Evaluating abdominal aortic aneurysm and carotid artery surgery in the Netherlands: variations in indication, treatment and outcomes measures

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CHAPTER 5

Patients with a Ruptured Abdominal Aortic Aneurysm are Better Informed in Hospitals with an 'EVAR-preferred' Strategy: An Instrumental Variable Analysis of the DSAA

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ABSTRACT

Background and objective

While several observational studies suggested a lower postoperative mortality after minimal invasive endovascular aneurysm repair (EVAR) in RAAA-patients compared to conventional open surgical repair (OSR), landmark RCTs have not been able to prove the superiority of EVAR over OSR. RCTs contain a selected, homogeneous population, influencing external validity. Observational studies are biased and adjustment of confounders can be incomplete. Instrumental variable (IV)-analysis (pseudo-randomization) may help to answer the question if ruptured abdominal aortic aneurysm (RAAA) patients have lower postoperative mortality when undergoing EVAR compared to OSR.

Methods

Observational study including all RAAA-patients, registered in the Dutch Surgical Aneurysm Audit between 2013-2017. The risk difference (RD) in postoperative mortality (30-days/in-hospital) between patients undergoing EVAR and OSR was estimated, in which adjustment for confounding was performed in 3 ways: linear model adjusted for observed confounders, propensity-score-model (multivariable-logistic-regression analysis) and IV-analysis (two-stage-least-square regression), adjusting for observed and unobserved confounders, with the variation in percentage of EVAR per hospital as the IV-instrument.

Results

2419 RAAA-patients (1489 OSR, 930 EVAR) were included. Unadjusted postoperative mortality was 34.9% after OSR and 22.6% after EVAR (RD 12.3%, 95%CI 8.5-16%). The RD, adjusted for observed confounders using linear regression analysis and propensity score analysis was respectively 12.3% (95%CI 9.6-16.7%) and 13.2% (95%CI 9.3-17.1%) in favor of EVAR. Using IV-analysis, adjusting for observed and unobserved confounders, RD was 8.9% (95%CI -1.1-18.9%) in favor of EVAR.

Conclusion

Adjusting for observed confounders, RAAA-patients undergoing EVAR had a significant better survival compared to OSR in a consecutive large cohort. Adjustment for unobserved confounders resulted in a clinical relevant RD. An 'EVAR-preference-strategy' in RAAA-patients could result in lower postoperative mortality.

INTRODUCTION

In the elective treatment of abdominal aortic aneurysms (AAA), minimal invasive endovascular aneurysm repair (EVAR) has proven to be superior to conventional open surgical repair (OSR) in the short/mid-term, with a lower postoperative mortality and morbidity.[1] Several randomized controlled trials (RCTs) failed however to establish superiority of EVAR in patients with a life-threatening ruptured abdominal aortic aneurysm (RAAA), and no significant differences in immediate postoperative survival were found.[2-5] A drawback of these trials is that they might contain only a selected population of RAAA patients, which hampers the external validity (generalizability) of the results.[6] Additionally, randomization methods were different between these trials and some were underpowered, affecting the internal validity.[6] Large observational studies, adjusting for known confounders, suggested a lower postoperative mortality in RAAA patients treated with EVAR.[7-9]. However, observational studies suffer from indication bias by important prognostic baseline differences between patients and the adjustment of confounders can be incomplete as clinical and social interactions in the diagnostic-treatment pathway are often not measured.[10] For example, anatomic characteristics of the aneurysm or the surgeon's preference for one or the other surgical procedure may influence the choice of treatment in RAAA patients. Using large databases with consecutive patients and different treatment preferences of hospitals, treatments, as applied in daily practice, can be compared with pseudo-randomization techniques. Instrumental variable (IV) analysis is such a technique, as it is developed to control the unobserved and/or unmeasured bias between different treatment groups and tries to find a randomized experiment embedded in an observational study, to subsequently estimate the difference in treatment effect.[11]

The aim of this study was to investigate if patients with a RAAA registered in the nationwide and compulsory Dutch Surgical Aneurysm Audit (DSAA) have a better postoperative survival when treated with EVAR compared to OSR, correcting for observed confounders with standard statistical methods and unobserved confounders with IV analysis (pseudo-randomization). Secondly, the postoperative mortality between hospitals with a high and low preference for EVAR were compared.

METHODS

Study design

This is a prospective observational study, which examines if patients with a RAAA have a lower postoperative mortality after EVAR compared to OSR, adjusting for observed and unobserved confounders.

Data source, participants and setting

The dataset was retrieved from the Dutch Surgical Aneurysm Audit (DSAA). This nationwide and compulsory audit started in 2013 and registers all patients, including patient and treatment characteristics, with an aortic aneurysm and/or dissection undergoing surgical treatment in the Netherlands. We included all patients with a primary RAAA registered in the DSAA between January 2013 and December 2017. All patients with a thoracic aortic aneurysm/dissection, undefined aneurysm/dissection and all patients with a secondary reintervention of a previous aortic aneurysm repair were excluded.
Verification of the DSAA data was carried out in 2015 by a third trusted party, through a random sample of hospitals.[12,13]

Primary outcome

The primary outcome of this study was postoperative mortality, which was defined as mortality within 30 days after surgery or during admission (30-days/in-hospital).

Statistical analysis

Patients were divided in two groups, EVAR or OSR, based on 'start-of-treatment'. Patient characteristics and hospital related factors were compared between the groups, using T-tests and chi-square tests.
Crude postoperative mortality rates between patients treated with EVAR and OSR were compared, using a linear regression model. When considering a binary outcome, it is standard practice to use logistic regression. The effect of EVAR versus OSR will then be estimated as a (log) odds ratio. As we prefer to estimate the effect as a risk difference (RD), we used linear regression.
Subsequently, we used 3 different methods to adjust for confounding when estimating the RD: a linear model adjusted for confounders, a propensity score, i.e. the probability of getting a certain treatment, adjusted for observed confounders, and an IV analysis adjusted for observed and unobserved confounders.

Adjusted linear regression analysis

In order to correct for observed confounders we used a linear regression model to compare adjusted mortality rates between patients treated with EVAR and OSR. Patient characteristics based on V(p)-POSSUM variables, year of surgery and hospital volume of RAAA patients, were entered as co-variables in this model.[14,15]

Propensity score analysis

The propensity score (PS) analysis was carried out in two successive steps. In the first step, a multivariable logistic regression analysis (ENTER model with a p-value at 0.05) for the 'choice of treatment' was performed. The same patient and hospitals characteristics as used in the adjusted linear regression analysis were entered as co-variables in this model.

In the second step a RD was estimated, using a multivariable linear regression analysis for the primary outcome 'postoperative mortality', adjusted for the PS obtained in step 1 and the choice of treatment as co-variables.

Instrumental variable analysis

First, we divided all hospitals in 2 groups with the median %EVAR per hospital as a cut-off point: those with a low %EVAR in RAAA patients (0-37% EVAR) and those with a high %EVAR (38-100% EVAR). We demonstrate the distribution of measured possible confounders between these two groups.

An IV-analysis can be used to estimate the effect of a treatment in observational data, corrected for unobserved confounders. The IV is a factor that highly influences the choice of treatment, but has no independent influence on patient outcome. The IV is thus not related to the prognosis of the patient. An IV-analysis behaves as a pseudo-randomization, in which patients are weighed based on the probability of getting a certain treatment. When using an IV-analysis, one does not compare individual patients with different treatments, but one compares the outcomes of patients with a different chance of getting a certain treatment. The methods of IV-analysis have also been described in detail elsewhere.[11]

When using an IV-analysis to compare postoperative mortality after OSR and EVAR in patients with a RAAA, we had to make two assumptions:

1. There is no association between patient characteristics and the hospital where patients are treated. In the Netherlands, patients with a RAAA are admitted to nearest hospital performing acute AAA surgery.
2. As the Netherlands has a homogeneous care landscape with an overall high quality standard, quality of care is comparable between hospitals performing acute AAA surgery

Based on these assumptions the following analysis was performed. The percentage of RAAA patients treated with EVAR per hospital (%EVAR) (i.e. treatment preference of the hospital), was chosen as the IV. The strength of the IV was tested with a partial F statistic. Subsequently the IV-analysis was performed with a Two-Stage least square (2SLS) model. The co-variables used in this model were the same as in the first step of the PS-analysis. Outcome was reported in a RD between EVAR and OSR. Finally, the IV-model itself was tested with a 'test for weak instruments' and a 'Wu-Hausman test'.

All statistical analyses were performed using R statistical software (version 3.4.0). When data were missing for continues variables used in the regression analyzes, the mean was imputed. Data were most frequently missing for preoperative heart rate (13%) and systolic blood pressure (9.0%).

RESULTS

Participants and descriptive analysis

We identified 2660 RAAA patients operated between January 2013 and December 2017. All patients with a thoracic aneurysm (76, 2.8%), undefined aneurysm (45, 1.7%), revision of a previous aortic aneurysm repair (80, 3.0%) or incomplete data (40, 1.5%) were excluded. A total of 2419 patients were included for analyses, of which 1489 (61.6%) were treated with OSR and 930 (38.4%) with EVAR. Twenty-seven (1.1%) of EVAR patients were converted to OSR and remained in the EVAR group for analysis. The EVAR group consisted of 86% males, compared to 84% of males in the OSR group (p=0.075). EVAR patients were significantly older than OSR patients (75.3 SD 8.8 versus 73.6 SD 7.8, p<.001) and had significantly more often a normal Glasgow Coma Scale (GCS) (72% versus 63%, p<.001). Other differences in co-morbidity and clinical presentation are displayed in table 1. Over the years 2013-2017 there was an increase in the use EVAR from 29% to 46%.

Outcome data and main results

The unadjusted postoperative mortality after OSR was 34.9% (n=519) and 22.6% (n=210) after EVAR. Using an unadjusted linear regression, the RD in postoperative mortality after OSR and EVAR was 12.3%, with a 95% confidence interval (CI) of 8.5-16%.

Case-mix adjusted linear regression analysis

The mortality difference, adjusted for measured confounders was 12.3% (95%CI 9.6-16.7%), in favor of RAAA patients treated with EVAR (table 2.).

Propensity score analysis

Step 1**:** Patient characteristics of RAAA patients associated with receiving EVAR were increased age (odds ratio (OR) 1.03, 95%CI 1.02-1.04), leukocytes between $10.0x10^9$/L-$14.9x10^9$/L (OR 1.26, 95%CI 1.00-1.59) or more than $20x10^9$/L (OR 1.55, 95%CI 1.23-2.14) and current malignancy (OR 1.67, 95%CI 1.02-2.74) (table 3a). Patients with female gender (OR 0.64, 95%CI 0.49-0.83), GCS of 9-11 (OR 0.59, 95%CI 0.35-0.98), GCS <9 (OR 0.34, 95%CI 0.21-0.54) or an unknown GCS (OR 0.67, 95%CI 0.50-0.91), increased aneurysm diameter (OR 0.99, 95%CI 0.98-0.99), systolic blood pressure of <80mmHg (OR 0.73, 95%CI 0.55-0.96), and/or unknown pulmonary status (OR 0.75, 95%CI 0.59-0.97) were less likely to receive EVAR. Additionally, patients operated in hospitals with a higher volume and patients operated in later years of the study were significantly more likely to receive EVAR. Step 2: In RAAA patients the RD, adjusted for the probability of treatment with EVAR (PS for EVAR calculated in step 1), was 13.2% (95%CI 9.3-17.1%) in favor of treatment with EVAR (table 3b).

Table 1. Patient characteristics per surgical treatment

	EVAR		OSR		
	N	%	N	%	
Number of patients	930		1489		
Age (mean, years)	75.3 SD 8.8		73.6 SD 7.8		.000
Sex					.075
Male	802	86%	1244	84%	
Female	128	14%	245	17%	
Year of surgery					.000
2013	122	13%	301	13%	
2014	198	21%	325	21%	
2015	192	21%	321	21%	
2016	205	22%	293	22%	
2017	213	23%	249	17%	
Cardiac state					.039
No abnormalities	385	41%	659	44%	
Peripheral edema, cardiomegaly	68	7.3%	82	5.5%	
Raised CVP, use of coumarin, borderline cardiomyopathy	15	1.5%	18	1.2%	
Medication for hypertension, angina pectoris, diuretics or digoxin	324	35%	465	31%	
Unknown	138	15%	265	18%	
Pulmonary state					.002
No dyspnea	580	62%	904	61%	
Dyspnea	141	15%	205	14%	
Severe Dyspnea	48	5.2%	45	3.0%	
Unknown	161	17%	335	23%	
Malignancy					.002
None	816	88%	1367	92%	
Current	40	4.3%	33	2.2%	
History of malignancy	74	8.0%	89	6.0%	
Last pre-operative ECG					.001
No abnormalities	274	30%	421	28%	
Atrial fibrillation	59	6.3%	68	4.6%	
Ischemia	33	3.5%	43	2.9%	
Other abnormalities	222	24%	292	20%	
Unknown/No ECG performed	342	37%	665	45%	
Diameter (mean, mm)	76 SD 16.0		80 SD 16.6		.000
Hart rate (mean, BPM)	87 SD 21		87 SD 22		.852
Systolic blood pressure (mean, mmHg)	112 SD 33		109 SD 34		.007
Glasgow Coma Scale					.000
GCS 15	673	72%	931	63%	
GCS 12-14	127	14%	206	14%	
GCS 9-11	24	2.6%	56	3.8%	
GCS <9	26	2.6%	114	7.7%	
Unknown	80	9.3%	182	12%	
Preoperative laboratory results					
Hemoglobin (mmol/L)	7.2 SD 1.4		7.3 SD 1.4		.613
Leukocytes (10^9/L)	14.2 SD 5.5		13.6 SD 5.4		.013
Creatinine (mmol/L)	112 IQR 91-133		111 IQR 88-131.5		.195
Sodium					.077

Table 1 continued

	EVAR		OSR		
	N	%	N	%	
Normal sodium	725	78%	1205	81%	
Hypo/hypernatremia	205	22%	284	19%	
Potassium					.493
Normal potassium	763	82%	1205	81%	
Hypo/hyperpotassemia	167	18%	284	19%	

Table 2. Linear regression analysis for postoperative mortality in RAAA patients

	Estimate	SE	p-value
Procedure			
OSR			
EVAR	-0.131	0.018	<0.001
Gender			
Male			
Female	0.025	0.025	0.313
Age			
Age	0.010	0.001	<0.001
Glasgow Coma Scale			
GCS 15			
GCS 12-14	0.089	0.026	0.001
GCS 9-11	0.232	0.049	<0.001
GCS <9	0.190	0.038	<0.001
GCS unknown	0.168	0.029	<0.001
Year of surgery			
2013			
2014	-0.068	0.028	0.013
2015	0.000	0.028	0.990
2016	0.010	0.028	0.724
2017	0.042	0.029	0.148
Volume of ruptured patients in hospital of treatment			
<25			
25-40	-0.005	0.036	0.881
40-55	0.016	0.027	0.546
55-70	-0.021	0.031	0.477
>70	-0.975	0.001	0.014
Aneurysm diameter			
Diameter	-0.001	0.001	0.061
Preoperative systolic blood pressure			
110-139			
>140	-0.035	0.025	0.156
80-109	0.025	0.022	0.258
<80	0.078	0.027	0.004
Preoperative heart rate			
70-79			
80-99	0.010	0.027	0.713
>100	0.013	0.029	0.655
<70	-0.016	0.030	0.596

Table 2 continued

	Estimate	SE	p-value
Creatinine			
<90			
90-109	0.007	0.025	0.790
110-139	0.083	0.024	0.001
>140	0.101	0.028	<0.001
Hemoglobin			
>8.50			
7.5-8.49	-0.038	0.026	0.148
6.0-7.49	-0.022	0.025	0.386
<6	0.026	0.031	0.404
Leukocytes			
<10.0			
10.0-14.9	-0.001	0.022	0.978
15.0-19.9	-0.024	0.027	0.375
>20.0	-0.014	0.032	0.673
Sodium			
Normal sodium			
Hyponatremia	0.023	0.022	0.301
Hypernatremia	0.231	0.071	0.001
Potassium			
Normal potassium			
Hypokalemia	-0.019	0.027	0.489
Hyperkalemia	0.027	0.034	0.418
Malignancy			
None			
Current Malignancy	0.095	0.050	0.059
History of malignancy, curatively treated	0.065	0.034	0.058
Preoperative ECG			
No abnormalities			
Atrial fibrillation (60-90 bpm)	0.084	0.042	0.045
Ischemia (ST depression >2mm at rest)	0.209	0.051	<0.001
Other abnormalities	0.029	0.025	0.252
No preoperative ECG performed	0.080	0.022	<0.001
Cardiac status			
None			
Peripheral edema, cardiomegaly	0.069	0.038	0.070
Raised CVP, use of coumarin, borderline cardiomyopathy	0.050	0.075	0.502
Medication for hypertension, angina pectoris, diuretics or digoxin	0.058	0.020	0.004
Unknown	0.081	0.027	0.003
Pulmonary status			
No dyspnea			
Dyspnea	0.050	0.026	0.038
Severe dyspnea	0.198	0.046	<0.001
Unknown	0.061	0.024	0.013

Table 3a. Propensity score for treatment with EVAR

	Odds	95% CI
Gender		
Male	Ref	
Female	0.64	0.49-0.83
Age		
Age	1.03	1.02-1.04
Glasgow Coma Scale		
GCS 15	Ref.	
GCS 12-14	0.83	0.64-1.08
GCS 9-11	0.59	0.35-0.98
GCS <9	0.34	0.21-0.54
GCS unknown	0.67	0.50-0.91
Year of surgery		
2013	Ref.	
2014	1.48	1.11-1.97
2015	1.45	1.09-1.95
2016	1.61	1.20-2.15
2017	2.15	1.60-2.90
Volume of ruptured patients in hospital of treatment		
<25	Ref.	
25-40	1.26	0.86-1.84
40-55	1.64	1.23-2.18
55-70	1.81	1.32-2.50
>70	1.48	1.08-2.04
Aneurysm diameter		
Diameter	0.99	0.98-0.99
Preoperative systolic blood pressure		
110-139	Ref.	
>140	0.94	0.73-1.20
80-109	0.93	0.75-1.15
<80	0.73	0.55-0.96
Preoperative heart rate		
80-99	Ref.	
>100	0.89	0.68-1.18
70-79	0.99	0.74-1.32
<70	0.98	0.72-1.32
Creatinine		
<90	Ref.	
90-109	1.08	0.84-1.40
110-139	1.13	0.89-1.44
>140	1.12	0.85-1.48
Hemoglobin		
>8.50	Ref.	
7.5-8.49	0.89	0.70-1.26
6.0-7.49	0.88	0.61-1.10
<6	1.05	0.64-1.30
Leukocytes		
<10.0	Ref.	
10.0-14.9	1.26	1.00-1.59

Table 3a continued

	Odds	95% CI
15.0-19.9	1.08	0.82-1.41
>20.0	1.55	1.23-2.14
Sodium		
Normal sodium	Ref.	
Hypo/hypernatremia	1.14	0.94-1.39
Potassium		
Normal potassium	Ref.	
Hypo/hyperkalemia	0.99	0.85-1.15
Malignancy		
None	Ref.	
Current Malignancy	1.67	1.02-2.74
History of malignancy, curatively treated	1.15	0.82-1.61
Preoperative ECG		
No abnormalities	Ref.	
Atrial fibrillation (60-90 bpm)	1.21	0.80-1.83
Ischemia (ST depression >2mm at rest)	1.23	0.74-2.05
Other abnormalities	1.05	0.82-1.34
No preoperative ECG performed	0.86	0.69-1.07
Cardiac status		
None	Ref.	
Peripheral edema, cardiomegaly	1.24	0.85-1.82
Raised CVP, use of coumarin, borderline cardiomyopathy	1.22	0.58-2.57
Medication for hypertension, angina pectoris, diuretics or digoxin	1.07	0.87-1.31
Unknown	1.11	0.84-1.47
Pulmonary status		
No dyspnea	Ref.	
Dyspnea	0.86	0.67-1.11
Severe dyspnea	1.51	0.96-2.37
Unknown	0.75	0.59-0.97

Table 3b. Comparison of mortality in patient treated with OSR and EVAR, corrected for the propensity score

	Beta	Lower 95% CI	Upper 95% CI
Surgical Procedure			
OSR	Ref.		
EVAR	-0.13	-0.17	-0.09
Propensity score for treatment with EVAR	-0.11	-0.03	0.24

Instrumental variable analysis

The percentage of treatment with EVAR in RAAA patients ranged from 0-100% (median: 37% EVAR) between 61 hospitals. 1220 patients were operated in hospitals with a low %EVAR and 1199 patients in hospitals with a high %EVAR. The mean %EVAR in hospitals with a low %EVAR was 25.2% (0-37%) compared to mean of 52.0% (38-100%) in hospitals with a high %EVAR in RAAA patients (p<.001).

Table 4 shows the distribution of observed possible confounders between the two groups

of hospitals. The crude mortality in hospitals with a low %EVAR was 31.1% (380/1220) versus 29.1% (349/1199) in hospitals with a high %EVAR: RD 2.0% (95%CI -1.6–5.7%). To adjust also for unobserved confounders, we used the %EVAR per hospital as an IV (partial F statistic >10). The estimated RD in RAAA patients treated with EVAR, using an IV-analysis (2SLS model), was 8.9% (95%CI -1.1-18.9%) compared to RAAA patients treated with OSR.

Table 4. Distribution of measured confounders between hospitals with a low and high percentage of treatment with EVAR, divided by the median of 37% as cut-off point

	Hospitals with low % EVAR (0-37%)		Hospitals with high % EVAR (38-100%)		
	N = 1220	%	N = 1199	%	P
Surgical procedure					.000
OSR	913	75%	576	48%	
EVAR	307	25%	623	52%	
Year of surgery					.143
2013	218	18%	205	17%	
2014	259	21%	264	22%	
2015	277	23%	236	20%	
2016	254	21%	244	20%	
2017	212	17%	250	21%	
Volume of ruptured patients in hospital of treatment					.000
<25	192	16%	147	12%	
25-40	124	10%	100	8.3%	
40-55	518	43%	426	36%	
55-70	124	10%	301	25%	
>70	262	22%	225	19%	
Gender					.375
Male	1024	84%	1022	85%	
Female	196	16%	177	15%	
Age					.466
Age	74.1 SD 7.9		74.4 SD 8.6		
Pulmonary status					.140
No dyspnea	743	61%	741	62%	
Dyspnea	168	14%	178	15%	
Severe dyspnea	40	3.3%	53	4.4%	
Unknown	269	22%	227	19%	
Cardiac status					.001
None	520	43%	524	44%	
Peripheral edema, cardiomegaly	62	5.1%	88	7.3%	
Raised CVP, use of coumarin, borderline cardiomyopathy	16	1.3%	17	1.4%	
Medication for hypertension, angina pectoris, diuretics or digoxin	384	32%	405	34%	
Unknown	238	20%	165	14%	
Preoperative ECG					.000
No abnormalities	341	28%	354	30%	
Atrial fibrillation (60-90 bpm)	58	4.8%	69	5.8%	
Ischemia (ST depression >2mm at rest)	34	2.8%	42	3.5%	

Table 4 continued

	Hospitals with low % EVAR (0-37%)		**Hospitals with high % EVAR (38-100%)**		
	N = 1220	**%**	**N = 1199**	**%**	**P**
Other abnormalities	224	18%	290	24%	
No preoperative ECG performed	563	46%	444	37%	
Malignancy					.477
None	1108	91%	1075	90%	
Current Malignancy	32	2.6%	41	3.4%	
History of malignancy, curatively treated	80	6.6%	83	6.9%	
Aneurysm diameter (mm)					.253
Diameter	78,7 SD 16,3		78,0 SD 16,4		
Glasgow Coma Scale					.157
GCS 15	789	65%	806	67%	
GCS 12-14	158	13%	175	15%	
GCS 9-11	39	3.2%	41	3.4%	
GCS <9	80	6.6%	60	5.0%	
GCS unknown	145	12%	117	9.8%	
Preoperative systolic blood pressure (mmHg)					.253
110-139	396	33%	387	32%	
>140	260	21%	225	19%	
80-109	385	32%	383	32%	
<80	179	15%	204	17%	
Preoperative heart rate (BPM)					.751
70-79	158	13%	165	14%	
80-99	498	41%	466	39%	
>=100	327	27%	336	28%	
<70	327	19%	232	19%	
Hemoglobin (mmol/L)					.541
>8.50	240	20%	215	18%	
7.5-8.49	310	25%	328	27%	
6.0-7.49	469	38%	450	38%	
<6	201	17%	206	17%	
Leukocytes (10^9/L)					.955
<10.0	273	22%	259	22%	
10.0-14.9	561	46%	558	47%	
15.0-19.9	254	21%	247	21%	
>20.0	132	11%	135	11%	
Creatinine (mmol/L)					.359
<90	306	25%	305	25%	
90-109	280	23%	256	21%	
110-139	401	33%	377	31%	
>140	233	19%	261	22%	
Sodium					.894
Normal sodium	969	79%	961	80%	
Low sodium	233	19%	220	18%	
High sodium	18	1.5%	18	1.5%	
Potassium					.347
Normal potassium	983	81%	985	82%	
Low potassium	150	12%	125	10%	
High potassium	87	7.1%	89	7.4%	

Finally, the test for weak instrument was not rejected, which suggests that the %EVAR per hospital is not a weak instrument. The Wu-Hausman test was rejected, from which we can conclude that the IV-analysis can be used additional to a standard linear regression.

DISCUSSION

Between 2013-2017, 2419 patients underwent RAAA surgery in the Netherlands, of which 62% was treated with OSR and 38% with EVAR. Patients were treated in 61 hospitals, and percentage of treatment with EVAR varied from 0-100%. The crude postoperative mortality after OSR was 34.9% and 22.6% after EVAR. With standard linear regression analysis and PS-analysis adjusting for observed confounders a significant 30 days/in-hospital survival benefit of 12.3% and 13.2% respectively, could been demonstrated for RAAA patients undergoing EVAR, compared to RAAA patients undergoing OSR. Using IV-analysis (pseudo-randomization) to adjust for observed and unobserved confounders, a postoperative survival benefit of approximately 8.9% was seen in EVAR patients. Additionally, patients operated in hospitals with a high %EVAR in RAAA patients had a 2.0% lower crude postoperative mortality compared to patients operated in hospitals with a low %EVAR in RAAA patients.

The landmark trials evaluating treatment strategies in RAAA patients could not show a significant survival benefit after treatment with EVAR compared OSR.[2-5] Respectively for the AJAX, ECAR and IMPROVE trial, mortality differences of 4.0% (OSR 25% vs EVAR 21%, p=0.66), 6.0% (OSR 25% vs EVAR 18%, p=ns), and 2.0% (OSR 37.4% vs EVAR 35.4%, p=0.62) were found. The inclusion of patients and randomization methods turned out to be obstacles in these trials. The AJAX and ECAR trial only included RAAA patients suitable for both surgical techniques, which led to the exclusion of respectively 61% and 80% of all presented RAAA patients.[2-5] Also, the inclusion seemed to be rather conservative. The IMPROVE trial, on the other hand, included all RAAA patients and randomized patients by treatment strategy, which led to many cross-overs especially from the EVAR to OSR group.[3] Some observational studies, using standard statistical methods, comparing mortality between both techniques in RAAA patients, demonstrated significant survival benefits after treatment EVAR, varying from 6% to 33%.[7-9,16,17] These results are in line with the 12.3% adjusted mortality difference in our study. However, other observational studies did not establish a significant mortality difference between OSR and EVAR.[18-20] The results of observational studies can be biased due to missing or incomplete adjustment for confounding. PS-methods are previously used to control for the selection bias in RAAA patients, which confirmed a postoperative survival benefit for RAAA patients treated with EVAR.[21,22] Gunnarsson et al. suggested that besides differences in baseline characteristics, the primary treatment strategy of a hospital in RAAA patients could influence the results of the comparison between EVAR

and OSR.[23] However, they found no association with outcome and EVAR preference, but they only used conventional logistic regression analysis adjusting for observed confounders. IV-methods have long been used in economic studies and are being increasingly used in health studies.[11] In studies of various medical specialties, this technique has been used to control for unobserved confounders, such as treatment preference of a physician, when comparing treatments.[10,24-27] IV-analysis is particularly useful when large differences in treatment strategy exists. This applies for instance to RAAA care in the Netherlands, where the percentage of treatment with EVAR varied from 0 to 100% between hospitals.

With the use of IV-analysis in RAAA patients undergoing surgical treatment in the Netherlands, a survival benefit of 8.9% in EVAR patients compared to OSR patients was established. However, the CIs were wide (-1.1%-18.9%) resulting in a non-significant RD. Wide CIs are inherent to IV-analysis, as it compares the outcome of patients with a different chance of getting a certain treatment, instead of comparing the outcome of individual patients. In our study, we used the %EVAR per hospital as the IV, by which data was aggregated on the level of the 61 RAAA hospitals in the Netherlands and therefore resulted in a RD with broad CIs. IV-analyzes are particularly useful in larger cohorts, in which more patients with a different chance of receiving a certain treatment (i.e. hospitals) can be identified. International collaboration and the merging of national datasets might be useful for repeating this analysis and could possibly result in a more precise estimation.

The mortality difference resulting from our IV-analysis, represents the difference in mortality between the situation when all patients were treated with EVAR compared to the situation where all patients were treated with OSR. The daily practice is obviously more differentiated, as not all RAAAs are anatomically suitable for treatment with EVAR.

The current mean treatment ratio in RAAA patients in the Dutch population is 37% EVAR versus 63% OSR. The EVAR percentage is relatively high compared to Denmark (8.2%) and Norway (21%), and more comparable to Sweden (30%) and the United Kingdom (41%).[28,29] Moreover, the VASCUNET collaboration reported that 23% of RAAA patients was treated with EVAR in the 11 participating countries between 2010-2013.[30] Over time, the percentage of EVAR increased from 29% in 2013 to 46% in 2017. This numbers gives the impression that experience with EVAR in ruptured AAAs and adaptation of the care system to be able to use EVAR in an acute setting, could play a role in the choice for EVAR in these patients. As OSR is less and less performed in the elective setting, there are concerns that experience with the OSR declines. The survival benefit we found in RAAA-patients treated with EVAR could therefore also be the result of the loss of experience with OSR. However, when comparing mortality rates of OSR in RAAA patients of the DSAA, SWEDVASC and the Cochrane review of the trials, respectively 30%, 34% and 37%, the outcome of OSR did not decline over time.[6,23] Moreover, the lower mortality of EVAR in the DSAA (22%) and SWEDVASC (22%) compared to the trials (34%) indicates a possible improvement of EVAR results in RAAA patients. One can speculate that the trials came to early, where the EVAR technique for RAAA was still in development.

When comparing surgical procedures, it is also important to evaluate long-term survival. A meta-analysis of the three randomized trials showed a non-significant trend to lower mortality in EVAR patients after 1-year follow-up.[31] Additionally, the IMPROVE Trial investigators reported a lower overall mortality in EVAR patients at 3-year follow-up (EVAR 48% vs OSR 56%, hazard ratio 0.92, 95%CI 0.75-1.13) and a comparable overall mortality of approximately 60% at 7-years follow-up.[32] Unfortunately, the DSAA cannot provide information on long-term survival. In the future, this may be possible through a link with other population databases.

As the DSAA only registers patients that received surgical intervention, it does not provide information on the number of patients presented with an RAAA who were denied for surgery or died before surgical intervention could take place. When evaluating the outcomes of RAAA care, it would be useful to have this information, as the decision for surgical intervention can differ between hospitals and might be associated with EVAR preference, or not. Hospitals could potentially influence their outcomes by selecting patients for surgical treatment.
In order to use an IV-analysis, two assumptions were made. When comparing two pharmaceutical treatments you can safely state that the quality of the treatment is equal in all hospitals. When comparing surgical treatments, this is more uncertain, as surgeon's skills affects the quality of the treatment. The broad CIs around the RD, which are previously mentioned and inherent to the use of IV-methods, are another limitation. Randomization remains the golden standard, but has other obstacles in comparing results in RAAA patients. Therefore, the IV-method can be a good alternative for this research question, as it tries to find a randomized experiment embedded in an observational study.

Our findings suggest that an EVAR-first strategy in RAAA patients may improve postoperative survival. An EVAR-team must then be available 24/7. This has substantial implications for the organization of RAAA care. Currently there are 61 hospitals in the Netherlands that perform RAAA surgery and improvement of care necessitates further concentration of RAAA care. A new volume standard of at least 40 interventions (elective and/or acute) yearly is set by our National Healthcare Institute and Inspectorate of Healthcare, which will contribute to concentration of RAAA care with 24/7 availability of an EVAR-team.

CONCLUSION

Using standard statistical methods, the postoperative 30-day/in-hospital survival of RAAA patients undergoing EVAR was approximately 12% lower than in those undergoing OSR in a large consecutive series of unselected patients in the DSAA. Additionally, an IV-analysis showed a clinical relevant mortality difference in favor of EVAR patients. By taking both

results into account, it is plausible to think that a strategy with a preference for EVAR in RAAA patients will result in a decreased postoperative mortality.

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