry for the later part of the study period. Postoperative complications were defined as complications occurring within 30 days after AAA repair and were identified through systematic case record review.

Predefined postoperative complications registered included circulatory failure (≥ 24 hours of inotropic or vasopressor support to maintain adequate mean arterial pressure), respiratory failure (≥ 48 hours of invasive or non-invasive ventilation support), renal failure (requirement for dialysis), abdominal compartment syndrome (need for laparotomy or open abdomen treatment), mesenteric ischaemia (clinical diagnosis and/or need for bowel resection), major amputation (above the ankle), and infections (clinically relevant infections such as pneumonia or sepsis).

Outcomes

The primary outcome recorded was prolonged ICU LOS. Secondary outcomes included postoperative complications within 30 days of surgery and short- and long-term survival following AAA repair.

Temporal trends in ICU LOS were analysed across the study period. Associations between patient characteristics, perioperative factors, postoperative complications, and prolonged ICU LOS were explored in a multivariable model. Survival analyses were performed among patients surviving ≥ 48 hours postoperatively, with survival compared across ICU LOS strata and further stratified by rupture or intact AAA repair.

Study II

Patient population

Patients who underwent radical surgical explantation for an abdominal AGI in Sweden between January 1995 and May 2017, and who fulfilled the MAGIC criteria for AGI, were included in the study. Patients were identified using Swedvasc.

Due to changes in registry variables over time, all patients registered in the Swedvasc aortic module as well as the reoperation module with the indications "infection" or "graft infection," and with anatomically suitable inflow and

outflow vessels, were included in the initial screening (n = 795). All vascular centres in Sweden were invited to participate in the study; all but one centre accepted, resulting in 670 patients undergoing secondary eligibility screening.

Following detailed case record review during the secondary screening process, a total of 169 unique patients fulfilled the MAGIC criteria for AGI. Of these, 126 patients who underwent radical surgical treatment were included in the final study cohort (Figure 10). Patients were subsequently stratified according to surgical treatment strategy: EAB or in situ repair.

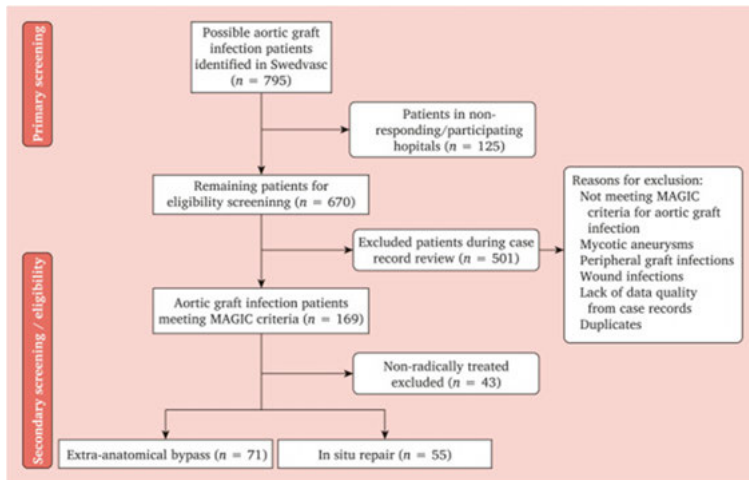


Figure 10. Study flow chart for the identification, inclusion and exclusion of patients treated surgically for an abdominal aortic graft infection in Sweden between 1995 and 2017 for Study II. MAGIC = Management of Graft Infection Collaboration (Lyons, 2016).

Data collection

Data on patient characteristics, comorbidities, perioperative parameters, microbiological findings, and short- and long-term complications were primarily retrieved through retrospective case record review, according to a prespecified study protocol. A total of 17 vascular centres contributed patient data, and each centre designated a vascular surgeon responsible for data extraction and quality control.

The American Society of Anesthesiologists Physical Status Classification System (ASA) score was recorded, with a high ASA score defined as ≥ 4 . GEF was defined as a perioperative finding of bowel erosion with a connection between the gastrointestinal tract and the infected aortic graft or stent-graft at any level, with or without intravascular communication. Recurrent infection of the newly implanted conduit is not defined within the MAGIC criteria and was therefore diagnosed at the discretion of the reviewing vascular surgeon.

Survival data and postoperative complications were collected and defined in the same manner as in Paper I.

Microbiological data included results from blood cultures and perioperative tissue and/or graft cultures. Potential contaminants were classified as normal skin flora in accordance with the MAGIC criteria. Polymicrobial infection was defined as the identification of more than two microbial species. To ensure feasibility of data collection, information on the type and duration of antimicrobial therapy at hospital discharge and/or 30 days after AGI repair, extending to last follow-up, was recorded. Prolonged antimicrobial therapy was defined as treatment exceeding three months.

Outcomes

The primary outcome was overall survival following radical surgical treatment of abdominal aortic graft infection. Secondary outcomes included short-term postoperative complications and recurrent graft infection.

Outcomes were compared between patients treated with EAB and ISR. Early (perioperative) and long-term outcomes were analysed separately. Factors associated with early and late mortality as well as recurrent infection were explored using multivariable models, with treatment strategy included as a hypothesized key explanatory variable.

Study III

Patient population

Patients undergoing surgical treatment for abdominal AGI in Sweden between January 1995 and May 2017 were identified using Swedvasc. Patients fulfilling the MAGIC criteria for a diagnosed AGI were eligible for inclusion.

The patient identification and primary screening process was identical to that used in Study II. Briefly, all patients registered in the aortic module or reoperation module with indications related to graft infection were initially screened. Following secondary eligibility screening, including detailed case record review, a total of 169 unique patients met the MAGIC criteria for abdominal AGI and were included in the study.

In contrast to Study II, which included only patients treated with radical surgical explantation, the present study also included patients treated surgically by any means including semi-conservative, graft-preserving surgical strategies. Radical surgery (RS) was defined as attempted complete explantation of the infected graft or endograft, followed by either EAB or ISR. Semi-conservative (SC) treatment was defined as a graft-preserving approach, including surgical debridement (with potential addition of percutaneous

drainage of infected tissue), endovascular adjuncts, and/or partial graft or endograft resection, while leaving part of the infected conduit in situ.

Patients were stratified according to treatment strategy into a semi-conservative cohort and a radical surgery cohort (EAB or ISR). The RS cohort served as the comparator group and corresponds to the cohort previously described in Study II.

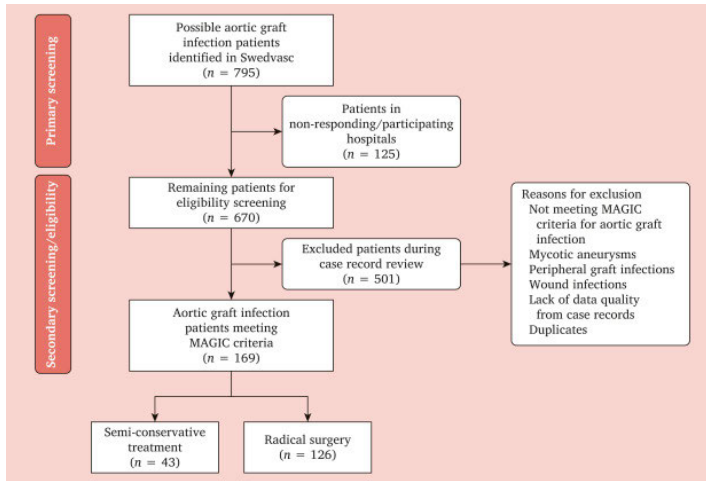


Figure 11. Study flow chart for the identification, inclusion and exclusion of patients treated surgically for an abdominal aortic graft infection in Sweden between 1995 and 2017 for Study III. MAGIC = Management of Graft Infection Collaboration (Lyons, 2016).

Data collection

Data collection was performed in the same manner as described for Study II. Briefly, data on patient characteristics, comorbidities, perioperative parameters, microbiological findings, and short- and long-term outcomes were retrieved through retrospective case record review using a prespecified protocol. Seventeen vascular centres contributed data, each with a designated vascular surgeon responsible for data extraction.

Definitions of the ASA score, presence of GEF, postoperative complications, survival outcomes, and microbiological variables were identical to those used in Study II. Recurrent or persistent graft infection, not covered by the MAGIC criteria, was diagnosed at the discretion of the reviewing physician.

Information on antimicrobial therapy administered at hospital discharge and/or ≥ 30 days post-operatively was collected to last follow-up, and prolonged antimicrobial therapy was defined as treatment exceeding three months.

Outcomes

The primary outcomes included overall survival and recurrent/persistent graft infection, comparing RS vs SC. Secondary outcomes included postoperative complications.

Outcomes were analysed according to treatment strategy. Survival analyses were performed for early and long-term follow-up. Multivariable analyses were used to explore factors associated with mortality and recurrent/persistent infection.

Study IV

Patient population

All patients undergoing complex endovascular aortic repair (cEVAR) at Uppsala University Hospital, Sweden, between September 2010 and May 2024 were retrospectively identified. Patients were identified using a local institutional registry and cross-checked against Swedvasc.

cEVAR was defined as an endovascular treatment of the aorta with fenestrated and/or branched endografts, including custom-made fenestrated or branched devices as well as physician-modified or in situ laser-fenestrated endografts targeting the renovisceral or supra-aortic vessels for any aortic pathology. Patients treated with isolated iliac branched devices or parallel grafting techniques (chimney EVAR) without fenestrated or branched components were excluded.

A total of 527 patients undergoing 542 cEVAR procedures were included in the study cohort. Patients were followed longitudinally for the development of aortic endograft infection (AeGI), which was defined and classified according to the MAGIC criteria. Patients were stratified at last follow-up as having no AeGI, suspected AeGI, or MAGIC-diagnosed AeGI based on retrospective case record review.

The study population constituted the denominator cohort for incidence analyses, while patients who developed MAGIC-diagnosed AeGI formed the outcome cohort for analyses of risk factors, management strategies, and clinical outcomes.

Data collection

Data on patient characteristics, comorbidities, procedural details, perioperative variables, and outcomes were retrieved retrospectively using a predefined study protocol. Information was obtained from an institutional cEVAR registry as well as Swedvasc and complemented/validated through individual case record review.

Data collected included index aortic pathology, anatomical extent of repair, cEVAR configuration, staging procedures, perioperative events, and early and late aortic related complications. Clinically suspected aortic endograft infections were identified through review of vascular surgery, infectious diseases, and radiology records. An aortic endograft infection was defined and classified according to the MAGIC criteria, and cases were stratified at last follow-up as: no AeGI, suspected AeGI, or MAGIC-diagnosed AeGI. All cases were reviewed by the primary author (HG), and MAGIC-equivocal cases were additionally discussed with a second author (AW), with consensus reached for MAGIC stratification in all instances.

Follow-up time was accrued from the date of the index cEVAR procedure to the date of death or last follow-up.

Microbiological data were obtained from blood cultures and image-guided deep tissue cultures when available. As no endograft explantations were performed, graft cultures were not available. Antimicrobial treatment strategies, including duration of therapy, and use of adjunctive drainage or surgical debridement were recorded.

Survival data were obtained by linkage of unique personal identity numbers with the Swedish Population Register, ensuring complete follow-up for mortality. Long-term infectious outcomes were classified at last follow-up as treatment failure, disease in remission, or cure, according to contemporary vascular graft and endograft infection reporting standards (Sörelius, 2025).

Outcomes

The primary outcomes were the incidence and risk factors of MAGIC-diagnosed AeGI following cEVAR as well as overall survival following cEVAR AeGI. Secondary outcomes included microbiological findings, description of treatment strategies, and long-term infectious outcomes.

Incidence of AeGI was assessed using time-to-event methodology, with death treated as a competing risk. Risk factors for development of AeGI were explored using regression models accounting for variable follow-up time. Survival and long-term infection outcomes among patients with MAGIC-diagnosed AeGI were analysed descriptively due to limited event numbers.

Statistical analyses

For all studies, data were initially assessed for normality using a combination of histograms, Q-Q plots, and the Shapiro-Wilk test. Normally distributed data are presented as means with appropriate measures of dispersion, typically 95% confidence intervals (CI95), or interquartile ranges (IQR) as appropriate.

Dichotomous variables were compared using the χ^2 test of homogeneity, and continuous variables were compared using one-way analysis of variance (ANOVA) or Student's t-test when assumptions of normality, absence of outliers, and homogeneity of variance were met. When these assumptions were violated, Fisher's exact test and the Mann-Whitney U test were used as appropriate.

Overall survival (Study I-III) was assessed using Kaplan-Meier (KM) survival curves, with truncation generally applied (with exceptions mentioned) when the standard error exceeded 10% or numbers at risk fell <10. The log-rank or Generalized Wilcoxon test was used to compare survival between groups when assumptions of independent censoring, absence of secular trends, and comparable degrees of censoring between groups were fulfilled.

Multivariable analyses were performed across studies to identify factors associated with prolonged ICU LOS (Study I), short-term and long-term survival (Studies II and III), recurrent or persistent graft infection (Studies II and III), and development of aortic endograft infection following complex endovascular aortic repair (Study IV). For dichotomous outcomes without censored observations, binary logistic regression models were used, whereas Cox proportional hazards regression models were applied for time-to-event outcomes. Effect estimates are reported as odds ratios (OR) or hazard ratios (HR), as appropriate, with corresponding CI95.

Candidate variables for multivariable modelling were restricted to factors with $p < .20$ (Study I-III) and $p < .05$ (Study IV) in univariable analyses and/or deemed clinically relevant a priori. To minimise overfitting, the number of variables included in multivariable models was limited to approximately one variable per five recorded events (Vittinghoff, 2007). Assumptions regarding independence of observations, linearity of continuous variables, proportional hazards (when applicable), and absence of multicollinearity were assessed a priori.

In Study IV, incidence of aortic endograft infection was additionally analysed using the cumulative incidence function (CIF) with death treated as a competing risk. Due to limited event numbers, multivariable model complexity was further constrained and survival analyses within the infected cohort were interpreted descriptively.

A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software (versions 26–28; IBM Corp., Armonk, NY, USA) in general and Python (version 3.11; Python Software Foundation, Wilmington, DE, USA) with the *lifelines* package (version 0.30.0) for CIF calculations and output. Generally, no adjustments were made for multiple testing apart from when comparisons were conducted within the same dataset (e.g. omnibus testing followed by pairwise group comparisons), Bonferroni-adjusted p-values were applied to account for multiple testing (Study I).

Ethical considerations

All studies were reviewed and approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2014/078 and 2017/027). Studies I–IV were retrospective in nature and did not involve any study-related interventions, and therefore posed no additional risk of harm to the included patients. All data were handled and reported in a pseudonymised manner and presented at an aggregated level. Beyond the initial case record review, no procedures entailed any risk of invasion of patient privacy or personal integrity.

Results

Study I

Between 1999 and 2013, 725 patients underwent surgery for infrarenal abdominal aortic aneurysm, of whom 707 (97.5%) survived beyond 48 hours and were included in the analysis. In total, 159 patients required >48 hours of critical care. Of the remaining 548 patients, 297 did not require any critical care. Patient characteristics, as well as the distribution according to indication for treatment and operative technique, are presented in Table 2.

Table 2. Patient characteristics for the different intensive care unit (ICU) cohorts.

Co-morbidities	ICU <48h (n = 548)	ICU 2 - 6 days (n = 115)	ICU ≥7 days (n = 44)	p ^{a,*}
Age (years):	73.3	73.6	72.3	0.681
Male gender:	85.0%	82.6%	84.1%	0.803
Diabetes:	9.9%	8.0%	2.3%	0.213
Hypertension:	71.5%	67.9%	80.0%	0.349
Heart disease:	48.2%	56.6%	53.5%	0.231
Pulmonary disease:	22.5%	22.1%	21.4%	0.984
Renal insufficiency:	12.0%	11.1%	23.3%	0.180
Smoking ^b :	36.9%	41.4%	51.5%	0.197
Cerebrovascular disease:	12.5%	13.4%	7.1%	0.554
Open repair:	43.0%	88.7%	95.5%	<0.001*
Rupture:	10.9%	48.7%	63.6%	<0.001*

^a Comparison of all groups with χ^2 cross-tabulation for dichotomous variables and one-way ANOVA for continuous variables. ^b Cases of regular smoking ≤ 5 years before the operative date were included. * P < 0.05 versus other groups.

Time trends

Over the study period, the proportion of patients with prolonged ICU stay after AAA repair decreased, from 41.4% in 1999 to 7.3% in 2013 ($p < 0.001$). During the same period, the use of EVAR for both intact and ruptured AAA increased significantly, rising from 6.9% to 78.0% ($p < 0.001$). (Figure 12). The mean frequency of prolonged ICU LOS during the 15-year study period was 5.0% for EVAR, with no significant declining trend over time ($p = 0.177$), and 38.4% for open repair, declining from 40.7% in 1999 to 22.2% in 2013 ($p < 0.001$).

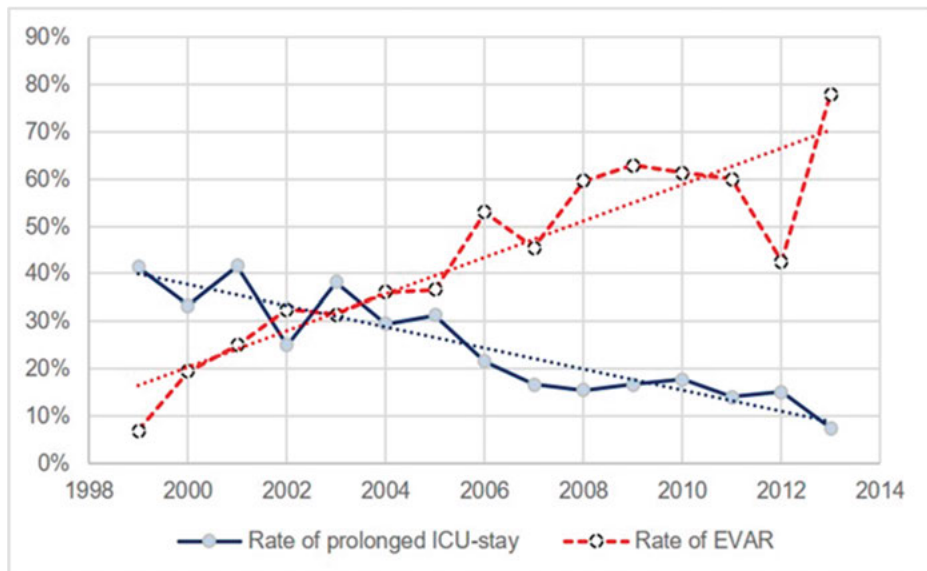


Figure 12. Rate of prolonged intensive care unit length of stay and rate of endovascular aortic repair illustrating the declining trend for prolonged intensive care unit length of stay defined as ≥ 48 h ($R^2=0.83$, $p<0.001$) and the increasing trend for endovascular aortic repair ($R^2=0.81$, $p<0.001$) using linear regression.

After repair of ruptured AAA, the rate of prolonged ICU LOS was 73.6% (CI95: 63–82%) for open repair and 15.8% (CI95: 1.2–30%) for EVAR. The overall rate of prolonged ICU LOS after ruptured AAA repair declined significantly from 60.0% (CI95: 23–97%) in 1999 to 33.3% (CI95: 0–72%) in 2013 ($p = 0.003$). The proportion of ruptured AAA repairs relative to all AAA repairs was 20.3% and declined significantly over time, from 34.5% in 1999 to 23.8% in 2013 ($p = 0.001$). There was no significant change in the absolute number of ruptured AAA repairs during the study period.

Predictors of prolonged ICU LOS

Preoperative and perioperative predictors of prolonged ICU LOS were assessed using binary logistic regression (Table 3). In multivariable binary logistic regression, prolonged ICU stay was independently associated with open repair (OR: 5.5, CI95: 2.7–11.3), ruptured AAA (OR: 3.8, CI95: 2.1–7.0), and increasing transfusion requirements (OR per unit of plasma: 1.1, CI95: 1.06–1.15) (Table 3).

Table 3. Predictors of prolonged intensive care unit (ICU) length of stay.

Co-morbidities	Univariable analysis ^a			Multivariable analysis ^b	
	ICU <48h (n = 548)	ICU ≥48h (n = 159)	p ^c	Odds ratio (CI 95%)	p ^c
Male gender:	85.0%	83.0%	0.534	-	-
Diabetes:	9.9%	6.4%	0.209	-	-
Hypertension:	71.5%	71.1%	1.00	-	-
Heart disease:	48.2%	55.8%	0.102	1.6 (1.0 – 2.6)	0.060
Pulmonary disease:	22.5%	21.9%	0.913	-	-
Renal insufficiency:	12.0%	14.2%	0.525	-	-
Smoking ^d :	36.9%	43.9%	0.157	1.0 (0.6 – 1.6)	0.998
Cerebrovascular disease:	12.5%	11.7%	0.890	-	-
Open repair:	42.9%	90.1%	<0.001	5.5 (2.7 – 11.3)	<0.001*
Rupture:	10.9%	52.8%	<0.001	3.8 (2.1 – 7.0)	<0.001*
Plasma ^d :	2.5	15.8	<0.001	1.1 (1.06 – 1.15)	<0.001*

^a Comparison of all groups with χ^2 cross-tabulation for dichotomous variables and one-way ANOVA for continuous variables. ^b Comparison using a binary logistic regression model for all variables with $p < 0.200$. ^c Cases of regular smoking within the last 5 years before the operative date were included. ^d Odds ratio per bag of plasma. * $P < 0.05$ versus other groups.

Postoperative complications

Reoperation rates increased progressively across all ICU LOS categories for both intact (7.6% vs. 29.8% vs. 53.3%) and ruptured AAA (11.7% vs. 23.2% vs. 57.7%) respectively. In addition, infectious complications, including pneumonia and sepsis during the index hospital stay, increased in frequency with

longer ICU LOS. The full spectrum of postoperative organ dysfunction complications stratified by ICU LOS is presented in Table 4.

Table 4. Postoperative complications in the different intensive care unit (ICU) cohorts.

Complications ^a	ICU <48h % (95% CI)	ICU 2 - 6 days % (95% CI)	ICU ≥ 7 % (95% CI)	p ^{b,*}
Intact AAA¹ (OR²/EVAR):	<i>n</i> = 488 (207/281)	<i>n</i> = 59 (52/7)	<i>n</i> = 16 (16/0)	
Circulatory:	3.7% (2.0-5.4)	38.6% (25.6-51.6)	80.6% (57.1-100)	<0.001*
Dialysis:	0.8% (0.0-1.6)	0.0% (-)	46.7% (18.1-75.3)	<0.001*
Infection:	4.1% (2.3-5.9)	15.8% (6.0-25.6)	53.3% (24.7-81.9)	<0.001*
Cardiac:	3.9% (2.2-5.6)	22.8% (11.6-34.0)	40.0% (11.9-68.1)	<0.001*
Respiratory:	1.0% (0.1-1.9)	38.6% (25.6-51.6)	80.0% (57.1-100)	<0.001*
Stroke:	0.2% (0.0-0.6)	3.5% (0.0-8.4)	6.7% (0.0-20.1)	<0.001*
Open abdomen:	0.0% (-)	1.8% (0.0-5.3)	33.3% (6.3-60.4)	<0.001*
Reoperation:	7.6% (5.2-9.9)	29.8% (17.6-42.1)	53.3% (24.7-81.9)	<0.001*
Ruptured AAA (OR/EVAR):	<i>n</i> = 60 (28/32)	<i>n</i> = 56 (51/5)	<i>n</i> = 28 (27/1)	
Circulatory:	11.7% (3.3-20.0)	28.6% (16.4-40.8)	65.4% (45.8-85.0)	<0.001*
Dialysis:	6.7% (0.2-13.2)	5.4% (0.0-11.4)	73.1% (54.8-91.4)	<0.001*
Infection:	10.0% (2.2-17.8)	14.3% (4.8-23.7)	65.4% (45.8-85.0)	<0.001*
Cardiac:	11.7% (3.3-20.0)	23.2% (11.8-34.6)	23.1% (5.7-40.4)	0.202
Respiratory:	8.3% (1.1-15.5)	60.7% (47.5-73.9)	76.9% (59.6-94.3)	<0.001*
Stroke:	1.7% (0.0-5.0)	5.4% (0.0-11.4)	15.4% (0.5-30.3)	0.016*
Open abdomen:	3.3% (0.0-8.0)	7.1% (0.2-14.1)	26.9% (8.7-45.2)	0.001*
Reoperation:	11.7% (3.3-20.0)	23.2% (11.8-34.6)	57.7% (37.3-78.0)	<0.001*

¹ Abdominal aortic aneurysm. ² Open repair. ³ Endovascular aortic repair. ^a Criteria for respective complication as defined in materials and methods. ^b Comparison of all groups with χ^2 cross-tabulation. * $P < 0.05$ versus other groups.

Survival

Patients requiring prolonged ICU LOS had lower early (90-day)- and five-year survival rates following both intact and ruptured AAA repair. Kaplan–Meier estimates of 5-year survival after intact AAA repair are shown in Figure 13 (Figure 13A and 13B). The most pronounced differences in both short- and long-term survival were observed between patients with <48 hours and ≥7 days of ICU LOS.

Among patients surviving beyond 90 days, long-term survival was similar regardless of the duration of the initial ICU stay. One- and five-year survival was 97% and 73%, respectively, for patients with <48 hours of ICU LOS, compared with 95% and 70% for those with >48 hours of ICU LOS (Figure 13C).

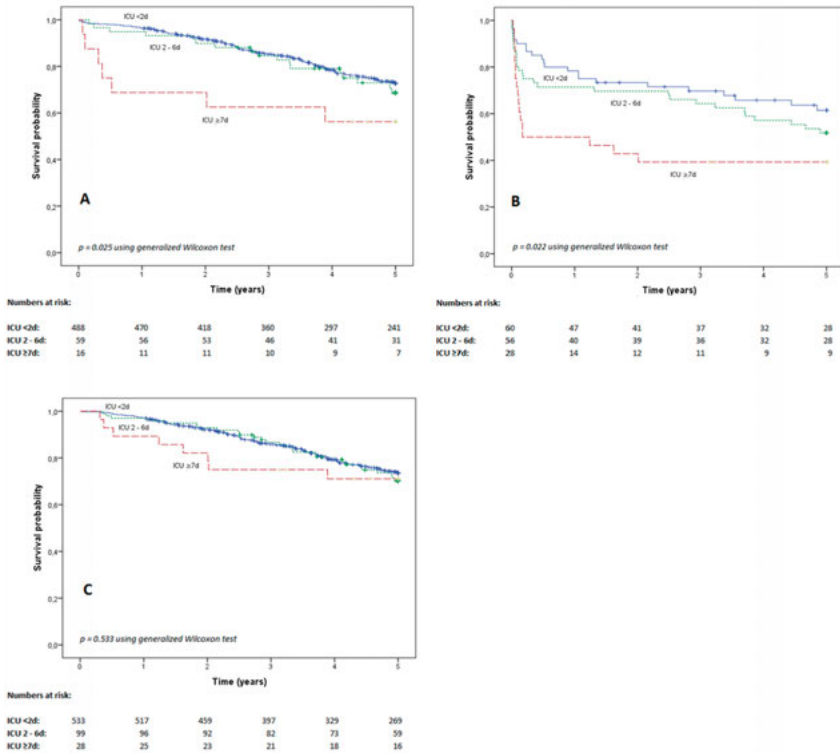


Figure 13 A-C. **A:** Intact AAA - overall 5-year survival for the different intensive care unit (ICU) cohorts, $p = 0.007$. **B:** Ruptured AAA – overall 5-year survival for the different ICU-cohorts. There was a significant difference in survival distribution only between the ICU <48h and ICU ≥ 7 days cohorts, $p = 0.004$. **C:** Overall 5-year survival for all AAA with 90-day mortality excluded.

Study II

Study population and time trends

The study included 126 patients with MAGIC-defined AGI (102 graft- and 24 endograft infections) who underwent radical surgical treatment, either by EAB (n = 71) or ISR (n = 55) (Figure 10). Among patients with endograft infection, ten were treated with EAB and 14 with ISR.

Over the duration of the study, treatment strategy shifted away from extra-anatomic bypass toward increased use of in situ reconstruction. When dividing the study period into an early (1995–2008) and a late (2009–2017) period, the proportion treated with EAB declined from 63.9% to 48.4%, while the use of ISR increased from 36.1% to 51.6%.

Baseline characteristics and comorbidities

Baseline characteristics at the time of AGI repair, as well as presenting symptoms and biochemical markers, are shown in Table 5. Overall, 77 patients (81.0%) were treated with open repair, and 25.4% of the total cohort had a history of ruptured AAA as the primary pathology at the index operation preceding AGI repair. There were no significant differences in preoperative comorbidities between the EAB and ISR cohorts, including the frequency of a high ASA score (>3) or the presence of GEF.

Outcome of surgical treatment with EAB and ISR

The 30-day postoperative complication rates were similar between the two surgical cohorts (Table 6). A higher incidence of postoperative dialysis was observed after EAB cohort although this difference did not reach statistical significance (EAB: 20.3% vs. RS: 8.0%, $p = .067$). Intensive care unit length of stay and total in-hospital length of stay after AGI repair did not differ significantly between the two cohorts.

Crude frequencies of long-term complications during clinical follow-up are presented in Table 7. The median duration of follow-up among survivors was significantly longer in the EAB cohort than in the ISR cohort. The overall rate of recurrent graft infection was 20.3% after EAB following a median follow-up of 5.5 years and 17.0% after ISR following a median follow-up of 3.1 years ($p = .56$).

Table 5. Comparison of preoperative baseline characteristics among 126 patients in the extra-anatomical bypass and in-situ repair cohorts.

Baseline characteristics	Extra-anatomical bypass	In-situ repair	p-value*
<i>n (%)</i>	<i>(n = 71)</i>	<i>(n = 55)</i>	
Age (standard deviation)	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	(7.5)	(10.9)	.51
ASA-score > 3†	16 (24)	17 (31)	.41
Graft-enteric fistulae	34 (50)	28 (51)	.92

* $p < .05$

† *American Society of Anaesthesiologists Physical Status Classification System score*

Table 6. Comparison of postoperative (30-day) outcomes between 126 patients treated with extra-anatomical bypass and in-situ repair for aortic graft infections.

Postoperative complications <i>n (%)</i>	Extra-anatomical bypass (n = 71)	In-situ repair (n = 55)	p-value*
Mesenteric ischemia	6 (9)	3 (6)	.73
Acute limb ischemia	4 (6)	6 (10)	.50
Multi organ dysfunction syndrome	16 (25)	9 (18)	.37
Acute kidney injury	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	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
Intensive care unit stay -h (IQR) [†]	41 (133)	72 (62)	.48
In hospital stay - d (IQR) [†]	24 (24)	24 (23)	.61
30-day survival (%; 95% CI) [‡]	81.7 (72.7-90.7)	76.4 (65.2-87.6)	.46

* $p < .05$
[†] Median time reported (interquartile range)
[‡] 95% confidence interval

Table 7. Comparison of crude rates of long-term complications among 126 patients during clinical follow-up after radical surgical repair for aortic graft infection using extra-anatomical bypass versus in-situ repair.

Long-term complications <i>n (%)</i>	Extra-anatomical bypass <i>(n = 71)</i>	In-situ repair <i>(n = 55)</i>	p-value*
Median follow-up - y (IQR) [†]	5.5 (8.1)	3.1 (4.1)	.039*
Graft infection (%)	13 (21)	9 (17)	.56
Stump blow-out (%)	6 (10)	0 (0)	.029*
Anastomosis dehiscence (%)	1 (2)	5 (9)	.095
Amputation (%)	3 (5)	2 (4)	1.0
Reintervention (%)	18 (28)	13 (25)	.70

* $p < .05$

[†]Median clinical follow-up among survivors in years (interquartile range)

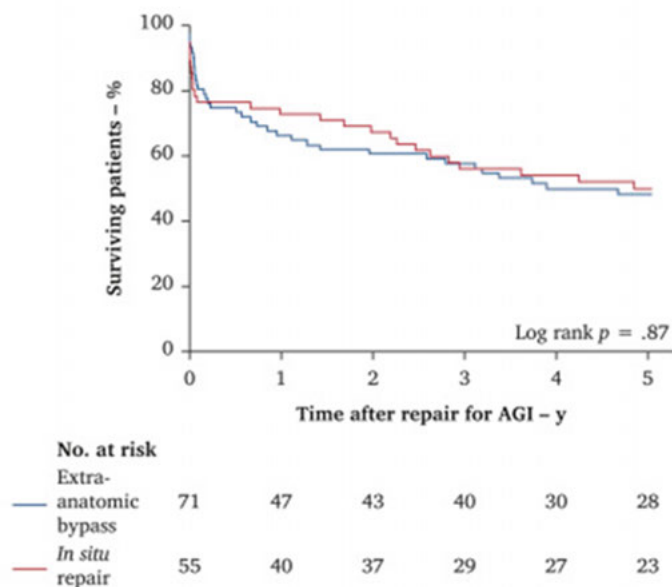


Figure 14. Kaplan-Meier curve on 126 patients, comparing unadjusted overall long-term (5-year) survival for extra-anatomical bypass vs in-situ repair. No survival difference was identified using log-rank test ($p = .87$).

Survival

Short-term and long-term survival did not differ between patients treated with EAB and those undergoing ISR (Figure 14). In addition, no difference in overall survival was observed when comparing patients with early versus late AGI.

Neither early nor long-term survival differed significantly according to the presence of GEF: GEF 72.6% vs. no GEF 85.2% ($p = .085$) (Figure 15). Long-term survival was also similar, with five-year Kaplan–Meier estimated survival of 41.2% for patients with GEF and 56.6% for those without GEF (log-rank $p = .12$). No differences in short- or long-term survival were observed when comparing NAIS reconstructions with other ISR techniques ($p = .51$). Furthermore, overall survival did not differ between patients with graft AGI and those with endograft AGI ($p = .89$).

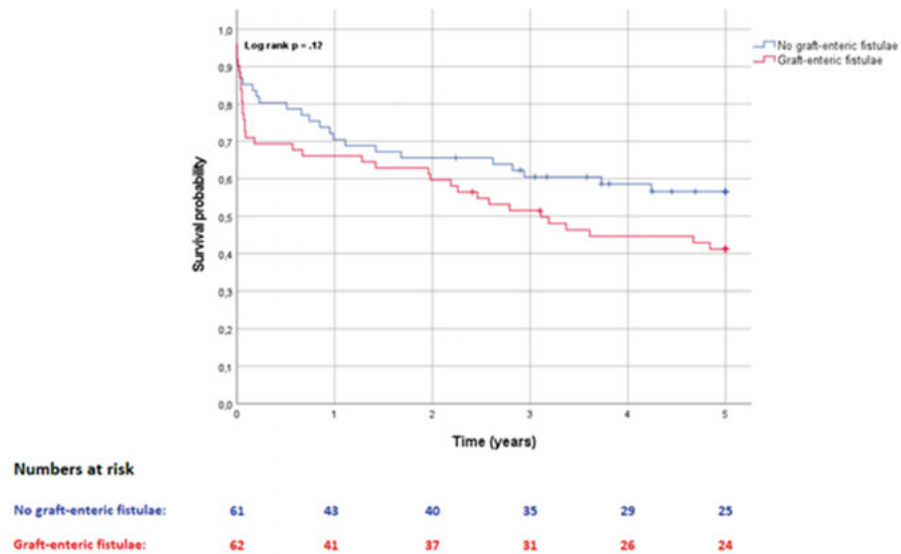


Figure 15. Comparison of overall survival on 123 patients after radical surgical repair for aortic graft infections between patients with or without a graft-enteric fistulae.

After adjustment for relevant perioperative confounders in a multivariable Cox regression analysis, the choice of operative method (EAB vs ISR) did not influence overall five-year mortality, using EAB as the reference. Compared with EAB, non-NAIS ISR was associated with a hazard ratio (HR) of 0.7 (CI95: 0.4–1.2), and NAIS with an HR of 1.1 (CI95: 0.6–2.3) (Table 8).

Table 8. Multivariable Cox-regression on 126 patients identifying impact of operative method on overall (5-year) mortality after radical surgical repair for an aortic graft infection adjusting for predefined confounders. Hazard ratios (HR) reported with 95% confidence intervals (CI95) in parentheses.

Factors	Hazard ratio (95% CI)	p-value*
Age \geq 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
<u>Extra-anatomical bypass vs:</u>		
<i>In situ repair excluding vein grafts</i>	0.7 (0.4-1.2)	.18
<i>Neo aorto iliac systems (NAIS/vein grafts)</i>	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
* $p < .05$		

In a separate multivariable Cox regression analysis excluding 90-day mortality, advanced age (≥ 75 years; HR 2.9, CI95: 1.1–7.7), chronic kidney disease (HR 7.0, CI95: 2.4–20.4), and coronary artery disease (HR 3.7, CI95: 1.1–12.7) were independently associated with increased five-year overall mortality (Table 9). No association between long-term mortality and treatment strategy (EAB vs. ISR) was identified.

Table 9. Multivariable Cox-regression on 91 patients, with 90-day mortality excluded, identifying factors associated with 5-year mortality after radical surgical repair for an aortic graft infection. Hazard ratios (HR) reported with 95% confidence intervals (CI95) in parentheses.

	Factors	Hazard ratio (95% CI)	p-value*
<i>Preoperative</i>	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†	-	-
<i>Perioperative</i>	Shock	5.1 (1.1-24.2)	.045*
	Extra-anatomical bypass vs in-situ repair‡	0.5 (0.2-1.3)	.15
	Graft-enteric fistula	0.9 (0.4-2.2)	.88
	Non-complete graft excision	0.5 (0.2-1.5)	.24
<i>Postoperative</i>	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

* $p < .05$
† Only one case occurred.
‡ Extra-anatomical bypass used as index-comparator.
§ Time period 1995-2006 vs 2007-2017

Microbiology, antimicrobial treatment, and recurrent infections

Microbiological findings were available for 120 patients in the cohort. The median number of microbial species identified per patient (excluding contaminants) from blood, perigraft, or graft cultures was 1 (range 0–6). Gram-negative and gram-positive bacteria were identified in 51.3% and 47.0% of cases, respectively, and polymicrobial growth was present in 24.1% of the total cohort. As expected, polymicrobial growth was more common in patients with GEF than in those without GEF (37.1% vs. 8.8%, $p < .001$).

Candida spp. were identified in blood, perigraft, or graft cultures in 20.5% of patients. The frequency of *Candida* was significantly higher in patients with GEF compared with those without GEF (30.5% vs. 10.3%, $p < .001$). The full microbiological spectrum is presented in Table 10.

The impact of prolonged antimicrobial therapy (>3 months) was assessed using Cox regression analysis. A total of 59 patients fulfilled the predefined criteria and had complete data available. After adjustment for treatment strategy (EAB vs. ISR), prolonged antimicrobial therapy was associated with reduced long-term mortality (HR 0.3, CI95: 0.1–0.9).

Table 10. Microbiological aetiology of the 120 abdominal aortic graft infection patients, with available microbiological data, treated with radical surgical repair.

Bacterial species	Graft-enteric fistula (%)	No graft-enteric fistula (%)
	n = 60	n = 60
<i>Staphylococcus aureus</i> :	2 (3)	6 (10)
<i>Enterococcus</i> spp.:	18 (30)	12 (20)
<i>Faecium</i> :	6 (10)	4 (7)
<i>Faecalis</i> :	5 (8)	4 (7)
Unspecified:	7 (12)	4 (7)
CoNS ¹ :	8 (13)	18 (30)
<i>Streptococcus</i> spp. ² :	18 (30)	8 (13)
Alfa hemolytic <i>Streptococci</i> :	17 (28)	7 (12)
Beta hemolytic <i>Streptococci</i> :	1 (2)	1 (2)
<i>Enterobacteriaceae</i> :	30 (50)	10 (17)
<i>Escherichia coli</i> :	17 (28)	7 (12)
<i>Citrobacter</i> spp.:	2 (3)	0 (0)
<i>Salmonella</i> spp.:	0 (0)	1 (2)
<i>Proteus</i> spp.:	0 (0)	0 (0)
<i>Klebsiella</i> spp.:	11 (18)	0 (0)
<i>Enterobacter</i> spp.:	8 (13)	2 (3)
<i>Serratia</i> spp.:	1 (2)	0 (0)
Unspecified:	0 (0)	0 (0)
<i>Bacteroides</i> spp.:	7 (12)	6 (10)
<i>Haemophilus</i> spp.:	1 (2)	2 (3)
<i>Candida</i> spp.:	20 (33)	6 (10)
<i>albicans</i> :	12 (20)	4 (7)
<i>non-albicans</i> :	4 (7)	0 (0)
Unspecified:	4 (7)	2 (3)
Other:	8 (13) ³	9 (15) ⁴
Culture negative:	12 (20)	12 (20)

¹Coagulase negative *Staphylococci*

²Excluding *Enterococci*

³ 1x *Fusibacterium* spp., 3x *Lactobacillus* spp., 2x *Peptostreptococcus* spp. 1x *Propionibacterium* spp., 1x *Pevotella* spp., and 1x *Pseudomonas aeruginosa*.

⁴ 2x *Fusibacterium* spp., 2x *Corynebacterium* spp., 1x *Actinomyces* spp., 1x *Pseudomonas aeruginosa* and 5x *Propionibacterium* spp.

Study III

Study population and time trends

In total, 169 patients with MAGIC-diagnosed abdominal aortic graft infection were identified during the study period, including 129 graft infections and 40 endograft infections. Of these, 126 patients underwent radical surgery (RS), corresponding to the cohort described in Study II, while 43 patients were managed using a semi-conservative (SC) approach. The relative use of RS and SC remained stable over time; during the first half of the study period, 77.5% of patients were treated with RS compared with 71.9% in the second half ($p = .40$).

Within the RS cohort, six patients required emergency endovascular intervention as bridging therapy prior to definitive surgery, primarily due to bleeding.

Among patients managed with SC repair, treatment strategies varied: 44% underwent surgical debridement and/or percutaneous drainage with complete graft preservation, 44% underwent partial graft explantation, and 12% were treated using endovascular adjuncts alone.

Baseline characteristics and comorbidities

Baseline characteristics are summarised in Table 11. The primary indication for the index aortic repair was predominantly aneurysmal disease (62.7%), followed by occlusive disease (21.7%), while 22.0% of patients had undergone repair for iliac or aortic rupture.

Patients undergoing SC (vs RS) were older (73.6 years vs 70.0 years, $p = .039$), as well as more comorbid with a higher frequency of heart failure (23.3% vs 7.4%, $p = .010$), coronary artery disease (60.5% vs 30.6%, $p < .001$) and high (>3) ASA-score (53.7% vs 27.3%, $p = .002$) at the time of treatment. GEF prevalence was comparable between treatment groups (SC 53.5% vs RS 50.4%; $p = .73$).

Table 11. Comparison of baseline characteristics and comorbidities between semi-conservative (SC) and radical surgery (RS) repair among 169 aortic graft infection patients included in the study.

Baseline characteristics, n (%)	Semi conservative repair (n = 43)	Radical surgical repair (n = 126)	p-value*
Age (median, interquartile range)	73.6 (11.3)	70.0 (10.4)	.039*
Male sex (%)	35 (81)	104 (83)	.98
Hypertension (%)	28 (65)	79 (65)	1.0
Smoking (%)	7 (16)	48 (40)	.005*
Chronic kidney disease (%)	9 (21)	13 (11)	.092
Diabetes (%)	8 (19)	10 (8)	.062
Heart failure (%)	10 (23)	9 (7)	.010*
Coronary artery disease (%)	26 (60)	37 (31)	<.001*
Lung disease (%)	8 (19)	13 (11)	.19
Circulatory shock (%)	7 (16)	11 (9)	.19
ASA-score > 3 [†]	22 (54)	33 (27)	.002*
Graft-enteric fistulae (%)	23 (53)	62 (50)	.73

* $p < .05$

[†] American Society of Anaesthesiologists Physical Status Classification System score

Postoperative outcomes and survival

The frequency of 30-day post-operative complications, including mesenteric ischemia, acute limb ischemia, sepsis and multi-organ dysfunction syndrome were common, ranging from 10.0 - 28.3%, but similar for the SC and RS cohorts without any significant differences (Table 12).

Table 12. Comparison of postoperative (30-day) complications among 169 patients treated with semi conservative repair and radical surgical repair for aortic graft infections.

Postoperative complications	Semi conservative repair (n = 43)	Radical surgical repair (n = 126)	p-value*
Mesenteric ischemia (%)	4 (10)	9 (8)	.71
Acute limb ischemia (%)	5 (12)	9 (8)	.53
Multi organ dysfunction syndrome (%)	8(20)	25 (22)	.75
Acute kidney injury (%)	3 (7)	17 (15)	.21
Respiratory (%)	11 (27)	32 (28)	.90
Circulatory (%)	11 (28)	28 (25)	.71
Myocardial infarction (%)	2 (5)	7 (6)	.78
Abdominal compartment (%)	1 (2)	3 (3)	.95
Sepsis (%)	8 (20)	(13)	.32
Lower extremity compartment syndrome (%)	0 (0)	4 (4)	.57
Stroke (%)	0 (0)	2 (2)	1.0
Pulmonary embolism (%)	0 (0)	3 (3)	.57
Intensive care unit stay -h (IQR) [†]	30 (106)	60 (83)	.074
In hospital stay – d (IQR) [†]	25 (23)	24 (22)	.58

* $p < .05$

[†]Median time reported (interquartile range)

Short-term postoperative survival rates up-to 1-year were similar in both cohorts (1-year survival; SC: 58.1% vs RS: 69.1%, $p = .19$). At five years, unadjusted Kaplan–Meier estimates suggested lower survival in the SC cohort, although the difference did not reach statistical significance (30.2% vs 48.4%, $p = .066$) (Table 13 and Figure 16).

Table 13. Overall survival after aortic graft infection repair of 169 patients comparing semi conservative repair with radical surgical repair with 95% confidence intervals (CI95) in parentheses.

Survival	Semi conservative repair (n = 43)	Radical surgical repair (n = 126)	p-value*
30-day survival	83.7% (72.2-95.2)	79.4% (72.2-86.5)	.53
90-day survival	76.7% (63.6-89.9)	75.4% (67.8-83.0)	.86
1-year survival	58.1% (42.8-73.5)	69.1% (60.9-77.2)	.19
5-year survival ¹	30.2% (16.5-43.9)	48.4% (29.7-47.1)	.066

* $p < .05$

¹ *Unadjusted Kaplan-Meier estimated 5-year survival*

When stratified by the presence of GEF, overall survival was significantly worse in the total cohort (Figure 17A). Among patients treated with SC, outcomes appeared poorer in those with a fistula compared with those without, although this difference did not reach statistical significance (Figure 17D).

In a multivariable Cox-regression model, adjusting for predefined pre-operative variables, surgical treatment exposure with SC (vs RS) did not impact overall mortality (HR: 1.0, CI95: 0.6-1.5, $p = .94$). Instead, advanced age (≥ 75 years, HR: 2.0, CI95: 1.4-3.0, $p < .001$) and high ASA-score (>3 , HR: 1.9, CI95: 1.2-2.9, $p = .006$) were independently associated with overall long-term (5 year) mortality (Table 14).

Similar findings were observed in a landmark analysis, excluding early (90-day) mortality but including postoperative events, where advanced age (HR: 2.0, CI95: 1.2-3.2, $p = .009$) negatively impacted overall 5-year mortality, while exposure to SC vs RS did not (HR: 0.6, CI95: 0.4-1.0, $p = .055$) (Table 15).

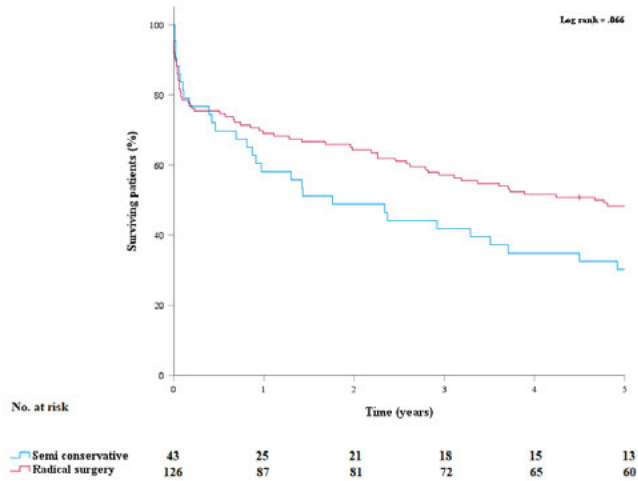


Figure 16. Cumulative Kaplan-Meier estimate of overall survival of 169 aortic graft infection patients comparing semi-conservative repair with radical surgical repair using log rank test.

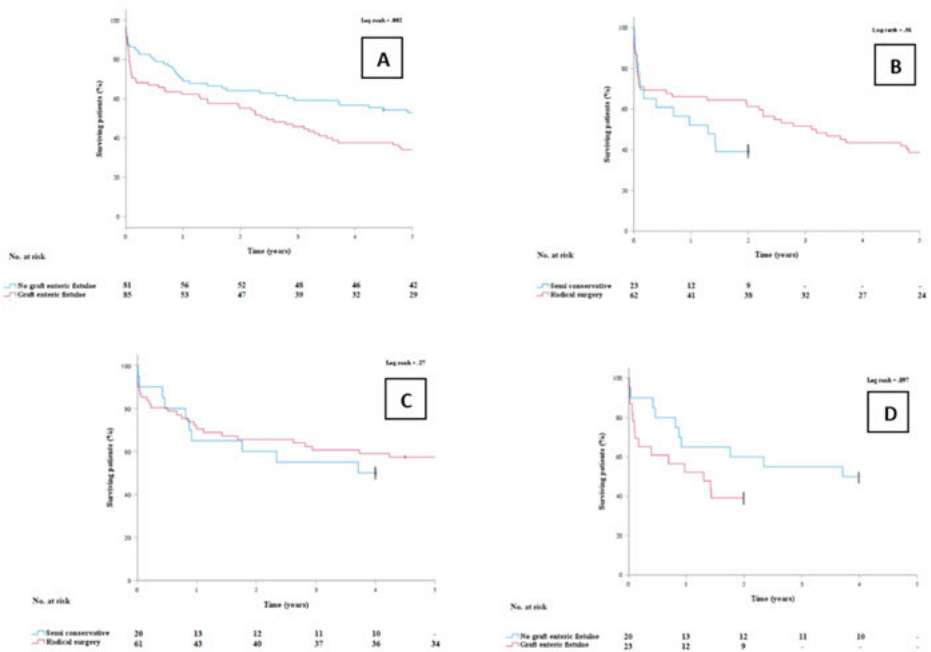


Figure 17 A-D. Cumulative Kaplan-Meier estimates comparing overall survival of (A) 166 patients in the entire cohort of aortic graft infections with vs. without graft-enteric fistulae; 85 patients treated with semi-conservative repair vs. radical surgical repair in patients with aortic graft infection (B) with or (C) without graft enteric fistulae; and (D) 43 patients with an aortic graft infection with vs. without graft enteric fistulae treated with semi-conservative repair using the log rank test.

Table 14. Multivariable Cox-regression on 169 patients identifying impact of operative method on overall (5-year) mortality after radical surgical repair for an aortic graft infection adjusting for predefined confounders. Hazard ratios (HR) reported with 95% confidence intervals (CI95) in parentheses.

Factors	Hazard ratio (95% CI)	p-value*
Age \geq 75 years	2.0 (1.4-3.0)	<.001*
Coronary artery disease	1.0 (.7-1.5)	.97
Chronic kidney disease	1.3 (.8-2.3)	.28
Pulmonary disease	.8 (.5-1.4)	.53
ASA-score $>$ 3 [†]	1.9 (1.2-2.9)	.006*
Semi conservative repair [‡]	1.0 (.6-1.5)	.94
Graft-enteric fistulae	1.4 (1.0-2.0)	.087
Shock	.9 (.5-1.7)	.85
Time period (early vs late) [§]	.8 (.3-1.9)	.63

* $p < .05$

[†] American Society of Anaesthesiologists Physical Status Classification System score

[‡] Radical surgery used as index comparator

[§] Time period 1995-2008 vs 2009-2017

Table 15. Multivariable Cox-regression landmark analysis, with 90-day mortality excluded, on 169 patients with abdominal aortic graft infections identifying risk factors associated with overall (5-year) mortality after surgical treatment adjusting for predefined confounders. Hazard ratios (HR) reported with 95% confidence intervals (CI95) in parentheses.

Factors	Hazard ratio (95% CI)	p-value*
Age \geq 75 years	2.0 (1.2-3.2)	.009*
Coronary artery disease	1.2 (0.7-1.9)	.55
Chronic kidney disease	2.0 (1.0-3.8)	.040*
Pulmonary disease	1.0 (0.5-1.9)	.92
ASA-score $>$ 3 [†]	1.5 (0.9-2.6)	.13
Semi conservative repair [‡]	0.6 (0.4-1.0)	.055
Graft-enteric fistulae	1.3 (0.8-2.0)	.29
Post-operative dialysis	1.6 (0.8-3.5)	.19
Time period (early vs late) [§]	1.6 (0.8-3.0)	.32

* $p < .05$
[†] American Society of Anaesthesiologists Physical Status Classification System score
[‡] Radical surgery used as index comparator
[§] Time period 1995-2008 vs 2009-2017

Long-term complications observed during follow-up are summarised in Table 16. Follow-up time was similar (SC: 5.1 years vs. RS: 3.9 years, $p = .18$) and long-term complication rates mainly differed in the increased frequency of recurrent or persistent (endo)graft infection in the SC cohort (SC: 45.4% vs. RS: 19.3%, $p < .001$).

Table 16. Comparison of crude rates of long-term complications of 169 aortic graft infection patients during clinical follow-up after semi conservative repair versus radical surgical repair.

Long-term complications	Semi conservative repair (n = 43)	Radical surgical repair (n = 126)	p-value*
Median follow-up (years, IQR) ¹	5.1 (10.7)	3.9 (6.3)	.18
Recurrent graft infection (%)	45.4	19.3	<.001*
Anastomosis dehiscence or stump blow-out (%)	2.3	10.5	.10
Amputation (%)	9.3	4.3	.23
Reintervention (%)	23.3	26.3	.70

* $p < .05$

¹Median clinical follow-up among survivors in years (interquartile range).

Microbiology and antimicrobial treatment

Microbiological results were available for 154 of 169 patients (94.1%). The overall frequency of positive blood-, deep tissue-, or graft cultures was 74.2%, with similar distribution of gram-positives (SC: 53.5% vs. 47.6%, $p = .63$), polymicrobial growth (SC: 28.6% vs. RS: 23.9%, $p = .55$) and *Candida* spp. (SC: 19.0% vs. RS: 20.5%, $p = .84$). Similarly to Study II, presence of a GEF in the overall cohort was associated with an increased frequency of identified *Candida* spp. (GEF: 30.5% vs no GEF: 9.1%, $p < .001$).

A total of 135/169 patients that survived the initial 30-day postoperative period were eligible for antimicrobial treatment review, of whom data was available in 109/135 (80.7%). In a landmark analysis looking at the patients that were alive after 90-days, prolonged antimicrobial therapy exposure (>3 months) was more common in the SC-cohort (SC: 84.0% vs. RS: 50.0%, $p < .001$). Analysing it further in a multivariable Cox-regression (adjusting for advanced age, chronic kidney disease and exposure to SC vs RS) prolonged antimicrobial therapy did not impact overall mortality (HR: 0.8, CI95: 0.4-1.2, $p = .15$).

Study IV

Patient characteristics - total cEVAR cohort

During the study period, a total of 542 separate cEVAR procedures were performed in 527 unique patients. Some 56/527 (10.6%, CI95: 8.3–13.5%) patients had a work-up for a *clinically* suspected AeGI during the study period, of which 19 were assessed as MAGIC-diagnosed AeGI during follow-up and further analysed in the survival and outcome section (Figure 18).

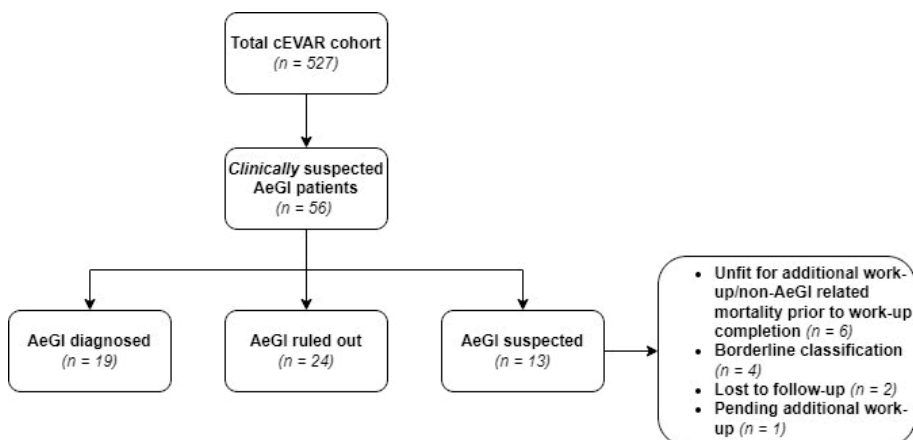


Figure 18. Flowchart of the all patients identified for Study IV, including those who developed a clinically suspected aortic endograft infection (AeGI) in the total complex endovascular aortic repair (cEVAR) cohort and the Management of Aortic Graft Infection Collaboration (MAGIC)-stratification at last follow-up.

Incidence and risk factors for MAGIC-diagnosed cEVAR AeGI

The long-term (5-year) cumulative incidence of MAGIC-diagnosed cEVAR AeGI in the total cohort was 3.9% (CI95: 2.4-5.9%) when adjusting for death as a competing risk, using CIF. This corresponded to an incidence rate of 723/100 000 patient-years of follow-up. When excluding primary infectious aortic pathology as index cEVAR indication, the same incidence was 3.2% (CI95: 1.8-5.1%) and 584/100 000 patient-years of follow-up, with a median time from index repair to diagnosis of 19 months (IQR: 9-38 months). For the 17 patients treated with cEVAR for a primary infectious aortic pathology, 4/17 (24%, CI95: 10-47%) developed an AeGI with a median time from index repair to diagnosis of 4 months (IQR: 1-6 months). Figure 19 A and B shows the AeGI incidence over time using the CIF, accounting for death as a competing risk, stratified by non-infectious and infectious primary cEVAR-indication.

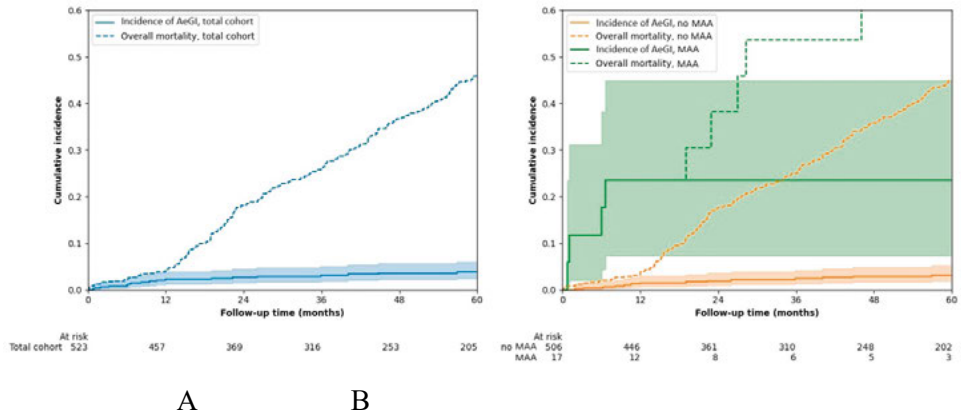


Figure 19 A and B. Estimated cumulative incidence of complex endograft infection (AeGI) after complex endovascular aortic repair and the competing total mortality (dashed lines) in: (A) the total cohort, and (B) stratified by index-pathology (infected native aortic aneurysm/mycotic aortic aneurysms [MAA] vs no MAA), using the cumulative incidence function with mortality as a competing risk with 95% confidence interval bands (shaded areas).

Table 17 and 18 illustrates the baseline characteristics and procedural details of the index aortic repair of the total cEVAR cohort stratified by AeGI diagnosis. In univariable analyses, patients with AeGI had a higher prevalence of MAA as the index pathology (21.1% vs 2.6%, $p = .002$), a greater incidence of late major complications (68.4% vs 37.4%, $p = .008$), and more frequent late aortic-related reinterventions (63.2% vs 31.6%, $p = .001$). Additionally, thoracoabdominal repair was more common in patients with AeGI (57.9% vs 30.8%, $p = .021$), a higher median number of fenestrations/branches (4 vs 3, $p = .046$), and a staged repair strategy (42.1% vs 16.1%, $p = .008$).

In a multivariable Cox-regression model, including a sub-set of the variables that differed significantly on univariable analysis based on effect size and clinical collinearity (as described earlier to minimize overfitting), MAA as index pathology (HR: 10.2, CI95: 3.1-33.2, $p < .001$), and late aortic reinterventions (HR 3.0, CI95: 1.1-7.9, $p = .028$) were independently associated with an AeGI diagnosis during follow-up (Table 19).

Table 17. Comparison of baseline characteristics and comorbidities of all patients at the time of primary complex endovascular aortic repair, stratified into a cohort with and without a Management of Aortic Graft Infection (MAGIC) diagnosed endograft infection respectively. Percentages, presented with total numbers and 95% confidence interval in parentheses, unless otherwise specified. Continuous variables were compared using the Student's t-test or Mann-Whitney U test as appropriate, and categorical variables using the χ^2 test or Fisher's exact test when expected cell count <5.

Baseline characteristics and comorbidities	MAGIC diagnosed endograft infection <i>Total n = 19</i> <i>%(n, CI95)</i>	No MAGIC diagnosed endograft infection <i>Total n = 508</i> <i>%(n, CI95)</i>	p-value [†]
Age (years) ¹	69.6 (63.8-75.5)	74.4 (69.5-78.8)	.053
Male sex	68.4 (13/19, CI95: 47.5-89.3)	73.2 (372/508, CI95: 69.4-77.1)	.84
Active smoker	21.4 (3/14, CI95: 0.00-42.9)	25.4 (105/414, CI95: 21.1-29.6)	.98
COPD ²	36.8 (7/19, CI95: 15.1-58.5)	27.6 (140/506, CI95: 23.7-31.5)	.54
Hypertension	83.3 (15/18, CI95: 66.1-100)	89.4 (402/506, CI95: 86.7-92.1)	.92
Diabetes	15.8 (3/19, CI95: 0.00-32.3)	11.1 (56/506, CI95: 8.33-13.8)	.79
Ischemic heart disease	35.3 (6/17, CI95: 12.6-58.0)	36.4 (172/473, CI95: 32.0-40.7)	1.00
TIA ³ /Stroke	0.00 (0/18, CI95:0.00-17.1)	11.0 (56/507, CI95: 8.31-13.8)	.27
Chronic kidney disease	26.3 (5/19, CI95: 6.50-46.1)	17.6 (89/507, CI95: 14.2-20.9)	.50
Previous aortic repair	52.6 (10/19, CI95: 30.2-75.1)	32.9 (167/508, CI95: 28.8-40.0)	.085
Emergency repair (non-elective)	21.1 (4/19, CI95: 2.63-39.5)	18.3 (93/507, CI95: 15.0-21.7)	.76
Pathology:			
Standard aneurysm	63.2 (12/19, CI95: 41.4-85.0)	77.5 (393/507, CI95: 73.9-81.2)	.17
Dissection	10.5 (2/19, CI95: 0.00-24.2)	11.6 (59/507, CI95: 8.84-14.4)	1.00
MAA ⁴	21.1 (4/19, CI95: 2.63-39.5)	2.56 (13/507, CI95: 1.19-3.94)	.002*
Other ⁵	5.26 (1/19, CI95: 0.00-15.3)	8.28 (42/507, CI95: 5.89-10.7)	1.00
In-hospital major complication	42.1 (8/19, CI95: 19.9-64.3)	24.6 (124/506, CI95: 20.8-28.3)	.091
Late major complication	68.4 (13/19, CI95: 47.5-89.3)	37.4 (176/471, CI95: 33.0-41.7)	.008*
Late aortic-related reintervention	63.2 (12/19, CI95: 41.5-84.8)	31.6 (149/471, CI95: 27.5-35.8)	.001*

* p <.05; ¹ Median (interquartile range); ² Chronic obstructive pulmonary disease; ³ Transient ischemic attack;

⁴ Mycotic aortic aneurysm; ⁵ Endoleak as pathology/indication in 32/43 cases

Table 18. Comparison of anatomical, surgical/technical characteristics and frequency of complications of the complex endovascular aortic repair, stratified into a cohort with and without a Management of Aortic Graft Infection (MAGIC) diagnosed endograft infection respectively. Total number presented with percentages in parentheses. Categorical variables were compared using the χ^2 test or Fisher's exact test when expected cell count <5 and number of fenestrations/branches was compared using Mann-Whitney U test.

Anatomical and technical characteristics	Endograft infection	No endograft infection	p-value
	Total n = 19 % (n, CI95)	Total n = 508 % (n, CI95)	
Anatomical extent of endovascular repair:			
Arch	5.26 (1/19, CI95: 0.00-15.3)	7.33 (36/491, CI95: 5.02-9.64)	1.00
Thoracic	0 (0/19, CI95: 0.00-14.6)	0.41(2/491, CI95: 0.00-0.97)	1.00
Thoracoabdominal	57.9 (11/19, CI95: 36.3-76.9)	30.8 (151/491, CI95: 26.7-34.8)	.021*
Abdominal	36.8 (7/19, CI91: 19.1-59.0)	61.4 (302/491, CI95: 57.1-65.7)	.055
Type of endograft:			
Arch-branched TEVAR	5.26 (1/19, CI95: 0.94-24.6)	3.98 (20/502, CI95: 2.27-5.70)	.55
Arch-fenestrated TEVAR	0.00 (0/19, CI95: 0.00-16.8)	9.16 (46/502, CI95: 6.64-11.7)	.40
Distally fenestrated TEVAR	5.26 (1/19, CI95: 0.94-24.6)	1.79 (9/502, CI95: 0.63-2.96)	.31
BEVAR ²	26.3 (5/19, CI95: 11.8-48.8)	12.0 (60/502, CI95: 9.11-14.8)	.075
FEVAR ³	42.1 (8/19, CI95: 23.1-63.7)	69.2 (348/502, CI95: 65.2-73.3)	.024*
B/F-EVAR ⁴	21.1 (4/19, CI95: 8.51-43.3)	3.78 (19/502; CI95: 2.13-5.44)	.007*
Physician modification:			
In-situ laser	10.5 (2/19, CI95: 2.94-31.4)	10.2 (52/508, CI95: 7.60-12.9)	1.00
PMEG ¹	5.26 (1/19, CI95: 0.94-24.6)	2.95 (15/508, CI95: 1.48-4.43)	.45
Number of fenestrations/branches²			
Staged repair	4 (2.5-4)	3 (2-4)	.046*
	42.1 (8/19, CI95: 23.1-63.7)	16.1 (82/508, CI95: 12.9-19.3)	.008*

*p<.05; TEVAR - thoracic endovascular aortic repair; BEVAR - branched endovascular aortic repair; FEVAR - fenestrated endovascular aortic repair; B/F-EVAR - combined branched/fenestrated endovascular aortic repair; ¹physician modified endograft; ²median per patient (interquartile range)

Table 19. Multivariable Cox-proportional hazards regression model to identify risk factors independently associated with developing an aortic endograft infection following complex aortic endovascular repair.

Variables	Hazard ratio <i>HR (CI95)</i>	p-value*
MAA ¹	10.2 (3.13-33.2)	<.001*
Late aortic-related reintervention	2.98 (1.12-7.89)	.028*
Thoracoabdominal extent of endovascular repair	2.41 (0.90-6.50)	.082
<hr/>		
Late major complication ²	-	-
FEVAR ²	-	-
B/F-EVAR ²	-	-
Number of fenestrations/branches ²	-	-
Staged repair ²	-	-

**p*<.05; ¹ *Infected native aortic aneurysm*; ² *Variable excluded from the model á priori due to high collinearity with other variable(s) included and/or to reduce the number of variables to ≤1 per five events to minimize over-fitting; FEVAR - fenestrated endovascular aortic repair; B/F-EVAR - combined branched/fenestrated endovascular aortic repair.*

Clinical presentation, microbiology and treatment for cEVAR AEGI

Secondary aortic fistulae were identified in 6/19 patients (32%, CI95 15–54%), including aorto-bronchial (n = 2), aorto-esophageal (n = 1), aorto-enteric (n = 2), and iliaco-urethral (n = 1).

Microbiological cultures were positive in 18 of 19 patients (95%, CI95: 75–99%), yielding 20 pathogens overall; 14/20 gram-positive (70%, CI95: 48–85%), followed by 3/20 gram-negative (15%, CI95: 5% - 36%), 2/20 fungal (10%, CI95: 3–30%), and 1/20 *Mycobacterium* spp. (5%, CI95: 1–24%).

Treatment strategies were predominantly endograft-preserving; antimicrobial therapy alone 11/19 (58%, CI95 36–77%), image-guided percutaneous drainage 5/11 (26%, CI95 12–49%), open surgical debridement (1/19; 5%,

CI95 1–25%), combined percutaneous drainage and surgical debridement (1/19; 5%, CI95 1–25%), and staged explantation strategy initiated with extra-anatomic bypass which failed (1/19; 5%, CI95 1–25%).

Infectious- and survival outcomes for cEVAR AeGI

Median survival in the total AeGI cohort was 33.2 months (CI95 28.0–33.2 months). (Figure 20). When stratified by fistula status, median survival was 41.5 months (CI95 33.2–41.5) in patients without fistula, compared with 4.0 months (CI95 1.3–4.0) in those with fistula, among whom 4 of 6 patients (67%, CI95 30–90%) died within approximately six months. Of the 12 total deaths recorded during follow-up, 8 (67%, CI95 39–86%) were AeGI-related.

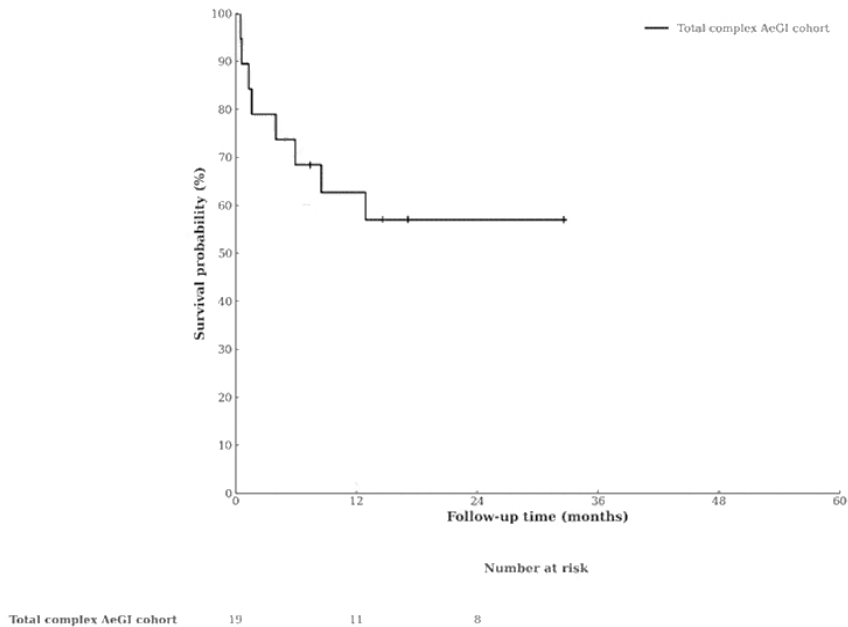


Figure 20. Kaplan-Meier curves illustrating overall survival for the total complex aortic endograft infection cohort, truncated when numbers at risk <10.

A total of 18/19 patients had sufficient follow-up for assessment of long-term infectious outcomes. In the overall cohort, treatment failure occurred in 8/18 patients (44%, CI95: 25-66), while remission or cure was achieved in 10/18 patients (56%; CI95: 34-75).

When further stratified into presence or absence of secondary fistula: in patients without fistula treatment failure occurred in 3/13 (23%, CI95: 8-50%) and remission or cure (10/13, 77%, CI95: 50-92%), while treatment failure occurred in 5/5 patients with a fistula (100%, CI95: 57-100%).

Discussion

Vascular surgery, and aortic surgery in particular, has dramatically transformed over the last two decades owing to the implementation and advancement of endovascular techniques. Complex aortic pathologies are now treatable, even in older and more comorbid populations (Gunnarsson, 2021). However, complex vascular surgeries in the elderly are associated with more complications (Han, 2017). The need for postoperative critical care after aortic surgery, the risk factors, complications, and outcomes associated with it is poorly understood. Additionally, with the broad adaptation of abdominal aortic screening, an increased population amenable for aortic repair due to endovascular options, the number of patients with an abdominal aortic graft/stent-graft at risk for future AGI is increasing (Budtz-Lilly, 2017). This thesis aimed to analyse risk factors and outcomes of complications after abdominal aortic surgery causing prolonged ICU care, to compare the survival and complication outcomes after radical surgery for abdominal AGI in a populationbased setting with long follow-up times, as well as to determine and describe the incidence, risk factors, management, and outcomes of cEVAR AeGI.

Complications and ICU requirement after AAA surgery

In Study I we showed that the frequency of prolonged ICU LOS after AAA repair diminished over time from 41% to 7% with a concomitant increase in the frequency of EVAR (7% to 78%) over the study period. Open repair (OR: 5.5) and rupture (OR: 3.8) were the strongest independent risk factors for prolonged ICU LOS in the multivariable model.

Outside of rupture status and type of repair, there was a high homogeneity in terms of baseline comorbidities between the different ICU LOS cohorts and none of the classical comorbidities could be identified as an independent risk factor for prolonged ICU LOS in the binary logistic regression. This is likely partly explained by better patient selection and use of EVAR in the high-risk patient population. Of note is that the frequency of prolonged ICU LOS for OR patients also reduced over time, highlighting the likelihood and

importance of better patient selection and advancements in the postoperative care over time (Jackson, 2012; Nathan, 2011). Additionally, the frequency of ruptured AAA cases diminished over time, contributing to the reduced need for prolonged ICU LOS, likely reflecting the impacts of the shift in smoking epidemiology, introduction of AAA screening programme during the study period (Wanhainen, 2016) and improvements in cardiovascular medicine and prevention with increased prevalence of exposure to e.g. statins in the population (Siika, 2025; Tomee, 2023).

In this study, a prolonged ICU LOS was a cumulative marker for adverse peri- and post-operative events and was associated with a progressively worsening short-term outcome and stepwise increase in frequency of postoperative complications (such as need for dialysis, prolonged invasive/non-invasive ventilation, vasopressor requirement, sepsis and open abdomen) as the ICU time increased. This ultimately reflects that a prolonged ICU LOS in the AAA cohort is a reliable marker for the accumulation of overall organ dysfunction associated complications. When the patient cohort was further stratified according to ICU LOS: <48 hours, 2-6 days and ≥ 7 days as well as rupture status, the negative impact on both short- and long-term survival was largest and significant only for the group requiring ≥ 7 ICU days, for both ruptured and intact AAA cases.

Interestingly, the impact of ≥ 7 days of ICU LOS on overall long-term (5-year) survival was ameliorated in the combined ruptured- and intact cohort when excluding early 90-day mortality (Figure 13C). Similar results on long-term mortality when adjusting for confounders has been seen in critically ill sepsis patients (Shankar-Hari, 2016). This finding indicates that the excess mortality contributed by the multiple complications after prolonged ICU LOS for AAA patients is mainly derived from early mortality. Additionally, this suggests that a limited mortality associated deterioration occurred in patients surviving the initial 90-days regardless of ICU requirement.

From a more pragmatic and contemporary viewpoint, the reduced morbidity and overall diminished need for critical care resources after aortic surgery has been important for the vascular aortic services provided to our patient population in the context of societal and health-economic challenges exemplified by the previous Covid-19 pandemic. Several inquiries have shown that the volume of elective vascular surgery diminished over the early periods of the pandemic, including elective aortic repairs (Hemingway, 2020; Lopez-Marco, 2021). One major contributor to the reduced surgical volumes during the pandemic has been hospital overcrowding and the increased need for hospital and ICU beds (Chew, 2021). It is thus likely that the current evolution of

endovascular aortic repair with the reduced critical care need at least ameliorated the overall impact on aortic services during this time period.

Utility and cost-effectiveness in terms of quality adjusted life years per incremental cost are already important factors of health-care systems globally. While the data is conflicting, contemporary studies are showing the cost-effectiveness per quality adjusted life years of EVAR vs open repair, at least in the short to mid-term in high-risk AAA populations (Canning, 2019; Nargesi, 2021). The major contributor to this is reduced early mortality and reduced need for in-hospital and critical care post-operatively. As the endovascular advancements continues, it is at least possible that the need for hospital resources will continue to diminish for both standard and complex aortic repairs.

Strength and limitations

The main strength of this study is the relatively large sample size of some 707 patients with a long duration of follow-up, thus both increasing the power to detect differences in the sub-groups of the prolonged ICU LOS cohort as well as giving the opportunity to identify possible long-term mortality impact of prolonged ICU LOS. Additionally, the follow-up index on mortality data was close to 100%, without any censor/loss-of follow up, as the Swedish population registry provides continuously updated survival data on all Swedish citizens (Allmen, 2015). As explained previously, the prospective Swedvasc registry provides excellent quality of data with ensured external and internal validity and as such reduces the risk for selection bias and misclassification (Sigvant, 2019).

The long study period can however in itself be a limitation as it reflects changes in critical care, patient selection and surgical experience that is difficult to account and adjust for. Additionally, the single-centre nature of this study raises some questions regarding the generalisability of the results.

Of importance is the fact that only infrarenal aortic repairs on aneurysmatic disease were included in the study. As such, a significant limitation is the fact that no conclusions can be drawn regarding other aortic pathologies such as dissections as well as fenestrated-, branched- or thoracic endovascular repairs in terms of the impact and changes of ICU LOS and its effect on mortality in this cohort.

The decision to continue critical care generates a selection bias in itself. For instance, patients that are deteriorating in terms of their organ dysfunction and where the continued critical care is deemed futile, are more likely to have their critical care discontinued. Ultimately this might cause a selection bias where the mortality in the longer ICU LOS cohorts is underestimated. One solution to account for this is to adjust for the changes in organ dysfunction

scores such as Sequential Organ Failure Assessment (SOFA) score over the ICU LOS (Ferreira, 2001). This data was however not available in this study.

Aortic (endo)graft infections

Study II compared outcomes after EAB versus ISR in a nationwide, population-based cohort of radically treated abdominal AGI patients in Sweden. Short-term 90-day survival (EAB: 75% vs ISR: 76%) and long-term 5-year survival (EAB: 48% vs ISR: 50%) were similar between treatment strategies and aligned with contemporary reports, particularly given the high prevalence of GEF of approximately 50% in the study population (Antonopoulos, 2019; Chakfé, 2020; Janko, 2021).

No survival differences were observed between NAIS and other ISR methods. Furthermore, long-term complication rates, including recurrent graft infection, anastomotic dehiscence versus aortic stump blow-out, major amputation, and reintervention, did not differ between EAB and ISR. Importantly, after adjustment for multiple pre-, peri-, and postoperative variables, the choice of EAB versus ISR was not independently associated with 90-day or long-term mortality in multivariable logistic and Cox regression analyses. This finding raises questions regarding ISR as the gold standard surgical treatment when considering real-world constraints such as anatomical limitations, and centre-specific surgical expertise.

Intra-ISR comparisons of Study II must be interpreted cautiously due to limited sample size and the associated risk of type II error. Nonetheless, the numerically higher crude rate of anastomotic dehiscence observed after NAIS repair (17.4% vs 3.3% for other ISR methods, $p = .15$) raises concerns regarding long-term durability. Conversely, the observed trend towards lower recurrent infection rates after NAIS (11.1% vs 20.0% for non-NAIS ISR and 21.3% for EAB, $p = .65$) is consistent with prior evidence suggesting increased infection resistance of autologous vein grafts (O'Connor, 2006).

Previous studies have consistently demonstrated worse outcomes for AGI patients presenting with GEF, including higher reinfection rates and reduced survival (Janko, 2021; Laser, 2011; Li, 2018). This association could not be statistically confirmed in Study II. However, the marked numerical difference in 90-day survival between patients with and without GEF (56% vs 76%) suggests limited statistical power and type II errors rather than true equivalence. An additional explanation may be the lack of differentiation between graft-enteric erosion and true graft-enteric fistula with intravascular

communication, where the latter represents a more severe pathological entity with a potentially greater impact on mortality.

In Study II, prolonged antimicrobial therapy (> 3 months) was independently associated with improved long-term survival (HR: 0.3) after adjustment for immortal-time bias. This observation is consistent with prior literature demonstrating an association between extended antimicrobial therapy and improved survival following AGI repair (Janko, 2021). However, prolonged therapy was not associated with a reduced risk of recurrent graft infection. As treatment duration was analysed based on actual exposure rather than intention to treat, this finding is likely confounded by collinearity between disease severity, treatment response, recurrent infection, and the clinical decision to prolong antimicrobial therapy. Due to limited use of biofilm-active regimens, including rifampicin and daptomycin, no conclusions could be drawn regarding their specific impact on outcomes.

Study III aimed to compare SC strategies, defined as non-radical surgical approaches with partial graft preservation, with RS for abdominal AGI. 90-day survival (76.7% vs 75.7%, $p = .86$) and one-year survival (58.1% vs 69.1%, $p = .19$) were similar between groups, with a non-significant trend towards worse five-year survival in the SC cohort (30.2% vs 48.4%, $p = .066$). In contrast, the risk of recurrent infection was substantially higher after SC treatment (45.5% vs 19.3%, $p < .001$). These findings are similar to those reported by Janko et al. in a multicentre cohort of 114 AGI patients undergoing partial resection that demonstrated a 30-day mortality of 17.5%, median survival of 3.6 years and risk of recurrent infection of 39% (Janko, 2021).

In contrast Shu et al. and Ljungquist et al. reported more favourable outcomes for partial resection and conservatively treated AGI patients respectively where Ljungquist et al. showed a 1-year survival of 88% and treatment failure of only 10% (Ljungquist, 2023; Shu, 2024). It is possible that the differences in the latter results could be partially attributed to a different case-mix with 84% endografts (vs 32.6% of SC patients in Study III), lower frequency of secondary fistula (6% vs 53.5%), different utilization of biofilm active therapy, and different microbiological aetiology where at least 26% of the causative pathogens in the Ljungquist et al. study was due to low-virulent bacteria including CoNS and *Cutibacterium* spp.

Importantly, in Study III, exposure to SC treatment was associated with older age and higher frequency of cardiac comorbidities, likely reflecting a systematic selection bias where more frail patients were assessed to not be amenable to RS. This interpretation is supported by the attenuation of survival differences after adjustment for preoperative confounders (SC vs RS HR: 1.0, CI95: 0.6–1.5). Similar to Study II, there was a large numerical reduction in

overall survival, that did not reach statistical significance, for patients with a GEF, particularly in the subgroup analyses of the SC-cohort (Figure 17D). In contrast when excluding patients with a GEF, long-term overall survival was descriptively more comparable between the RS and SC cohorts (Figure 17C). While these analyses are limited by power issues and increased risk of statistical type II errors, the negative impact of a GEF on overall survival in partial resection strategies of abdominal AGI has previously been shown by Janko et al. (HR for mortality: 1.9) (Janko, 2021).

The increased risk for treatment failure in terms of recurrent infection for the SC cohort vs. RS is biologically plausible, due to the prosthetic material left in-situ. This association remained robust after adjustment for confounders including GEF and graft type, (SC [compared to RS], HR: 4.1, CI95: 1.8-9.2, $p < .001$). At the time of Study II and III, no standardised definitions for treatment failure, remission, or cure existed. Consequently, heterogeneity in outcome classification likely contributes to the differences between reported re-infection rates across studies.

Exposure to prolonged (>3 months) antimicrobial therapy was more common in the SC cohort of Study III (SC: 84.0% vs. RS: 50.0%, $p < .001$). In contrast to Study II, we could not replicate the survival benefit of prolonged antimicrobial therapy in the total cohort (HR: 0.8, CI95: 0.4-1.2, $p = .15$) when adjusting for treatment exposure (SC vs. RS), chronic kidney disease and advanced age. Potential explanations could be the association and collinearity between recurrent graft infection, inadequate treatment response and the decision to prolong antimicrobial therapy during follow-up. These findings are consistent with a contemporary meta-analysis by Cremer et al., which included seven retrospective studies comprising 776 patients and found no association between antimicrobial treatment duration and survival outcomes in AGI (Cremer, 2026).

In Study IV, we analysed a single-centre cohort of patients undergoing cEVAR with the aim of characterising the incidence, risk factors, and outcomes of cEVAR AeGI. The 5-year cumulative incidence of AeGI following cEVAR for non-infectious aortic pathology was 3.2% (CI95: 1.8–5.1%) when accounting for death as a competing risk, which exceeds the incidence reported for standard EVAR-associated graft infection, typically below 1% (Argyriou, 2017; Murphy, 2013). In multivariable Cox regression analysis, infectious aortic pathology as the index indication (HR: 10.2, CI95: 3.1–33.2) and the occurrence of any late aortic reintervention (HR: 3.0, CI95: 1.1–7.9) were independently associated with subsequent AeGI. To put this in context, prior studies have demonstrated higher 5-year reintervention rates following

cEVAR (approximately 40%) compared with standard EVAR (approximately 20%) (Columbo, 2020; Oderich, 2024).

Notably, no plateau in the cumulative incidence of AeGI was observed during follow-up (Figure 19), suggesting a persistent long-term infection risk in this population. The extended duration of follow-up and the higher burden of secondary aortic interventions may therefore partially explain the higher observed incidence of AeGI compared with infrarenal EVAR cohorts. In addition, markers of more extensive aortic coverage and procedural complexity - such as a higher number of fenestrations or branches and thoracoabdominal disease extent - were more frequently observed among patients who developed AeGI in univariable analyses, although these factors were not retained in the final multivariable model. Nevertheless, this pattern raises the hypothesis that increased endograft surface area and procedural complexity may contribute to infection susceptibility following cEVAR.

While radical explantation with in situ reconstruction is routinely employed at the study centre for infrarenal aortic (endo)graft infections, treatment strategies in the AeGI cohort of Study IV were almost exclusively endograft-preserving (18/19 cases), reflecting both the anatomical complexity of cEVAR reconstructions and the frailty of the affected patient cohort. Among patients without a secondary fistula (13/19), outcomes were comparatively favourable, with a 1-year survival of 77%, a median survival of 41.5 months, and remission or cure achieved in 10 of 13 patients (77%) at last follow-up. These survival outcomes are comparable to those reported in the largest previously published AeGI series by Campolmi et al. (n = 10; 1-year survival 82%) (Campolmi, 2025).

In contrast, outcomes in patients with a secondary fistula were poor, with an estimated 1-year survival of 33% and treatment failure observed in all cases. Although the available evidence remains limited, taken together these findings suggest that AeGI complicated by secondary fistula represents a particularly high-risk phenotype. In such cases, or following failure of an initial conservative strategy, a more aggressive surgical approach may need to be considered when deemed feasible, potentially including surgical debridement and fistula resection with reconstruction despite the associated operative risk. Given the complexity of these cases, such management is likely best undertaken within a centralised, multidisciplinary framework at centres with specific expertise in cEVAR-associated AeGI.

Strength and limitations:

Study II and III represent the first nationwide population-based studies of surgically treated AGI patients, thereby mitigating the selection and publication

bias inherent to small single-centre series. As such, the findings are likely to reflect real-world outcomes rather than results from highly specialised centres employing specific AGI strategies. The use of the MAGIC criteria ensured a homogeneous case definition and facilitated comparison with contemporary literature. Furthermore, linkage to national registries enabled complete long-term follow-up without loss to follow-up, strengthening analyses of mortality and reintervention outcomes.

Study IV represents the largest reported cohort of cEVAR-associated AeGI with long-term follow-up to date. Generating structured evidence for this specific subgroup is clinically important, as epidemiological patterns and treatment paradigms derived from standard infrarenal AGI data are unlikely to be directly transferable to cEVAR-associated AeGI, given the substantially greater anatomical complexity and the extent of surgical intervention required for radical infection control. The extended follow-up period and inclusion of all cEVAR procedures, including non-surgically treated AeGI cases, are important strengths that likely improve the accuracy of incidence estimates and risk factor assessment. In addition, application of the MAGIC criteria, together with conservative downranking of ambiguous cases and use of the 2025 Delphi outcome definitions, enhances cohort validity and comparability with future studies while maintaining conservative incidence estimates (Sörelius, 2025).

The partially retrospective design of Study II–IV limited data granularity, particularly regarding aspects such as fistula morphology, bowel involvement, and in-hospital antimicrobial regimens due to constraints in historical data capture. This limitation weakened analyses exploring the association between antimicrobial treatment duration and clinical outcomes. In the absence of prospective intention-to-treat data, causal inference, either direct or reverse, between antimicrobial exposure and survival, reinfection, or treatment failure cannot be established.

It should also be noted that in Study II and III, the case-mix of ISR techniques may impact both outcomes and generalisability. While NAIS reconstructions accounted for 24 of 55 ISR procedures, seven standard prosthetic graft implantations were also performed, potentially influencing reinfection and treatment failure rates. In addition, bovine pericardial reconstructions were not utilised during the study period. This is relevant given the increasing number of case series over the past decade reporting outcomes for this technique comparable to NAIS (Weiss, 2024).

Similarly, the SC cohort in Study III was characterised by substantial treatment heterogeneity, ranging from endovascular adjuncts alone to open surgical debridement with or without partial graft or endograft explantation. This

heterogeneity limits generalisability, as different SC strategies are likely associated with varying degrees of source control and risk of persistent infection. However, the limited cohort size precluded meaningful subgroup analyses.

One weakness by design is that all completely conservatively treated AGI patients were excluded from Study II and III. This was both an active decision, in order to not introduce any additional heterogeneity, and a limitation of the method of case-identification – where Swedvasc only captures patients treated with a vascular surgical procedure. Non surgically treated AGI patients are both more difficult to diagnose according to the MAGIC criteria and the decision to omit surgical treatment is likely based on the degree of certainty/extent of graft infection as well as frailty and comorbidities in this selective cohort which introduces selection bias. As such, no comparisons of outcomes or conclusions regarding epidemiology such as incidence of AGI could be drawn.

Reported rates of recurrent infection in Study II and III must be interpreted in the context of the study period, which preceded the 2025 Delphi consensus statement. At that time, standardised definitions of treatment failure, remission, and cure were lacking (Sörelus, 2025). Consequently, a proportion of cases classified as recurrent infection, particularly among patients receiving ongoing or lifelong antimicrobial therapy, might under current terminology be more appropriately categorised as disease in remission rather than true treatment failure.

An important limitation of Study IV is the single-centre design and the low absolute number of AeGI cases, both of which restrict the generalisability of survival and infectious outcomes. The AeGI cohort was heterogeneous with respect to anatomical extent, index pathology, and microbiology. Although treatment was predominantly endograft-preserving, this exposure was itself heterogeneous, ranging from antimicrobial therapy alone to surgical debridement. The limited sample size precluded further meaningful subgroup analyses.

Treatment strategies for AeGI in Study IV were not protocolised during the study-period but determined on a multidisciplinary, case-by-case basis. In the absence of prospective intention-to-treat data, the specific rationale underlying selection of endograft-preserving strategies in individual cases cannot be reliably reconstructed. Furthermore, the small number of AeGI events constrained multivariable modelling to avoid overfitting. In the Cox regression analysis, late aortic reinterventions were not modelled as time-dependent variables due to unavailable timing data for the full cEVAR cohort. This likely introduced immortal time bias, resulting in attenuation of the estimated hazard associated with reintervention.

Conclusions

Study I

Prolonged ICU length of stay after abdominal aortic aneurysm repair has decreased over time, coinciding with increased use of EVAR. Open repair and rupture were the strongest predictors of prolonged ICU stay. While prolonged ICU stay was associated with increased short-term mortality, long-term survival differences were largely attenuated among patients surviving beyond 90 days.

Study II

In this nationwide population-based study of radically treated abdominal AGI, outcomes after extra-anatomic bypass and in situ reconstruction were comparable with respect to mortality, reinfection, and major complications. Surgical strategy did not independently influence survival. Prolonged antimicrobial therapy (>3 months) was associated with improved long-term survival.

Study III

Semi-conservative and radical surgical strategies for abdominal AGI resulted in similar short-term survival, but semi-conservative treatment was associated with a substantially higher risk of recurrent or persistent infection. Differences in long-term survival were at least partially explained by patient frailty and comorbidity. Graft-enteric fistula was associated with poor outcomes, particularly in semi-conservatively treated patients.

Study IV

The incidence of aortic endograft infection after cEVAR was higher than previously reported for standard infrarenal EVAR and increased continuously over time. Infectious index pathology and late aortic reintervention were independent risk factors. Conservative management yielded acceptable outcomes in selected patients without fistula, whereas secondary fistula was associated with poor survival and treatment failure.

Future aspects

While the results from Study I–IV provide important insights into complications after aortic surgery, several clinically relevant questions remain unanswered. The findings highlight areas where current evidence is limited by study design, cohort size, and heterogeneity in practice, underscoring the need for further investigation.

With respect to Study I, the observations related to perioperative morbidity, intensive care utilisation, and early outcomes following aortic surgery should be evaluated in future multicentre, and preferably international, settings to improve generalisability. Contemporary complex EVAR, including fenestrated and branched techniques, is increasingly performed across heterogeneous healthcare systems with marked variation in ICU structure, staffing models, and thresholds for organ support. This cohort was however not included in Study I. Reanalysing ICU length of stay, complications, and resource utilisation in a cEVAR cohort would provide a more accurate estimate of the true critical care burden associated with modern aortic surgery. In this context, future studies should move beyond crude ICU admission metrics and instead evaluate outcomes in relation to trends in organ dysfunction, for example using serial SOFA scores or comparable validated scoring systems. Such an approach would allow a more granular assessment of postoperative physiological stress and its relationship to short- and long-term survival.

To further improve comparability between centres and healthcare systems, future ICU-based analyses should consider standardising cohort definitions based on objective measures of critical illness, such as duration of vasopressor support and/or invasive mechanical ventilation, rather than ICU admission time alone. This may reduce heterogeneity introduced by institutional practice patterns and enhance the external validity of future studies examining postoperative outcomes after aortic repair.

Derived from Studies II, III, and IV, a consistent and overarching unmet scientific need is the establishment of large-scale international multicentre collaborations of AGI-research. While the nationwide design of Studies II and III mitigates selection and publication bias, the rarity and heterogeneity of AGI fundamentally limit statistical power and the ability to explore clinically important subgroups. Prospective international registries dedicated to AGI

and AeGI are therefore essential to capture the full spectrum of anatomical, microbiological, surgical, and antimicrobial variables required for meaningful analyses and comparisons of treatment outcomes. Such registries would also provide the necessary infrastructure for any future randomised or pragmatic comparative trials in this field.

Prevention remains a critical area for future AGI research. Continued efforts are needed to identify modifiable risk factors and preventive interventions targeting AGI development, including optimisation of antimicrobial prophylaxis in different clinical scenarios, such as emergency repair, prolonged operative times, groin exposure, and redo aortic interventions. In parallel, further evaluation of infection-resistant graft materials for off-the-shelf use is warranted, both as prophylactic adjuncts and as treatment options in infected fields. Materials incorporating antimicrobial agents such as silver and/or triclosan remain promising, but require robust comparative data addressing long-term durability, reinfection risk, and ecological risk assessments including cross-resistance development

The incidence, management, and outcomes of cEVAR-associated AeGI identified in Study IV highlight a particularly underexplored area. Multicentre collaborations are urgently needed to map the true incidence of AeGI following cEVAR, characterise contemporary treatment strategies, and identify predictors of treatment outcomes in much larger cohorts. Such efforts are essential given the increasing global utilisation of complex endovascular aortic repair and the sustained long-term infection risk observed in this population.

Another major unresolved issue across Studies II–IV concerns antimicrobial therapy in AGI. The optimal duration of treatment, the role of lifelong suppressive strategies, and the impact of biofilm-active agents remain incompletely defined. Future studies should aim to stratify antimicrobial strategies by surgical approach (radical resection versus conservative or semi-conservative treatment), microbiological profile, presence of fistulae, and host factors. Prospective data are particularly needed to disentangle treatment indication bias and better define scenarios in which prolonged or lifelong antimicrobial therapy confers true survival or infection-control benefit.

Diagnostic and follow-up strategies also warrant further refinement. Examples of this includes future work to re-evaluate the role of nuclear medicine imaging in both diagnosis and longitudinal surveillance, including reassessment of its incorporation into the MAGIC criteria. Semi-quantitative and pattern-based interpretation approaches, tracer uptake dynamics over time, and their relationship to clinical outcomes should be explored to improve specificity without compromising sensitivity. Importantly, future studies should address whether imaging-guided strategies and any dynamics in uptake patterns

can safely support earlier withdrawal of antimicrobial therapy, even in selected conservatively managed patients.

Finally, the cumulative findings from Studies III and IV, together with emerging data from cohorts demonstrating favourable outcomes with conservative management of AGI, raise fundamental questions regarding the current paradigm of radical surgery as the universal gold standard for AGI treatment (Ljungquist, 2023). It may be timely to re-evaluate whether a stepwise strategy of initial conservative management with escalation to radical surgery only in cases of treatment failure or local complications could be appropriate in carefully selected patients without secondary fistula or uncontrolled sepsis, analogous to contemporary management strategies for prosthetic valve endocarditis. Addressing this question will ultimately require prospective international registries as a foundation, coupled with collaborative efforts to design feasible and ethical comparative trials in this complex and high-risk patient population.

Building upon these identified gaps, an international effort to address this unmet need is currently underway. The Global Aortic Infection and Aortic Graft Infection Adaptive Platform (GRANDPA) registry has been designed as a prospective, international, multicentre platform registry dedicated to the systematic capture of patient-level data in AGI as well as INAA/MAA. The registry will include all adult patients with suspected or confirmed AGI according to MAGIC criteria and INAA/MAA defined by contemporary ESVS guidelines, with longitudinal follow-up and detailed recording of clinical, imaging, microbiological, surgical, antimicrobial, and patient-reported outcomes.

Importantly, GRANDPA is constructed not merely as a descriptive database but as an adaptive research platform with the long-term objective of enabling embedded registry-based RCTs. At the time of writing, the registry infrastructure is being established, with international centre recruitment and anticipated launch in 2026. If successfully implemented, GRANDPA may provide the large-scale, high-quality prospective data necessary to reduce treatment heterogeneity, improve risk stratification, and ultimately support evidence-based management.

Populärvetenskaplig sammanfattning (Lay summary in Swedish)

Aortasjukdomar omfattar ett spektrum av allvarliga tillstånd där kroppens största pulsåder, aortan, på olika sätt drabbas. Aortaaneurysm innebär att aortan successivt vidgas vilket kan leda till ruptur med mycket hög dödlighet som följd. Bland män över 65år är förekomsten av aortaaneurysm i buken ca 1-2%. Om aortaaneurysmet växer och blir tillräckligt stort är kirurgisk behandling ofta nödvändig för att förhindra ruptur, men ingreppen är förenade med komplikationsrisker, särskilt hos äldre patienter med annan samsjuklighet.

Under de senaste decennierna har behandlingen av aortasjukdomar förändrats i grunden genom införandet av endovaskulär teknik, där aortan behandlas inifrån med hjälp av tygklädda metallnät (stentgraft) som förs in via blodkärlen i lumsken. Denna metod är mindre belastande än öppen kirurgi och har lett till kortare vårdtider och lägre initial kroppslig påfrestning för patienten. Samtidigt har nya problem och komplikationer uppmärksamrats, däribland främmandekroppsinfektioner i aortaprotreserna och infektioner i mer komplexa stentgraft.

Denna avhandling syftar till att belysa komplikationer, utfall och behandlingsstrategier vid modern aortakirurgi, med särskilt fokus på intensivvårdsbehov och aortaprotresinfektioner efter både öppen och endovaskulär behandling.

I delarbete I analyserades behovet av långvarig intensivvård efter kirurgisk behandling av bukaortaaneurysm. Studien visade att behovet av förlängd intensivvård successivt har minskat, samtidigt med en ökad användning av endovaskulära tekniker. Öppen kirurgi och akut operation vid sprucket aortaaneurysm var det som var starkast förknippat med behov av lång intensivvård.

Patienter som krävde mycket lång intensivvård, >7 dagar, hade en tydligt ökad risk för död på kort sikt. Däremot minskade skillnaderna i långtidsöverlevnad bland de patienter som klarade den initiala fasen efter operationen, vilket talar för att intensivvårdsbehovet främst speglar den tidiga kirurgiska belastningen snarare än långsiktig prognos.

Delarbete II var en nationell studie av patienter med aortagraftinfektion i bukaorta som behandlats med kirurgiskt avlägsnande av aortaprotesen, i Sverige. Två huvudsakliga kirurgiska strategier jämfördes: extraanatomisk bypass (EAB) och in situ-rekonstruktion (ISR).

Studien visade att överlevnaden var likvärdig mellan metoderna, både på kort och lång sikt. 90-dagarsöverlevnaden var 75 % efter EAB och 76 % efter ISR, medan 5-årsöverlevnaden var 48 % respektive 50 %. Det fanns inga signifikanta skillnader i förekomst av återinfektion, större komplikationer, amputationer eller reoperationer mellan grupperna.

Användningen av EAB minskade tydligt över tid till fördel för ISR. Förlängd antibiotikabehandling (>3 månader) var förknippad med längre långsiktig överlevnad, men var inte kopplad till lägre risk för återinfektion.

I **delarbete III** jämfördes semi-konservativ behandling, där hela- eller delar av den infekterade aortaprotesen lämnas kvar, med radikal kirurgi vid aortagraftinfektion i bukaorta.

90-dagarsöverlevnaden var likartad mellan grupperna (77% för semi-konservativ behandling jämfört med 76% för radikal kirurgi). Ettårsöverlevnaden uppgick till 58 % respektive 69%. Däremot var risken för behandlingssvikt i form av kvarstående eller återinfektion betydligt högre i den semi-konservativa gruppen (46% jämfört med 19%).

När justering/hänsyn togs till ålder och samsjuklighet minskade skillnaderna i överlevnad tydligt, vilket tyder på att semi-konservativ behandling oftare används hos äldre och mer sköra patienter. Förekomst av fistel mellan aortaprotesen och tarm var förenat med sämre prognos, särskilt vid semi-konservativ behandling.

Delarbete IV fokuserade på stentgraftinfektioner i aortaprotiser (AeGI) i komplexa endovaskulära stentgraft med grenar eller fenestreringar (cEVAR). Denna patientgrupp har hittills varit mycket sparsamt studerad.

Vi identifierade totalt 527 patienter som behandlats med cEVAR varav 19 patienter diagnosticerats med AeGI. Förekomsten av AeGI efter cEVAR behandling för icke-infektiös aortasjukdom var 3,2% när man justerade för död av annan orsak, vilket är betydligt högre än vad som rapporterats efter vanlig EVAR. Infektiös aortasjukdom som ursprunglig indikation samt sena aortarelaterade reoperationer var förknippat med utveckling av AeGI.

Majoriteten av patienterna behandlades med antibiotika och icke-kirurgisk stentgraftbevarande strategier. Bland patienter utan sekundär fistel var ettårsöverlevnaden 77 % och 77 % uppnådde infektiös remission eller bot. Däremot

var prognosen mycket dålig vid sekundär fistel, med 33 % ettårsöverlevnad och 100 % behandlingssvikt.

Sammanfattande slutsatser

Avhandlingen visar att modern aortakirurgi har minskat behovet av lång intensivvård men postoperativa komplikationer, inklusive komplexa infektionsproblem, förekommer fortsatt. Vid abdominell aortagraftinfektion var resultaten jämförbara mellan etablerade kirurgiska strategier. Semi-konservativ behandling kan vara ett alternativ hos särskilda patienter, men är förenad med hög risk för behandlingssvikt, särskilt vid fistelbildning. Slutligen har vi visat att patienter som behandlas med komplex endovaskulär aortakirurgi har en högre och kvarvarande risk att drabbas av infektion i aortaprotesen över tid. Konservativ och stentgraftbevarande behandlingsstrategier gav preliminärt acceptabla resultat men hos patienter med sekundära fistlar var prognosen dystert – något som antyder att en mer individualiserad och aggressiv kirurgisk strategi bör övervägas.

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Scientific work is rarely the product of a single individual or a solitary effort. While this dissertation focuses on a narrow and highly specific clinical field, its completion has depended on the accumulated knowledge, guidance, and support of many others. My own contribution has been less about extending the boundaries of knowledge and more about carefully examining a small part of it, often in detail, occasionally from an imperfect angle, and sometimes with limited visibility, but always with curiosity and persistence.

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