Treatment of ruptured abdominal aortic aneurysms in the Amsterdam area

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CHAPTER 4

ENDOVASCULAR REPAIR VERSUS OPEN REPAIR OF RUPTURED ABDOMINAL AORTIC ANEURYSM, A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective - Randomized comparison of endovascular repair (EVAR) with open repair (OR) in patients with a ruptured abdominal aortic aneurysm (rAAA).

Background Data - In spite of advances in operative technique and perioperative management rAAA remains fraught with a high rate of death and complications. Outcome may improve with a minimally invasive surgical technique: EVAR

Methods - All patients with a rAAA in the larger Amsterdam area were identified. Logistics for rAAA patients was changed with centralization of care in three trial centers. Patients both fit for EVAR and OR were randomized to either treatment. Non-randomized patients were followed in a prospective cohort. Primary endpoint of the study was combined death and severe complications at 30 days.

Results - Between April 2004 and February 2011, we identified 520 patients with a rAAA of which 116 could be randomized. The primary endpoint rate for EVAR was 42% and for OR 47% (absolute risk reduction (ARR) 5,4% 95% CI; -13 to +23%) The 30 day mortality was 21% in patients assigned to EVAR vs. 25% for OR (ARR 4,4 % 95% CI; -11 to +20%). The mortality of all surgically treated patients in the non randomized cohort was 30% (95% CI: 26-35%) and 26% (95% CI; 20 to 32%) in patients with unfavorable anatomy for EVAR, treated by OR in trial centers,

Conclusion - This trial did not show a significant difference in combined death and severe complications between EVAR and OR. Mortality for OR both in randomized patients and in cohort patients was lower than anticipated which may be explained by optimization of logistics, preoperative CT imaging and centralization of care in centers of expertise.

INTRODUCTION

A ruptured aneurysm of the abdominal aorta (rAAA) is a potentially lethal condition for which immediate surgical intervention, traditionally by open repair (OR), is required. A meta-analysis has shown mortality of OR for rAAA to be 48.5%[1]. Endovascular Aneurysm Repair (EVAR), a minimally invasive technique, could potentially reduce this mortality rate[2, 3]. Support for this hypothesis comes from observational and population-based studies of OR versus EVAR in patients with rAAA [4-6]. The only study that randomized between OR and EVAR was terminated after randomizing 32 patients[7]. The current Amsterdam Acute Aneurysm Trial was designed with the hypothesis that EVAR would reduce mortality and severe complications when compared with open surgery for treating rAAA.

METHODS

Patients

In this regional multicenter randomifzed controlled trial we included patients with rAAA who were suitable for both EVAR and OR from April 8, 2004 to February 16, 2011. The study was conducted across the greater Amsterdam region (1.24 million inhabitants, 10 hospitals)[8] in which three Amsterdam hospitals, two academic medical centers, AMC and VUMC, and one teaching hospital, OLVG, referred to as the trial centers, provided alternating round-the-clock rAAA service. These three centers were experienced in both elective and acute EVAR of abdominal aortic and thoracic aortic pathology. All other seven regional hospitals agreed to participate in the trial by transferring patients suspected of an rAAA to one of the trial centers if possible, and by providing data on all patients who presented with an rAAA. Patients suspected of having an rAAA were taken to the trial center on call while a protocol of controlled hypotension was applied by both the ambulance services and emergency room staff[9]. Eligible patients were recruited from all patients suspected of a rAAA presented to the trial centers. After initial resuscitation by hospital staff (nurses, anesthesiologists and surgeons) abdominal ultrasound and/or Computed Tomographic Angiography (CTA) was done to either confirm or reject the diagnosis of rAAA. After diagnosis, anatomical suitability for EVAR based on CTA and clinical suitability for OR was documented by both the vascular surgeon and the radiologist. Patients suitable for both EVAR and OR were randomized. Patients with conditions that did not allow for CTA or either OR or EVAR were excluded from randomization (Table 1, inclusion and exclusion criteria). All patients in the trial region with proven rAAA were included in a prospective parallel cohort.

Study Design

This was a randomized study with an equally balanced parallel group design. The randomization sequence was generated by an independent clinical research unit using ALEA software for randomization in clinical trials[10] with a 1:1 allocation using random block sizes of 4 or 6, stratified for each participating center. Allocation was concealed using sequentially numbered opaque sealed envelopes. These envelopes, present in the emergency rooms at the trial centers, were opened by the surgeon after inclusion and prior to transport to the operating room.

Since rAAA constitutes an immediate threat, preoperative informed consent from the patients could not usually be obtained[11]. Alternatively, in compliance with Dutch law, written informed consent was obtained from the patients' relatives where possible. Finally, following recovery, patients were asked for their written consent to continuing participation in the trial. The study was approved by the Dutch national regulatory authority and the ethics committees of the

participating trial centers. Data were recorded on case record forms by the vascular surgeon and confirmed by the primary researcher using source data. Double database entry and analysis were performed in order to minimize errors. An endpoint adjudication committee, blinded with respect to treatment assigned and treatment received, assessed and graded all complications for primary endpoints. Disagreements were discussed and resolved at a consensus meeting. An independent data safety committee reviewed deaths and severe complications every 4 months to ensure safe patient recruitment. No interim analyses for efficacy were performed. All the authors vouch for the accuracy and completeness of the data and data analysis.

Table 1

Inclusion criteria
Male/female aged >18 years
With a clinical diagnosis of ruptured abdominal aortic aneurysm
With an aneurysm accompanied by acute hemorrhage outside the aortic wall on CTA
Patients is suitable for endovascular treatment
Patient is suitable for conventional open repair
Anatomic suitability
Suitable infra renal anchoring segment
A minimum length of the infra renal segment of at least 10-15mm
An infra renal diameter of 20-32mm
No obstructing calcifications, tortuosity or thrombus
Suitable iliac anchoring segment
An ipsilateral iliac diameter of 8-18mm
A contralateral iliac diameter of 10-20mm
At least one iliac artery should be able to accommodate an endograft
No obstructing calcifications, tortuosity or thrombus
Exclusion criteria
Extension of the aneurysm to juxta- or suprarenal aorta
Kidney transplant
Horseshoe kidney
Allergy to intravenous contrast
Connective tissue disease
Severe hemodynamic instability prohibiting CTA

Intervention

For patients assigned to EVAR we chose a technique that results in fast and easy exclusion of the rupture by using an aorto-uni-iliac endograft and a contra lateral iliac occluding device, preferably inserted under local anesthesia. A femoral-femoral crossover bypass graft was then inserted. We initially used the Talent unilateral graft (Medtronic AVE Europe) then later the Endurant aorto-uni-iliac graft (Medtronic BV, Heerlen), both with contra lateral iliac occluder and femoro-femoral crossover bypass (either Polyester or expanded Polytetrafluoroethylene). If required, an aortic occlusion balloon was used prior to insertion of the endovascular graft. The surgical treatment of patients assigned to OR comprised midline laparotomy and exclusion of the ruptured aneurysm by either a polyester tube or a bifurcated graft.

Study endpoints

The primary endpoint was the composite of death and severe complications at 30 days after intervention. Complications were graded according to the guidelines of the Society for Vascular Surgery/International Society of Cardiovascular Surgery[12, 13] Severe complications were defined

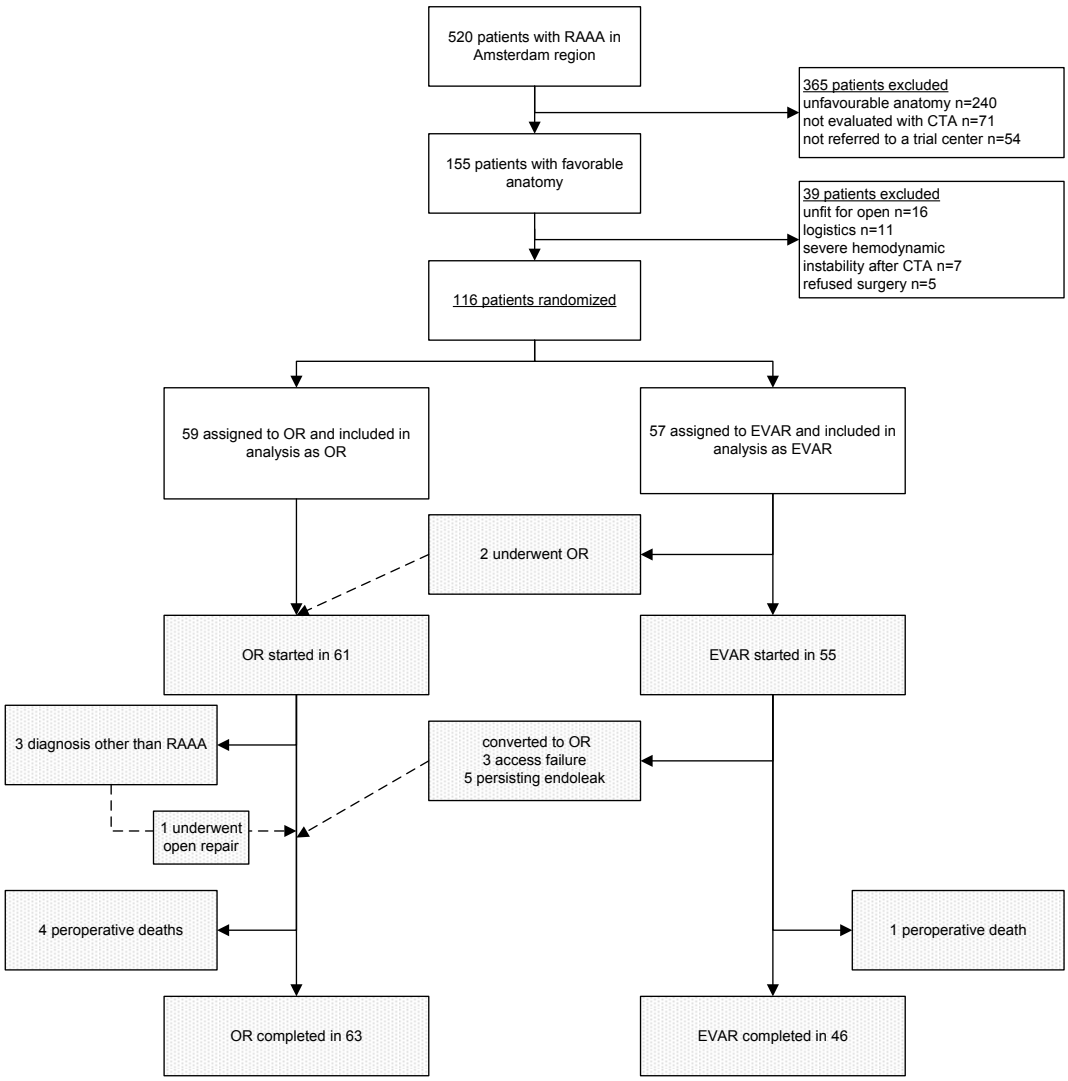
as severe cardiac complications (severe hemodynamic dysfunction necessitating resuscitation, cardiac arrest or fatal outcome), moderate or severe renal insufficiency (temporary or permanent dialysis or permanent renal insufficiency), severe bowel ischemia (bowel resection or fatal bowel ischemia), stroke, graft thrombosis, major amputation, spinal cord ischemia, prosthesis infection or acute reoperation. Visits and questionnaires were scheduled at 30 days, 3 months and 6 months. CTA , abdominal X-ray and Duplex ultra sonography were carried out within 30 days and 6 months after randomization. Long-term mortality rate for all patients after 6 months was derived from their status in the communal registry that registers all death certificates in the Netherlands (last search 17-09-2011).
Secondary endpoints were length of hospital and ICU stay, duration of intubation/ventilation, use of blood products, and for EVAR occurrence of endoleaks. Individual composites of the primary endpoint as well as the combined 30-day and in-hospital mortality were also assessed.

Statistical analysis
When designing the study in 2002-3, we expected a primary endpoint rate of 40% after EVAR and 70% after OR[14-16]. To detect an absolute reduction of 30% with a statistical power of 0.80 (β = 0.20) and one-sided significance level of α = 0.05, 2 groups of 40 patients were needed. A one-sided test was used to assess the potential superiority of EVAR. However, during the course of the trial while investigating those patients not fit for randomization, we found infra renal anatomy unsuitable for EVAR to be the single most frequent reason for exclusion[17]. We then postulated that by excluding anatomically EVAR-unsuitable patients, OR would be technically easier and lead to fewer endpoints than initially expected. This consideration resulted in the adjustment of expected primary endpoint rate of patients treated with OR to 65% and an unadjusted endpoint rate for EVAR of 40%. The updated sample size was 2 groups of 56 patients (Nov 2008). The investigators were unaware of the outcomes of each treatment arm when this decision was made.
All analyses were done according to the intention-to-treat principle. The absolute risk reduction (ARR) with the corresponding 95% confidence interval (95%CI) was reported for all categorical variables. Probability (p) values calculated by Fisher's exact test for categorical data and Mann-Whitney U-test for continuous data were reported and differences were considered significant at a cut-off point of 0.05. Survival was estimated with Kaplan-Meier curves and differences in survival were tested with a Mantel-Cox (log rank) test. Tests were done with PSAW statistical software (IBM SPSS release 18.0.2) and Prism (Graphpad Incorporated version 5.01).

RESULTS

Recruitment
Between April 2004 and February 2011, 520 patients with an rAAA presented at the 10 participating hospitals and 466 (90%) were admitted to one of the three trial centers. In 395 of these 466 patients (85%) the presence of an rAAA was confirmed with CTA. In 240 patients (61%) the anatomy was unsuitable for EVAR constituting the main reason for exclusion (*Figure* 1). Thirty-nine patients were excluded for other reasons (*Figure 1)*, the remaining 116 patients were randomized to EVAR or OR. Baseline clinical characteristics of the randomized patients were similar in both treatment groups (*Table 2)*. Forty-four patients (38%) were initially seen at another hospital and transferred to a trial center, 28 patients (24%) were hemodynamically unstable before arrival at the emergency room, and 14 patients (12%) were hemodynamically unstable in the hospital.

Figure 1 Flow diagram



Participant flow diagram of all patients with an rAAA presenting throughout the Amsterdam region. Follow-up of all 116 patients included in the randomized trial was completed and patients were analyzed for primary outcome in their assigned treatment arm. Procedural details showing cross-over before surgery, conversion during surgery and deaths during surgery are displayed. Three patients were diagnosed with another disease as well as non-ruptured aneurysm. OR, open repair, EVAR, endovascular aneurysm repair, CTA, computed tomograpic angiography.

Table 2, Patient characteristics

	EVAR n=57	OR n=59
Male - n	49 (86%)	50 (85%)
Mean age – yrs (95% CI)	74.9 (72.3-77.5)	74.5 (72.2-76.8)
Referral		
General practitioner	20 (35%)	22 (37%)
Ambulance services	16 (28%)	13 (22%)
Regional hospital	17 (30%)	19 (32%)
Hospital outside trial region	3 (5%)	5 (8%)
Self-presentation	1 (2%)	0
During transport		
Hemodynamically stable	33 (58%)	37 (63%)
Controlled hypotension	8 (14%)	10 (17%)
Hemodynamically unstable	16 (28%)	12 (20%)
Intubated	1 (2%)	1 (2%)
Unresponsive	1 (2%) +	3 (5%)
Cardiopulmonary resuscitation	2 (4%)	3 (5%)
First known systolic blood pressure (median mmHg	100	96
First known diastolic blood pressure (median mmHg	60	60
In hospital		
Stable	30 (52%)	28 (47%)
Controlled hypotension	21 (37%)	23 (39%)
Hemodynamically unstable	6 (11%)	8 (14%)
Cardiopulmonary resuscitation	2 (4%) +	2 (3%)
Intubated	4 (7%)+	3 (5%) +
Patients with first known systolic blood pressure <80 mmHg	11 (19%)	12 (20%)
First known systolic blood pressure hospital median mmHg	120	119
First known diastolic blood pressure hospital median, mmHg	70	68
First systolic blood pressure in operating room median mmHg	120	110
First diastolic blood pressure in operating room, median mmHg	62	60
Time until surgery – minutes, median (IQR)	74 (39-126)*	45 (35-70)*
Medical history, SVS risk factor 2&3		
Diabetes	2 (4%)	1 (2%)
Unknown	4 (7%)	2 (3%)
Hypertension	13 (23%)	10 (17%)
Unknown	7 (12%)	7 (12%)
Smoker	23 (40%)	20 (34%)
Unknown	12 (21%)	9 (15%)
Hyperlipidemia	13 (23%)	19 (32%)
Unknown	8 (14%)	4 (7%)
Renal disease	1 (2%)	2 (3%)
Unknown	5 (9%)	4 (7%)
Pulmonary disease	7 (12%)	3 (5%)
Unknown	10 (18%)	6 (10%)
Carotid disease	16 (28%)	10 (17%)
Unknown	6 (11%)	3 (5%)
Cardiac disease	16 (28%)	14 (24%)
Unknown	6 (11%)	3 (5%)
Diagnostics in emergency room		
Hemoglobin mean mmol/L (g/dl)	7.15 (11.53)	7.08 (11.41)
Creatinine median µmol/L (mg/dl)	111.5 (1.26)	104.0 (1.17)
pH – median	7.4*	7.3*
pO2 – median Kpa (mmHg)	19.9 (149)	26 (195)
pCO2 – mean Kpa (mmHg)	4.77 (36)	4.75 (36)
Bicarbonate – mean	20.18*	18.11*
Base-excess – mean	-4.49	-5.98

This table displays preoperative characteristics of included patients assigned to either OR (n=59) or EVAR (n=57). (*) denotes a statistically significant difference between both treatment arms between p=0.05 and p=0.01. (+) denotes missing data of one patient.

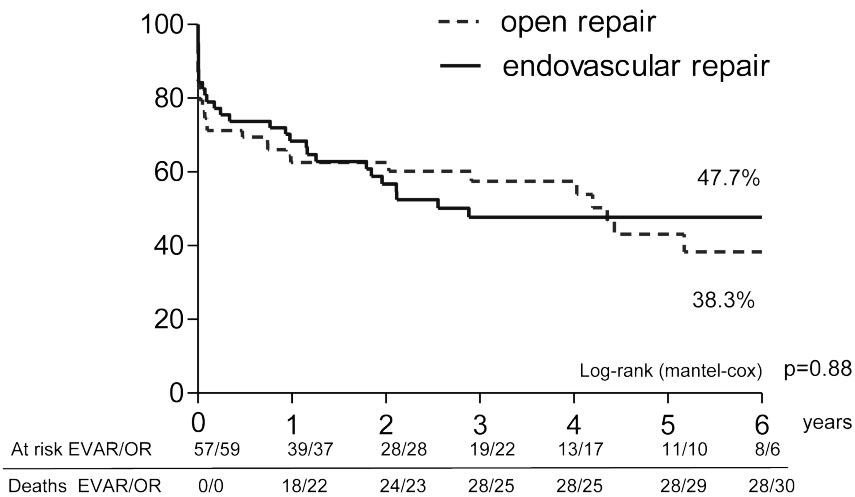
Procedural data

Two of fifty-seven patients assigned to EVAR were immediately treated with OR (1 cardiac arrest, 1 endovascular graft not available). Eight EVAR patients (14%) were converted to OR because of iliac access failure (3), or persisting endoleak (5). A further 4 needed additional laparotomy without endograft removal (2 type II endoleak with persistent bleeding, 2 abdominal compartment syndrome) *(Table 3, Fig 1)*. An aortic occlusion balloon was used in 4 patients randomized to EVAR. In 26 of 57 patients (46%), EVAR was started under local anesthesia, in 13 of these patients general anesthesia was needed at a later stage (5 conversion to OR and 8 discomfort). In 3 patients assigned to OR no rupture was found. The diagnosis in these patients was a combination of a non-ruptured aneurysm with respectively, a bleeding liver tumor, Crohn's disease, and inflammatory aneurysm. The patient with an inflammatory aneurysm was treated directly by OR, the other two by EVAR within a week.

Outcomes

The primary endpoint rate, combined death and severe complications at 30 days was 42% (24 of 57) in the EVAR group vs. 47% (28 of 59) in the OR group (ARR of 5.4%, 95% CI -13 to +23%) (*Table 3)*. The 30-day mortality was 21% (12 of 57) in patients assigned to EVAR vs. 25% (15 of 59) in those assigned to OR (ARR 4.4%; 95%CI -11 to +20%), whereas combining 30-day and in-hospital mortality resulted in a mortality rate of 28% (16 of 57) for EVAR vs. 29% (17 of 59) for OR, (ARR 0.7%; 95%CI: -16 to +17%).

Figure 2 Long term survival



Long term survival curves of patients randomized to EVAR (line) and OR (dotted line). Follow-up in years is displayed along the horizontal axis and survival percentage along the vertical axis. Patients at risk are shown in the table with the cumulative deceased patients below. A Mantel-Cox analysis showed no significant difference at any time during follow-up.

Of the individual composites of the primary endpoint, only moderate and severe renal insufficiency, defined as temporary or permanent dialysis, occurred significantly less often in the EVAR group (6 vs. 18 patients, ARR 20%, 95% CI 6–34%). Although the sum of the number of severe complications in patients assigned to EVAR was less (32 vs. 57), there was no statistically significant difference in individual complications other than renal insufficiency *(Table 3).* The composite rate of death and severe complications at 6 months after randomization was 46% (26 of 57) for EVAR vs. 47% (28 of 59) for OR (ARR 1.8%; 95% CI -16 to +20%) *(Table 3)*. Median long term follow-up was 1533 days (IQR: 780-2285 days). There were no significant differences in mortality between treatment groups at any point in time (p=0.88) *(Figure 2).*

Table 3 Primary Endpoint

Outcome at 30 d	**EVAR (57)**	**OR (59)**	**p**	**ARR (95% CI)**
Primary composite endpoint ±	24 (42%)	28 (47%)	0.58/0.35*	5% (-13 to + 23%)
Mortality	12 (21%)	15 (25%)	0.66	4% (-11 to + 20%)
Severe complications	18 (32%)	22 (37%)	0.56	6% (-12 to + 23%)
Severe cardiac complications	4 (7%)	2 (3%)	0.43	-4% (-12 to + 5%)
Renal insufficiency, moderate or severe	6 (11%)	18 (31%)	0.01	20% (6% to 34%)
Severe bowel ischemia	2 (4%)	5 (8%)	0.44	5% (-4 to + 14%)
acute reoperation	13 (23%)	12 (20%)	0.82	-3% (-17 to + 13%)
Stroke	-	2 (3%)	0.49	3% (-1 to + 8%)
Graft infection with graft removal	-	-	-	
Severe graft occlusion	-	1 (2%)	1.00	2% (-2 to + 5%)
Major amputation	-	3 (5%)	0.24	5% (-5 to + 11%)
Spinal chord ischemia	1 (2%)	-	0.49	-2% (-5 to + 2%)
Outcome at 6 months				
Primary composite endpoint	26 (46%)	28 (47%)	0.85	2% (-16 to + 20%)
of which <30 days or in-hospital	25 (44%)	28 (47%)	0.71	4% (-15 to + 22%)
Mortality	16 (28%)	18 (31%)	0..84	2% (-14 to + 19%)
of which <30days or in-hospital	16 (28%)	17 (29%)	1.00	1% (-16 to + 17%)
Severe complications	19 (33%)	22 (37%)	0.71	4% (-13 to + 21%)
Severe cardiac complications	5 (9%) +	3 (5%) +	0.48	-4% (-13 to + 6%)
Renal insufficiency, moderate or severe	6 (11%)	18 (31%)	0.01	20% (6% to 34%)
Severe bowel ischemia	2 (4%)	5 (8%)	0.44	5% (-4 to + 14%)
Acute reoperation	14 (25%) +	12 (20%)	0..66	-4% (-19 to + 11%)
Stroke	-	2 (3%)	0.49	3% (-1 to +8%
Graft infection with graft removal	1 (2%) +	-	0.49	-2% (-5 to +2%)
Severe graft occlusion	-	1 (2%)	1..00	2% (-2 to +5%)
Major amputation	-	3 (5%)	0.24	5% (-5 to +11%)
Spinal chord ischemia	1 (2%)	-	0.49	-2% (-5 to +2%)
Total number of acute reoperations**	17 (30%)	25 (42%)		
Total number of severe complications**	32	57		

*This table displays primary outcomes of 57 patients assigned to EVAR and 59 patients assigned to OR. All outcomes were analyzed as intention- to- treat. Only the most severe event was counted in the composite primary endpoint The reported p value with (*) is the additional one-sided analysis. ARR denotes absolute risk reduction and the corresponding 95 percentage confidence intervals (95%CI) are supplied. All individual composites of the primary endpoint are reported as the number of patients with that particular complication, except those denoted by **, in which the total sum of the number of that complication is reported. Outcome is reported as on 30 days and 6 months, and categories of patients in whom a new severe complication occurred after 30 days are marked by a +.*

Secondary Outcomes

On secondary outcomes, the median total hospital stay was 9 days (4-21) in patients assigned to EVAR vs. 13 days (5-21) in patients assigned to OR, p=0.57. Seventy-seven percent (77%, 44 of 57) of patients assigned to EVAR were admitted to the ICU from the operating room vs. 90% (53 of 59) of patients assigned to OR (ARR 13%; 95% CI -0.7 to +26%). The median stay of all patients admitted to the ICU was 42 hours (20-114) in patients assigned to EVAR vs. 60 hours (22-191) in patients assigned to OR p=0.24. Although significantly fewer patients assigned to EVAR needed postoperative mechanical ventilation,69% (39 of 57) in patients assigned to EVAR, compared to 92% (54 of 59) in patients assigned to OR (ARR 23%; 95% CI 9–37%), the median duration of ventilation for all ventilated patients did not significantly differ (20 hours (5-60) vs. 15 hours (7-102) hours, p=0.74). The estimated median blood loss during surgery was significantly lower in patients assigned to EVAR, 500 ml (IQR 200-1375) vs. 3500 ml (IQR 1000-4600) in patients assigned to OR, p<0.001) Intraoperatively blood products were used in 79%(45 of 57) of the patients assigned to EVAR and in 95% (56 of 59) of the patients assigned to OR (ARR 16%; 95% CI 4–28%). Autologous blood was used in 19% (10 of 57) of the patients assigned to EVAR and in 73% (43 of 59) of the patients assigned to OR (ARR 55%; 95% CI 40–70%, p<0.001). All 10 EVAR patients in whom autologous blood was given, had crossed over to OR. There was no difference between groups in total blood products administered during hospital stay (*Table 3*). Operating time (median 140 vs. 125 minutes, p=0.014) and operating room stay (median 185 vs. 157 minutes, p=0.001) were longer for EVAR than for OR *(Table 3*). Endoleaks were diagnosed during the initial EVAR procedure in 24 patients (42%). In 9 patients the endoleak was managed with an additional endovascular procedure, in 5 it necessitated conversion to open repair and in two patients a type II endoleak was treated by laparotomy without graft removal. In eight patients (14%) the endoleak was not resolved during initial surgery (4 type I and 4 type II endoleaks). During follow-up, 9 new endoleaks were discovered (5 type I and 4 type II). Of all 9 patients with new type I endoleaks, 5 needed additional OR, 2 died, 1 needed additional EVAR and in one patient the endoleak resolved spontaneously. No additional procedures were performed for 8 patients with type II endoleaks.

Regional rAAA cohort

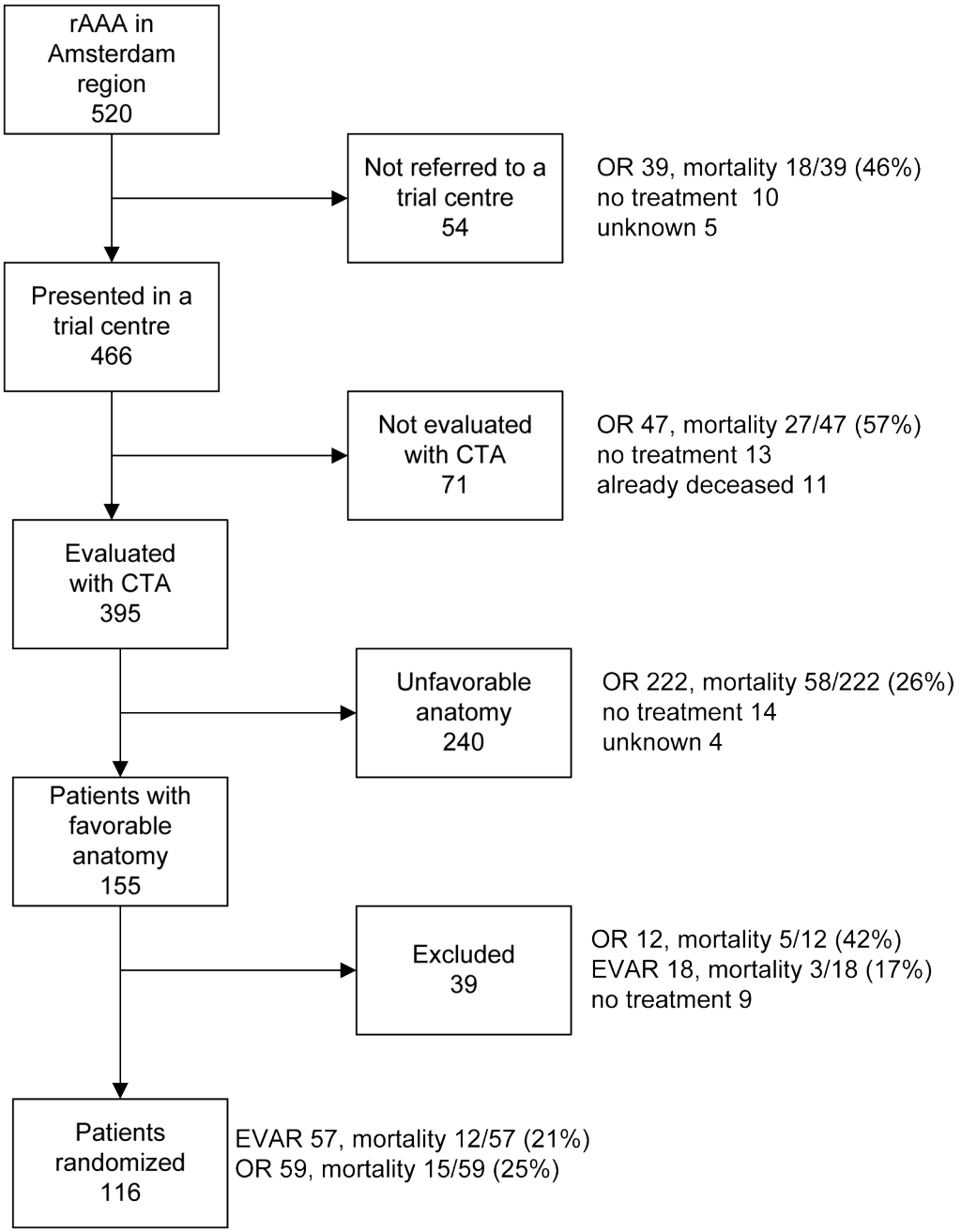
Of the 404 patients excluded from the randomized trial, the mean age (75.3 years) and sex distribution (80% male) did not differ significantly from the randomized patients (p=0.59 and p=0.10). Most excluded patients (320) were treated with OR and 18 patients were treated with EVAR because they were unfit for OR or because of logistic problems. Fifty-seven patients were not operated on. In 9 patients, no records could be traced (*Fig.3)*. The 30-day mortality of all patients that underwent operative treatment, either EVAR or OR, was 30% (138 of 454 patients 95% CI 26–35%). The 30-day mortality rate of non-randomized patients treated with EVAR was 17% (3 of 18 patients, 95% CI 4–41%), and for non-randomized patients treated with OR it was 34% (108 of 320 patients, 95% CI 29–39%) (9 unknown outcome) *(Fig. 3)*. In patients evaluated with CTA with anatomy unfavorable for EVAR, the 30-day mortality of OR in trial centers was 26% (58 of 222 patients, 95% CI 20–32%) *(Fig 3).*

Table 4, Secondary endpoints

	EVAR (57)	OR (59)	p	ARR (95%CI)
Intensive care				
Directly admitted to the ICU	44 (77%)	53 (90%)	0.08	13% (-1 to + 26%)
Admitted to MCU or recovery room only	8 (14%)	2 (3%)	0.05	-11% (-21 to -1%)
First MCU or recovery, later ICU	4 (7%)	-	0.06	-7% (-14 to + 0.4%)
Death during surgery	1 (2%)	4 (7%)	0.36	5% (-2 to + 12%)
Admitted to ICU during hospital stay	48 (84%)	53 (90%)	0.42	6% (-7 to + 18%)
Postoperative mechanical ventilation				
Number of patients ventilated	39 (68%)	54 (92%)	0.002	23% (9 to 37%)
Reintubation after extubation	2 (4%)	6 (10%)	0.27	7% (-2 to + 16%)
All patients, median hours (IQR)	5 (0-29)	11 (4-98)	0.14	
Ventilated patients, hours median (IQR)	20 (5-60)	15 (7-102)	0.74	
Length of ICU stay				
All patients, hours (IQR)	28 (11-87)	48 (15-161)	0.14	
Patients admitted to ICU, hours (IQR)	42 (20-114)	60 (22-191)	0.24	
Length of hospital stay				
All patients, days (IQR)	9 (4-21)	13 (5-21)	0.57	
Procedural				
Duration of surgery – minutes median (IQR)	140 (120 - 190)	125 (94-154)	0.014	
Time in operating room– minutes median (IQR)	185 (160-236)	157 (136-194)	0.001	
Estimated blood loss – milliliters median (IQR)	500 (200-1375)	3500 (1000 - 4600)	<0.001	
Blood products during surgery				
Any blood products administered - n	45 (79%)	56 (95%)	0.06	16% (4 to 28%)
Autologous blood – ml, median (IQR)	0 (0 – 0)	500 (0-1425)	<0.001	
Homologous blood – units, median (IQR)	3.5 (0-6)	4 (2-7)	0.10	
Fresh frozen plasma – units, median (IQR)	0 (0-2)	2 (0-4)	0.007	
Platelets – units, median (IQR)	0 (0-0)	0 (0-1)	0.97	
Any blood product – units, median (IQR)	4 (0-8)	9 (4-14)	0.02	
Total blood products during stay				
Homologous blood – units, median (IQR)	6.5 (3-12.5)	8 (5-13)	0.45	
Fresh frozen plasma – units, median (IQR)	2 (0-7)	4 (2-8)	0.04	
Platelets – units, median (IQR)	0.5 (0-1)	1 (0-2)	0.16	
Any blood product – units, median (IQR)	9 (4-20)	13 (8-22)	0.148	

This table displays secondary outcomes of 57 patients assigned to EVAR and 59 patients assigned to OR. All outcomes are analyzed as intention-to-treat. ARR denotes absolute risk reduction and the corresponding 95 percentage confidence intervals (95%CI) are supplied.

Figure 3 Regional Outcome



Outcome of all patients with rAAA presented throughout the Amsterdam region. The type of surgery; open repair (OR), endovascular repair (EVAR) or no intervention and corresponding 30-day mortality rate after surgery are displayed.

DISCUSSION

This study showed no significant difference in the primary endpoint of combined death and severe complications between EVAR and OR at 30 days after surgery: 42% vs. 47%. Although the primary endpoint rate for EVAR was close to our initial estimate (42% vs. 40%), the outcomes after OR were much better than anticipated (47% vs. 65%). In particular the 30-day OR mortality of 25% in our study was much lower than expected when taking into account a previous meta-analysis that showed a mortality of 48.5%[1]. Conceivably, selecting patients both hemodynamically fit for CTA and anatomically suitable for EVAR could explain this difference. However, closer inspection of the data reveals that only 17% of 466 patients analyzed in a trial center were excluded because of hemodynamic instability (71 no CTA + 7 instability following CTA/466 analyzed in trial centers) *(Fig 1),* while a 25-59% exclusion rate is common in other studies[7,18]. The fact that hemodynamic instability was not an exclusion criterion per se is also reflected by the 20% (23/116) hypotensive (P-systolic ≤80mmHg) patients in our trial (*Table 2)*. This is concordant with 20-28% hypotensive patients observed in pooled data, although the definition of hemodynamic stability varies greatly in individual studies[18-21]. Thus, selection of hemodynamically stable patients is not likely to be the explanation for the low mortality following OR in our randomized study.

By including those patients with anatomy suitable for EVAR only, i.e. adequate length and diameter of the infra renal neck and non-aneurysmatic, non-stenotic iliac arteries, we may have created a cohort of patients that is easier to treat by open repair [22]. This theory is not supported by the 30-day death rate of 26% of OR in non-randomized patients with unfavorable anatomy we observed in the cohort *(Fig.3)* which is low compared with other series [1, 7, 15, 23, 24].

We realize the large confidence interval regarding the risk difference for the primary endpoint, leaving room for uncertainty in the final interpretation of the study. However, we stress that the point estimate for the primary endpoint of EVAR is in line with the results from longitudinal cohort studies [18-21]. The question is therefore what the explanation is of the low point prevalence for the primary endpoint of open repair, which possibly also led to the fact that we did not observe the hypothesized risk difference between the two strategies. An explanation could be the introduction of the round-the-clock acute aneurysm service in the greater Amsterdam region, centralization of aneurysm care and the routine preoperative CTA that influences operative strategy. This is underlined by the 30-day mortality rate of 30% (95% CI 26–35%) in the entire cohort for all 520 patients who underwent operative treatment *(Figure 3)* and compares favorably with a population-based analysis of in-hospital operative mortality of rAAA in the Netherlands that showed 41% (95% CI 40–42%) mortality[25]. It is desirable that the role of centralization is further confirmed in other studies since this might have important implications for the care of these patients.

Although this study was not powered on individual composites of the primary endpoint, moderate and severe renal insufficiency, defined as the need for either temporary or permanent dialysis, were observed significantly less often after EVAR than after OR *(Table 3).* Supra renal clamping in OR patients might have an influence on this outcome since 7 out of the 14 OR randomized patients that were operated with suprarenal clamping, developed renal insufficiency. The threshold for dialysis was not strictly defined but rather a decision by intensive care physicians based on serum creatinine levels, urine production and the overall condition of the patient.

Outcomes that are influenced by physician judgment such as the decision for dialysis, are likely to be influenced by knowledge of the treatment group assignment and therefore, the dialysis threshold could have been lower for patients treated with OR than EVAR.
The intraoperative conversion rate from EVAR to OR of 14% (8/57) was high compared with 4-6% reported in observational studies[18-21]. Early conversion is a predictor for poor outcome and if reduced, might lead to lower death and severe complication rates after EVAR. Conversions from EVAR to OR in this study were caused by access failure (3) and persisting type I endoleaks (5). Results of EVAR will thus improve by reducing the conversion rate which is by selecting patients with more favorable anatomy.
In this trial we deliberately chose to use an aorto-uni-iliac endoprosthesis with contra lateral occluder and a femoral-femoral cross over bypass. The primary goal of surgery for rAAA is to stop bleeding from the ruptured aorta. The use of an aorto-uni-iliac device is a fast and easy way to reach hemostatis and was therefore preferred over the use of a more complex bifurcated endovascular graft system. The mortality rates in the non-randomized cohort patients, 17% for EVAR and 34% for OR, illustrate the difficulty in interpreting data from observational comparisons of these approaches highlighting the need for randomized controlled trials such as this.

Potential limitations of our study merit consideration. First, only 22% of all patients with rAAA in the trial region (116/520) were included in the randomized trial. The main reason for exclusion was unsuitable anatomy (46%, 240/520). Because of disappointing low patient inclusion early in the trial, the high exclusion rate was analyzed at an earlier stage [17]. Unsuitable infra renal neck anatomy with absent or very short necks and very wide necks was the main reason for not including patients. This remained a major reason for rejecting patients throughout the trial. It appears that ruptured aneurysms have shorter and wider infrarenaal necks. The minimum required neck-length for EVAR was 10 mm and the maximum allowed neck-diameter was 34 mm. Newer endovascular devices may have a broader applicability. Second, the low inclusion rate combined with the time span it took to complete the trial resulted in a yearly case load of 25 rAAA patients with only 5-7 randomized patients per trial center, while only 10% of all rAAA patients in the entire region of 1.2 million inhabitants were not referred to a trial center. One may argue that results for EVAR in particular might have improved if more procedures had been performed per year. Third, intraoperative cross-over from EVAR to OR occurred in 8 patients *(Fig.1)* and 6 patients required additional surgery because of a postoperatively discovered new type I endoleak. These 14 patients were responsible for a large percentage of deaths and complications in the EVAR group. Conversion from EVAR to OR, probably by selecting specifically those patients with ideal anatomy for EVAR, should be avoided. Use of newer endovascular devices with potentially fewer conversions might also have a positive effect on EVAR outcome. Fourth, although the unilateral endovascular graft is easy to use, the number of type I endoleaks and thus the number of conversions was high. It is to be expected that newer generations of endovascular grafts will perform better. Fifth, after analysis of our results, it could be concluded that the study is underpowered with regard to the primary endpoint. A very large trial would be needed to definitively demonstrate if EVAR is superior.

In conclusion, the hypothesized difference in mortality and severe complications between EVAR and OR was not observed. EVAR and OR in patients with rAAA give equivalent results in patients whose anatomy and physical condition makes them amenable to either approach. Mortality for OR was much lower than expected, which could be explained by optimization of logistics, preoperative CT-imaging and centralization of care in centers of expertise.

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