

Nationwide Study on Treatment of Mycotic Thoracic Aortic Aneurysms

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WHAT THIS PAPER ADDS

This nationwide study on mycotic thoracic aortic aneurysms (MTAAs) in Sweden encompasses the largest cohort reported to date. The study demonstrates that a large proportion of MTAAs are treated by thoracic endovascular aneurysm repair, and that short-term survival is good with acceptable long-term results, although risk of infection related complications remains a concern.

Objective: Mycotic aortic aneurysms are rare, life threatening, and complex. This nationwide study aimed to assess outcome after repair of mycotic thoracic aortic aneurysms (MTAAs).

Methods: Patients treated in Sweden for MTAAs between 2000 and 2016 were identified in the Swedish vascular registry (2010–16) and local patient registries (2000–09). Primary outcome was survival, and secondary outcomes included surgical strategy, rate of infection related complications (IRC), and re-operations.

Results: Fifty-two patients (median age 71 ± 8.1 years; 28 [54%] men, 13 [25%] ruptured) were identified (3.6% of all thoracic aortic aneurysm repairs in Sweden). Aneurysm location was aortic arch ($n = 6$; 11%), descending aorta ($n = 42$; 81%), and multiple locations ($n = 4$; 8%). Twenty-nine (56%) patients had positive cultures; the most prevalent agent was *Staphylococcus aureus* ($n = 16$; 31%). Operative techniques included thoracic endovascular aortic repair (TEVAR; $n = 35$ [67%]), fenestrated/branched TEVAR ($n = 8$; 15%), hybrid repair ($n = 7$; 14%), and open patch repair ($n = 2$; 4%). Survival was 92% (95% confidence interval [CI] 88–96) at 30 days, 88% (95% CI 84–93) at three months, 78% (73–84) at one year, and 71% (64–77) at five years. The mean follow up among survivors (> 90 days) was 45 months (range 4–216 months). Antibiotics were administered for a median of 15 weeks (range 0–220 weeks). IRCs occurred in nine patients (17%): sepsis ($n = 3$), graft infection ($n = 3$), recurrent mycotic aneurysm ($n = 1$), aorto-oesophageal/bronchial fistula ($n = 2$). Six (67%) IRCs were fatal; 80% occurred within the first year. Re-operations were performed in nine patients (17%).

Conclusions: TEVAR was often used as treatment for MTAAs, with acceptable short- and long-term survival when compared with open cohorts in the literature. IRCs are of concern and warrant follow up and long-term antibiotic treatment.

Keywords: Aneurysm, Aorta, Infected, Mycotic, Thoracic, Treatment

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INTRODUCTION

Mycotic aortic aneurysm (MAA), synonymously known as infected aortic aneurysm, is a rare, serious, and complex

disease. The incidence of MAA has been estimated to be 0.6–2% of all aortic aneurysms in Western countries, and up to 13% in Taiwan.^{1–4} MAAs have a particularly high risk of rupture, and patients often suffer severe comorbidities, in particular immunosuppressive disease or treatment, and co-existing infection or sepsis.^{5,6}

MAAs can occur throughout the aorta, and management of the disease is particularly challenging when the aneurysm is located in the thoracic segment.^{5,6} Successful

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management relates to early diagnosis and treatment comprising surgery and antibiotics. Traditional surgical management has been open repair (OR) with debridement of the infected area followed by revascularisation, using mostly synthetic grafts.^{7–10} OR has the major advantage of infection control by resection of the infected tissue, but comes at a high mortality and morbidity price. Endovascular repair for MAAs was first reported in 1998, and offers a less invasive treatment option, which is suitable for surgical high risk patients.¹¹ A disadvantage is the placement of a stent graft in an infected field, which is not resected, and thus may result in recurrent sepsis, stent graft infection, and development of recurrent MAA or fistulation.⁵

Lack of data from comparative studies or randomised controlled trials has resulted in the absence of guidelines for the management of MAAs. Most published case series on MAAs are small and usually single centre, including both thoracic and abdominal MAAs with inadequate follow up.^{12–}

¹⁴ A non-comparative European multicentre study of endovascular treatment for MAA included 38 patients with thoracic MAA, and showed acceptable results for endovascular treatment in the whole cohort, but were not detailed for this subgroup.⁵ A recently published study comparing open and endovascular repair for abdominal MAAs reported endovascular repair to be associated with superior survival up to 4 years, without increased risk of re-infection or re-operation.⁴ In the thoracic aorta, the approach with thoracic endovascular aortic repair (TEVAR) is particularly appealing, but larger series with adequate follow up are lacking.

This article assesses surgical practice in Sweden for the treatment of mycotic aneurysms of the thoracic aorta (MTAAs) based on the national Swedish vascular registry (Swedvasc) over a 17 year period. The primary aim was to assess short- and long-term survival after MTAA repair. Secondary aims included analysis of types of repairs, and rates of recurrent infections and re-operations.

METHODS

Patients treated for MTAAs were identified in the national Swedish vascular registry, Swedvasc, for the period 2010–2016, and in local patient registries at all tertiary referral vascular centres in Sweden ($n = 8$) for the period 2000–09. The reason for using local registries prior to 2010 was the fact that the Swedvasc registry did not fully capture all thoracic aortic procedures at that time. All the Swedish tertiary referral vascular centres participated in retrieving data. Survival was assessed by cross matching of patients based on the unique identification number against the Swedish population registry, ensuring 100% accurate mortality data without loss of follow up.

A combination of at least two of the following three criteria were used for the definition of a mycotic aneurysm in the thoracic aorta: (i) clinical presentation (pain, fever $\geq 38^\circ$ C, sepsis, and/or concomitant infection); (ii) laboratory tests (elevation of inflammatory markers such as C-reactive protein and white blood cells, and/or positive cultures); and (iii) radiological findings on computed tomography (CT) or

magnetic resonance imaging of aneurysm formation in the thoracic aorta with mycotic aneurysm appearance (rapid expansion of aneurysm, saccular aneurysm, multilobular aneurysms/eccentric aneurysms, peri-aortic gas, and peri-aortic soft tissue mass). Patients with other pathologies such as graft infection, or aorto-oesophageal or aorto-bronchial fistula, and patients who had previously had aortic surgery were excluded to make the cohort more homogenous. An infection related complication (IRC) was defined as recurrent sepsis, graft or stent graft infection, aorto-oesophageal and aorto-bronchial fistula, or recurrence of a new MAA, in the same or at a different location. The term renal insufficiency was defined as a creatinine level > 1.70 mg/dL or presence of renal replacement therapy.

A common study protocol (Appendix 1; Supplementary Material) was applied for the retrospective review of all cases, including data on (i) patient characteristics and clinical presentation (sex, age, medical history, immunodeficiency [including comorbidities and treatments associated with relative immunodeficiency], symptoms, concurrent infection, blood tests, and microbiological cultures); (ii) aneurysm characteristics (aneurysm status, location, CT findings; rapid expansion, saccular, multilobular, peri-aortic gas, peri-aortic mass); (iii) treatment (open repair or endovascular approach, hybrid: combined open and endovascular repair, and pre- and post-operative antibiotic treatment); and (iv) follow up time, outcome, and complications. All study protocols were sent to Uppsala for secondary reviews (K.S.).

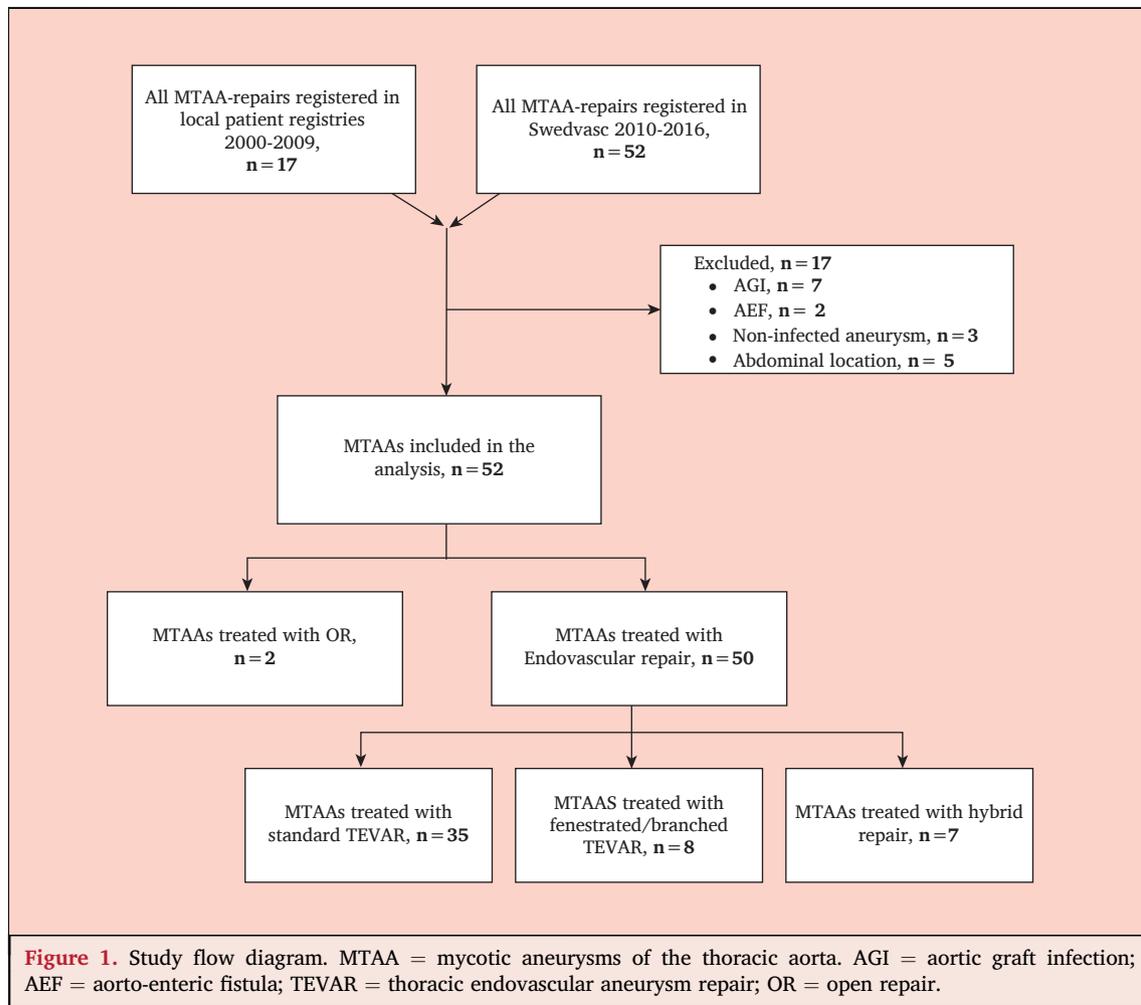
To assess the incidence of MTAA repair as a proportion of all thoracic aortic aneurysm (TAA) repairs, the number of identified MTAA cases for the period 2010–14 was compared to the total number of TAA repairs registered in the Swedish vascular registry and the national inpatient registry. The national inpatient registry includes data on all patients undergoing inpatient care in Sweden. Cases were selected based on the diagnosis of TAA (ICD codes I71.1, I71.2, I71.5, and I75.6) combined with an operation code for repair of descending thoracic aortic aneurysm for the years 2010–14.

This study was approved by the regional ethical review board in Uppsala, registration number 2018/062, which also waived the need for informed consent.

Statistical analysis

Data were analysed using a statistical software package (SPSS 22; IBM, Armonk, NY, USA). Data were assessed for normality with histograms. Continuous data are expressed as median (range), or mean \pm SD, and categorical variables as n (%). All statistical tests were two tailed, and $p < .05$ was considered significant. Univariable logistic regression (for peri-operative mortality) and Cox regression (for long-term mortality) analyses were performed, to assess predictors of post-operative mortality.

The cumulative incidence of infection related death accounting for the competing risk of death of other causes, and the cumulative incidence of re-operation (open or endovascular) with the competing risk of all cause death,



was calculated using the package `cmprsk` in R14 statistical analyses (Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

RESULTS

Baseline characteristics

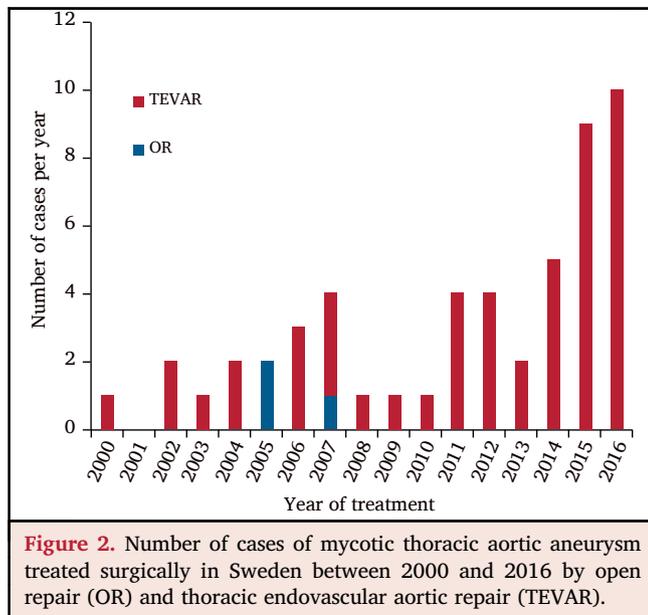
In total, 52 MTAA cases were included (Fig. 1). The incidence of MTAA treatment as a proportion of all (intact and ruptured) thoracic aortic aneurysm repairs in Sweden for the years 2010–14 was 3.6% ($n = 16/442$). The number of procedures performed per year with each approach is shown in Fig. 2.

Table 1 presents demographic data, laboratory results, aneurysm characteristics, and radiological features of the patients. Four patients had multiple MTAA: descending and infrarenal ($n = 3$), and descending and paravisceral ($n = 1$). A quarter of the patients presented with rupture. At least one positive blood culture was achieved in 56% of the patients. Bacteriological findings are presented in Table 1.

Overall outcome

Kaplan–Meier analysis demonstrated a total survival of 92% (95% confidence interval [CI] 88–96) at 30 days, 88% (95% CI 84–93) at three months, 78% (95% CI 73–84) at one year, and 71% (95% CI 64–77) at five years (Fig. 3). The mean follow up was 24 months (range 0–216 months), and mean follow up among those surviving the first peri-operative 90 day period was 45 months (range 4–216 months). The leading cause of death during the first post-operative year was infection related complications. Causes of death are presented in Table 2. The cumulative incidence of infection related deaths, with death due to other causes as competing risk is displayed in Fig. 4: 10.0% (95% CI 9.7–10.3) at three months, and 16.1% (95% CI 15.8–16.4) at one and five years.

The operating technique was TEVAR ($n = 35$, 67%) of which fenestrated/branched TEVAR ($n = 8$; 15%), and supra-aortic deviation and TEVAR ($n = 7$; 14%); two patients also had open visceral deviation and open repair with patch plasty ($n = 2$; 4%). Details on outcome after TEVAR



are shown in Table 3. The two open repairs were performed in 2005 and 2007, respectively.

The median pre-operative antibiotic time was one week (range one day – 24 weeks). Median post-operative antibiotic time was 14.5 weeks (range 0.5–220 weeks). Post-operative antibiotic treatment for > 6 months was not associated with better outcome in the univariable analyses (see “Subgroup analyses”).

All surviving patients underwent a post-operative CT approximately 30 days after surgery (for details of findings see Table 3). Further follow up included annual imaging. Reoperations were performed in nine patients (17%), owing to endoleak ($n = 5$; 10%), IRCs ($n = 3$), and graft occlusion ($n = 1$) (see Table 3). Two patients required open reoperation for aortic graft infection ($n = 1$; for details see below), and thrombectomy at the access site of the common femoral artery ($n = 1$).

Nine patients (17%) developed IRCs of which six (11.5% of the total cohort) were fatal (Table 4). Median time until first IRC was three months (range 0.1–30 months). All IRCs developed within the first post-operative year, except one. Those who developed an IRC had a median of six weeks of post-operative antibiotic treatment (range 1–104 weeks) versus a mean of 18 weeks of post-operative antibiotic therapy in those without IRCs (range 0–220 weeks; $p = .932$). Six of the nine IRC cases had a positive blood culture. Two patients developed graft infections with fistulation, both of which were fatal. One patient developed a recurrent MAA in the infrarenal aorta, and was treated successfully by EVAR and survived through 10 years of follow up. Three patients developed graft infections; one patient was treated for an MTAA in the aortic arch involving the left carotid artery, by TEVAR and chimneys to the brachiocephalic trunk and the left carotid artery. Eleven months later this was converted to an open repair due to

Table 1. Demographic and clinical characteristics

Parameters	Overall ($n = 52$)
Mean \pm SD age (y)	71.3 \pm 8.1
Sex (male)	28 (53.8)
Any cardiovascular disease	43 (82.7)
Hypertension	33 (63.5)
Ischaemic heart disease	5 (9.6)
Cerebrovascular disease	4 (7.7)
COPD	9 (17.3)
Any immunosuppressive state	14 (26.9)
Renal insufficiency	4 (7.7)
Diabetes	8 (15.4)
<i>Patient characteristics at presentation</i>	
Pain	47 (90.4)
Mean \pm SD CRP level (mg/L)	177 \pm 99
Mean \pm SD WBC count ($\times 10^9/L$)	12.9 \pm 4.3
Pre-operative BP < 90 mmHg	2 (3.8)
Pre-operative fever > 38 °C	47 (90.4)
<i>Bacteriology</i>	
<i>Staphylococcus aureus</i>	16 (30.8)
<i>Streptococcus pneumoniae</i>	7 (13.5)
<i>Salmonella</i> species	2 (3.8)
Miscellaneous	4 (7.7)
Negative	23 (44.2)
<i>Aneurysm characteristics</i>	
Rupture	13 (25.0)
Ascending or aortic arch	6 (11.5)
Descending aorta	42 (80.8)
Multiple aneurysms	4 (7.7)
Mean \pm SD aneurysm size (mm)	60.4 \pm 17.9
<i>Radiological features</i>	
Rapid expansion of aneurysm	20 (38.5)
Saccular aneurysm	29 (55.8)
Peri-aortic gas	1 (1.9)
Peri-aortic mass	24 (46.2)
Multilobular aneurysm	6 (11.5)

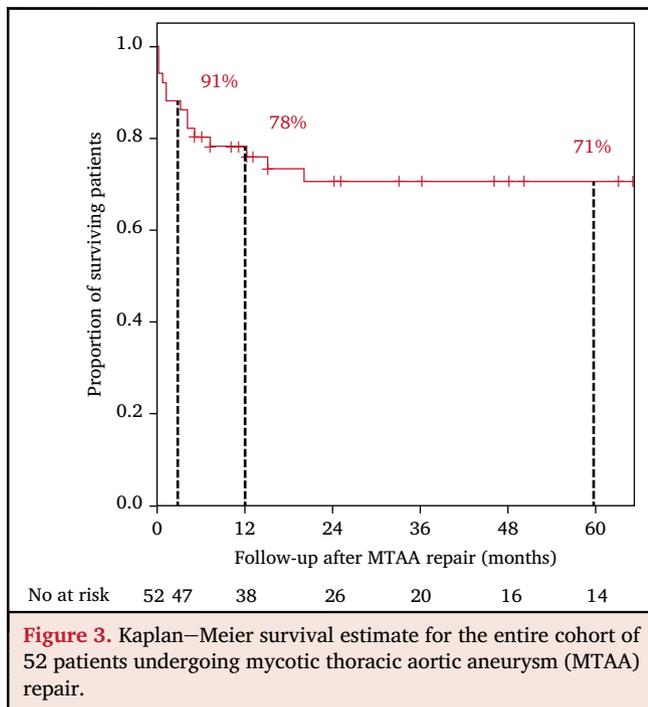
Data are n (%) unless otherwise indicated. COPD = chronic obstructive pulmonary disorder; CRP = C-reactive protein; WBC = white blood cells; BP = blood pressure; SD = standard deviation.

development of graft infection, and a concomitant type 1 endoleak. The patient survived this episode, and finally died of cancer. One patient developed a graft infection five months after surgery but was considered too frail to withstand surgical treatment. Another patient developed a graft infection after 2.5 years and was treated only with antibiotics and survived until the end of the study period (36 months). Fig. 5 illustrates the cumulative incidence of reoperation with all cause death as competing risk: 9.6% (95% CI 9.4–9.9) at three months, and 13.6% (95% CI 13.3–13.9) at one year and five years.

Of the two patients treated by open repair and patch plasty; one was positive for *Salmonella* species and the other was culture negative; neither suffered any IRC during follow up.

Subgroup analyses

Kaplan–Meier analyses regarding survival of patients with immunosuppression versus no immunosuppression, positive culture versus negative, and rupture versus intact



MTAA are presented in Fig. S1 (see Supplementary Material); however, these analyses are susceptible to type II errors owing to the low number of patients. Furthermore, they are limited by a bivariable comparison only. A univariable analysis revealed rupture to be the only factor associated with increased risk of mortality at both three months (odds ratio 13.5, 95% CI 2.29–79.60; $p = .004$) and five years (hazard ratio 3.67, 95% CI 1.38–9.47; $p = .009$) (see Table 5).

DISCUSSION

This nationwide study demonstrates that the majority of patients with MTAA in Sweden are treated by TEVAR. The survival for this complex and frail cohort of patients is surprisingly good: 92% at one month and 71% at five years. Although the literature on homogenous cohorts of MTAA for comparison are scarce, previous reports indicate a peri-operative survival rate of 88% in patients selected for

Table 2. Causes of death

	Time after surgery	
	< 3 months	> 3 months
Peri-procedural	3	—
Sepsis	1	2
Graft infection	—	1
AOF	1	1
Cardiac	—	3
Stroke	—	1
Cancer	—	2
Multiorgan failure	1	—
Unknown	1	4
Total	7	14

AOF = aorto-oesophageal fistula.

treatment, and 50% at a median follow up of 16 months.⁹ The risk of IRCs and re-operation is equal to that of OR of abdominal MAA.^{4,15}

This is the first estimated incidence of MTAA as a proportion of all treated thoracic descending aneurysms in a prospectively collected population based setting. The observed incidence of 3.6% of all descending aortic repairs being performed for MTAA is surprisingly high. The present authors previously reported the incidence of abdominal MAAs in Sweden to be 0.6%.⁴ The actual numbers of MAAs in the abdominal aorta in Sweden for the period 2010–14 was 57, which can be compared with 16 MTAA repairs in this study. However, neither of these studies was able to assess the number of patients who were treated conservatively. International consensus on a diagnostic algorithm for MAA is lacking, although the algorithm used in this study is the most frequent in the literature, the accuracy of the diagnosis might still be questioned. The role of positron emission tomography scanning in MAA is yet to be evaluated, but perhaps the investigation could add information and enhance the diagnostic accuracy, especially in patients with an intact MAA. Thus, both these factors may affect the estimated incidence.

Estimated survival in the present cohort is similar in the short term but better in the long term than after abdominal MAAs (abdominal MAA survival at 30 days is 94% and at five years is 59% vs. the results of the current report on MTAA of 92% at 30 days and 72% at five years).⁴ Estimated survival in this study is comparable with that reported in a study by Yu *et al.*,⁷ which included 14 patients treated by open repair with *in situ* prosthetic reconstruction, but superior to the that of Muller *et al.*, published in 2001, where three of four patients died in the peri-operative period.⁸ Open repair and patch plasty for MTAA, as described in two patients, is not standard practice, but may offer an option as a bail-out solution.

The frequency of IRCs (17%) is comparable with that of a report from Hsu *et al.* of an open surgical cohort of MTAA:⁹ 18% (four of 22 patients operated on developed an aortic graft infection), although the causative bacteria differ. The numbers are also equal to those seen after treatment of MAAs in the abdominal aorta in Sweden (21%) and comparable with those after EVAR for MAAs of all aortic locations in a large European multicentre study (19%).^{4,5}

The question of pre- and post-operative duration of antibiotic treatment is difficult to assess. However, most studies support longer durations of antibiotic treatment up to 6 months — one year post-operatively, and in selected cases for life.^{4–6} Prolonged pre-operative antibiotic treatment carries the risk of delaying surgical treatment, with the subsequent risk of rupture. This essential question of antibiotic therapy as an adjunct to surgery should ideally be addressed in a multi-institutional prospective study.

Blood culture results were positive in 56%, dominated by *Streptococcus* species and *Staphylococcus aureus*. The blood culture rate in previous studies on MAA has been reported to be 50–75%. The fact that many patients do not have a positive blood culture may partly be explained by early the

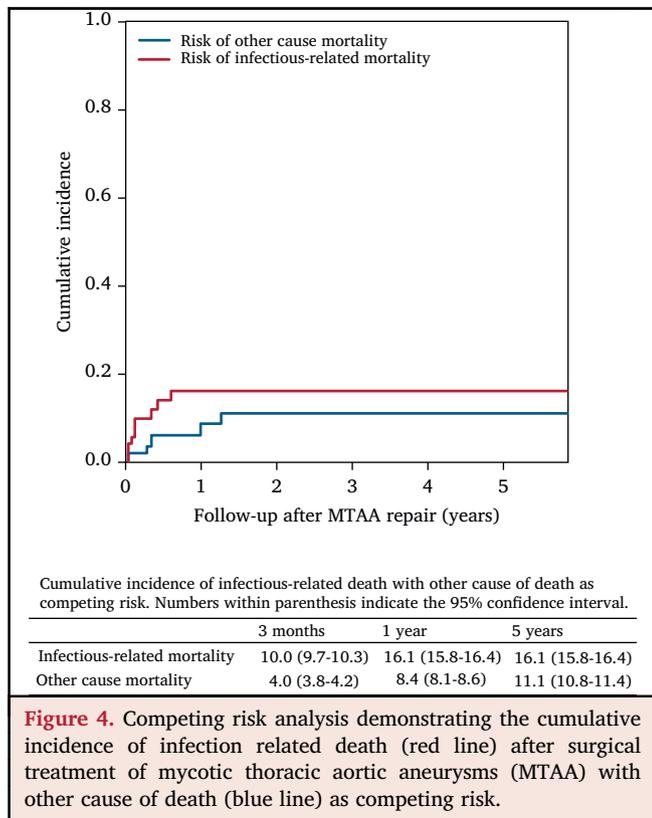


Figure 4. Competing risk analysis demonstrating the cumulative incidence of infection related death (red line) after surgical treatment of mycotic thoracic aortic aneurysms (MTAA) with other cause of death (blue line) as competing risk.

administration of broad spectrum intravenous antibiotic therapy.^{1,4,6,8,16} These culture findings provide support for previous recommendations of initiating empirical antimicrobial therapy with agents effective against not only Gram positive cocci, but also of Gram negative rods in cases of suspected mycotic aneurysm as *Salmonella* species is a known common infective agent.^{4,5}

Limitations

Although this study includes the largest cohort of MTAA reported to date, the cohort is still limited in size, which

Table 3. Surgical outcome of patients treated by thoracic endovascular aneurysm repair (TEVAR)

Outcome	TEVAR (n = 50)
Median (range) follow up (mo)	24 (0–216)
Peri-operative stroke	0 (0.0)
Transient paraplegia	3 (6.0)
Re-operation	9 (18.0)
Bridge to open repair	1 (2.0)
Cause of re-operation	
Occlusion of stent graft	1 (2.0)
Endoleak	T1EL = 3, T2EL = 1, T3EL = 1
Graft infection	1 (2.0)
Recurrent MAA	1 (2.0)
AOF	1 (2.0)

Note. Data are n (%) unless otherwise indicated. MAA = mycotic aortic aneurysm; T1EL = type 1 endoleak; T2EL = type 2 endoleak; T3EL = type 3 endoleak; AOF: aorto-oesophageal fistula.

Table 4. Post-operative infection related complications (IRC) in 52 patients undergoing MTAA repair

IRC	Overall	Fatal	Months after surgery, median (range)
Overall	9 (17.3%)	6 (11.5%)	3 (0.1–30)
Sepsis	3	3	0 (1–3)
Graft infection	3	1	5 (11–30)
Recurrent MTAA	1	0	1
AOF	2	2	1 (6)

MTAA = mycotic thoracic aortic aneurysm; AOF = aorto-oesophageal fistula.

reduces the impact of the results, and the possibility of robust multivariable analyses. In the Swedvasc registry, patients are only included if treated surgically, and hence the registry does not contain data on those treated conservatively with antibiotics only.^{17,18} Additionally, patients with thoracic aortic pathology may be treated by OR by cardiothoracic surgeons in Sweden who do not participate in the Swedvasc registry. Hence, this may have resulted in a selection bias for cases treated with TEVAR, which is primarily managed by vascular surgeons and thus registered in Swedvasc. The previous assessment of abdominal MAAs in Sweden, however, showed that there is a strong

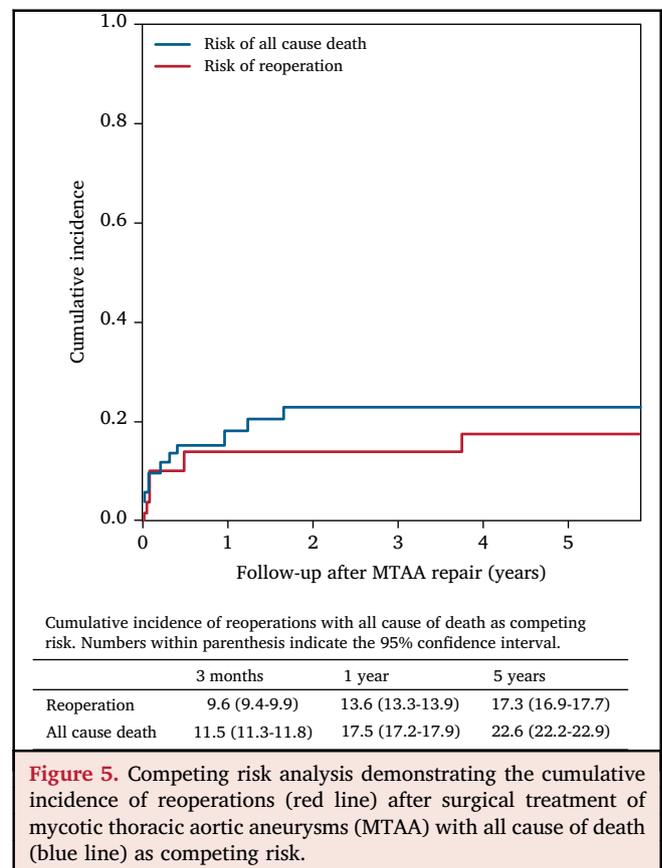


Figure 5. Competing risk analysis demonstrating the cumulative incidence of reoperations (red line) after surgical treatment of mycotic thoracic aortic aneurysms (MTAA) with all cause of death (blue line) as competing risk.

Table 5. Univariable analyses of predictors of post-operative mortality at three months and five years

Predictor	Univariable analysis, three month mortality		Univariable analysis, five year mortality	
	OR (95% CI)	p	HR (95% CI)	p
Age	1.02 (0.92–1.12)	.738	1.07 (1.00–1.15)	.068
Sex (male)	0.23 (0.04–1.28)	.093	0.89 (0.36–2.20)	.805
Any cardiovascular disease	0.31 (0.06–1.67)	.173	0.27 (0.11–0.68)	.006
COPD	1.56 (0.17–14.48)	.698	0.64 (0.18–2.31)	.498
Any immunosuppressive state	0.72 (0.29–1.80)	.484	0.63 (0.38–1.07)	.085
Renal insufficiency	0.51 (0.05–5.65)	.439	0.32 (0.09–1.15)	.081
Fever at surgery	1.51 (0.53–4.33)	.336	0.69 (0.33–1.45)	.329
Positive blood culture	0.53 (0.16–1.70)	.283	0.64 (0.36–1.15)	.137
Non- <i>Salmonella</i> positive culture	1.75 (0.37–8.24)	.481	1.25 (0.51–3.09)	.631
Rupture	13.50 (2.29–79.60)	.004	3.67 (1.38–9.47)	.009
Pre-operative BP < 90 mmHg	0.53 (0.24–1.19)	.124	0.81 (0.50–1.31)	.385
Year of surgery	0.88 (0.75–1.03)	.105	0.98 (0.88–1.09)	.655
Post-op ABx > 6 month	—	—	1.34 (0.16–11.5)	.791

OR = odds ratio; CI = confidence interval; HR = hazard ratio; COPD = chronic obstructive pulmonary disease; BP = blood pressure; ABx = antibiotic treatment.

predominance of endovascular repair for MAA in the abdominal segment for many years, and this can be expected to be even higher in the thoracic aorta where the risks associated with open surgery are generally greater.⁴ The surgical strategy in this study was not uniform, and was based on the preference of each participating centre during this period. The calculation of incidence was focused on the time period 2010–14, during which TEVAR was the primary treatment modality for thoracic aortic pathology. To ensure that open descending aortic repairs were included in the calculation of incidence, the national inpatient registry, which includes all patients undergoing surgical repair, was also interrogated. There is a significant delay in this registry, explaining why these numbers only could be retrieved for the years 2010–14. The current report does not allow clear recommendations regarding surgical approach with OR or TEVAR for MTAA, as no comparison was feasible, but does support the idea that TEVAR is as durable a treatment option as open repair when compared to historical reports. The definition of an MTAA used in this study is in accordance with the existing literature.^{4–6,19,20} However, it may also be defined as an aneurysm with proven bacterial infection in the aortic wall, which would create an inherent limitation in study of this disease when treated endovascularly, where bacterial culture from the aortic wall cannot be obtained without risk.²¹ Patients with MAA often receive broad spectrum antibiotics early, which could explain the observed rate of positive culture (56%).

CONCLUSION

Endovascular repair is currently the most common surgical approach in Sweden for the treatment of MTAA. The estimated survival after MTAA repair is acceptable in both the short and long term, and comparable with survival after MAA repair of the abdominal aorta. Adequate antimicrobial treatment is a key component of MTAA management, as IRCs are of concern and warrant close follow up.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2018.08.052>.

CONFLICTS OF INTEREST

None.

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