Advances in Abdominal Aortic Aneurysm Care

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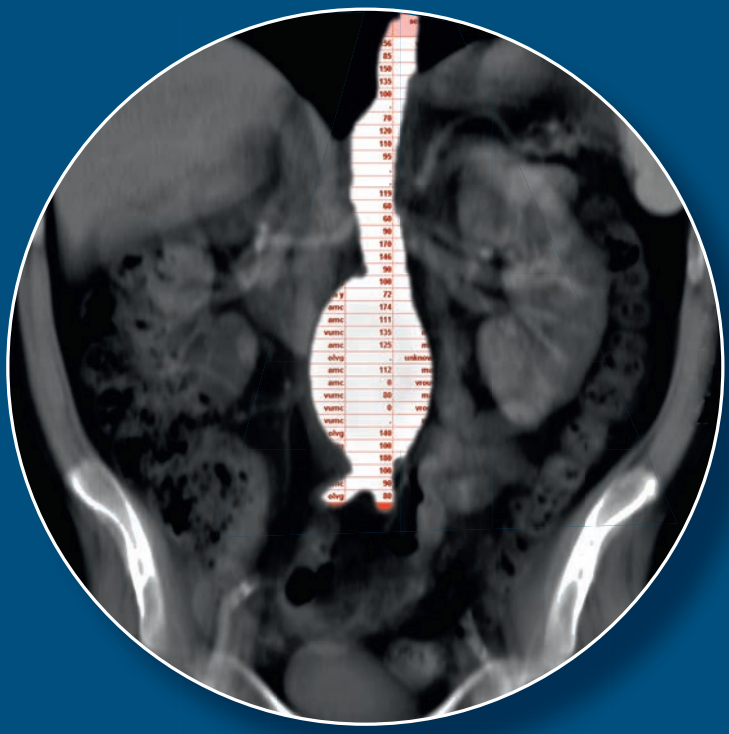
Towards personalized, centralized and endovascular care



Sytse C. van Beek

Advances in Abdominal Aortic Aneurysm Care

Towards personalized, centralized and endovascular care

door Sytse Cornelis van Beek

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Advances in Abdominal Aortic Aneurysm Care

Towards personalized, centralized and endovascular care

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D. C. van den Boom

ten overstaan van een door het college voor promoties ingestelde

commissie, in het openbaar te verdedigen in de Agnietenkapel

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door Sytse Cornelis van Beek

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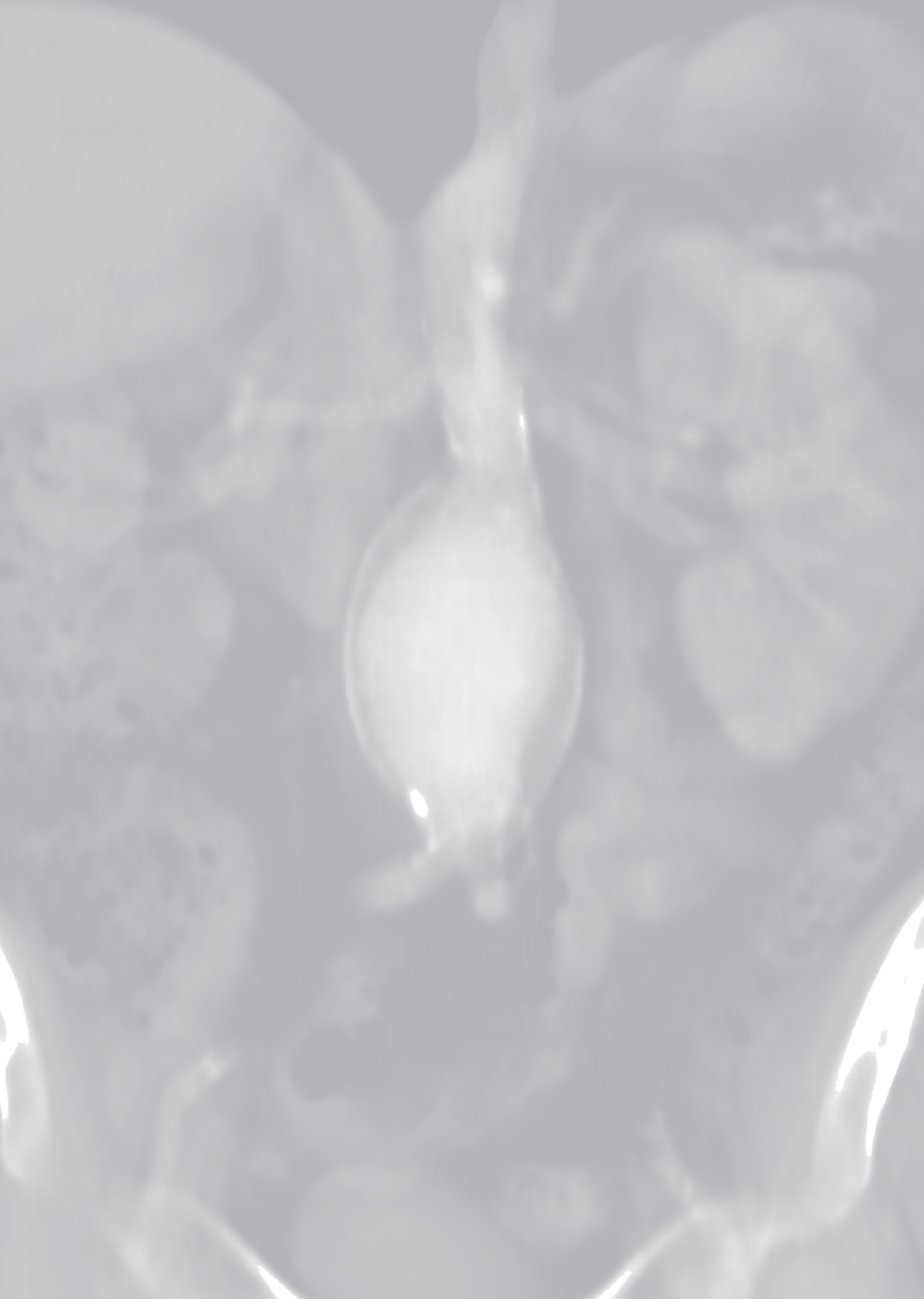

Chapter 1

Introduction and outline of the thesis

The infrarenal abdominal aorta is the largest abdominal artery and serves to supply blood to the lower part of the human body, specifically the most distal part of the intestines, the pelvic organs and the legs. An abdominal aortic aneurysm (AAA) is an aorta with a diameter exceeding 3 cm. Risk factors for developing an AAA are male gender, advancing age, a family history of AAA and smoking. In the most recent screening study in Swedish men aged 65 years, a prevalence of 2.2% was reported (95% confidence interval (CI) 2 to 2.4%).[1] Although sometimes a patient may have noticed a painless, pulsatile abdominal mass, in general there are no symptoms and the aneurysm is often found incidentally on physical examination or on imaging studies carried out for other reasons.

The natural course of an AAA is that it grows until it ruptures or until the patient dies from another cause. A 3 cm AAA has an estimated mean growth rate of 1.3 mm (95% CI 1 to 1.5 mm) per year and a 5 cm AAA has an estimated mean growth rate of 3.6 mm (95% CI 3.3 to 3.9 mm) per year.[2] The risk of AAA growth is higher in smokers and is lower in diabetics.[3] The precise moment of rupture cannot be predicted. In AAAs less than 5.5 cm in diameter the risk of rupture is less than 1% per year[2], in AAAs of 5.5-6 cm this is approximately 9% per year, in AAAs of 6-7 cm approximately 10% per year, and in AAAs exceeding 7 cm approximately 32% per year.[4] It is interesting to note that this reported risk of rupture of AAAs exceeding 5.5 cm is based on just a single study comprising a total of 198 patients only, which limits definite conclusions on this matter. Possibly, the risk of rupture is higher in women and in smokers.[3] Moreover, the risk of rupture seems to increase with higher age, blood pressure and pulse pressure.[3] Interestingly, in obese patients the risk of rupture seems to be lower.[3] Nonetheless, these reported risk factors for rupture have to be interpreted with caution since proper multivariable adjustment has never been done.

In patients with an AAA, the ultimate aim is to prevent rupture. So far, the only treatment to prevent rupture is surgical or endovascular intervention. The European Society for Vascular Surgery recommends possible surgical intervention for an asymptomatic AAA exceeding 5.5 cm in diameter in males and 5.2 cm in females.[5] Decision making for elective aortic surgery comprises three treatment options; endovascular aneurysm repair (EVAR), open repair (OR) or conservative/non-operative therapy. EVAR is the minimal-invasive placement of an endograft inside the aneurysm via the arteries of the groin. EVAR was developed in the nineteen-nineties and has since been used with ever-increasing frequency. OR is the traditional intervention and comprises

laparotomy and exclusion of the aneurysm by either a synthetic tube or a bifurcated graft.

Assessment of anatomical suitability for EVAR is an important part of decision making for surgical intervention. New developments in technical endovascular devices mean that patient suitability for EVAR is constantly changing. OR may be performed in those patients with unsuitable anatomy for EVAR or other specific situations in which OR is preferred. To date, in patients eligible for both interventions, four large randomized controlled trials (RCT) have been conducted.[6-9] These trials consistently reported a lower short-term death rate after EVAR than after OR, but from two years onwards the survival is comparable again throughout a follow-up of at least eight years. Moreover, there is a higher risk of reintervention and endograft-related complications after EVAR. Therefore, a lower short-term risk of death after EVAR has to be balanced with a lower long-term risk of complications after OR. Nowadays in the Netherlands, approximately 70% of patients are treated with EVAR.[10]

Another important part of decision making is whether patients unfit for OR benefit from EVAR when compared with no intervention at all. In a large RCT in patients physically unfit for OR who had an AAA exceeding 5.5 cm, 6-year survival was no better after EVAR than after conservative therapy.[7]

If unnoticed, an AAA can grow until it ruptures or until the patient dies from another cause. A ruptured abdominal aortic aneurysm (RAAA) is defined as bleeding outside the adventitia of an abdominal aorta with a diameter exceeding 3 cm. The incidence of an RAAA is approximately 10 to 14 per 100,000 person-years in a Western population.[11, 12] Of all patients with an RAAA, the death rate is estimated to be as high as 74% (95% CI 72 to 77%).[13] The only treatment to prevent death in these patients is immediate surgical intervention. A third of all patients with an RAAA do not reach hospital, a third do not have an intervention after reaching hospital and half of the remaining group do not survive the intervention.[13] As in elective aortic surgery, the traditional intervention is OR with exclusion of the aneurysm by a synthetic graft. The vast experience with elective EVAR has led to an increasing use of this technique in the emergency setting as well.

This thesis comprises several aspects of elective aortic surgery (**Chapters 2 and 3**) and of acute ruptured aneurysm care (**Chapters 4 to 10**).

Towards personalized care

Prediction models are helpful in assessing individual outcomes after an intervention and are able to contribute to tailoring individual patient care. Three phases can be distinguished in studies that evaluate prediction models. The first phase is the development of such a model including internal validation. The second phase is the external validation including updating of the model in other cohorts of patients. These 'external validation studies' answer the question of whether the predictions of a model also correspond with the observed outcomes in a group of patients other than the developing cohort. The third phase is to assess the impact and benefit of the prediction model on clinical practice. In patients in whom decision making is most difficult, risk-assessment by a prediction model can be expected to be the most beneficial. Predictions are based on a small number of preoperative variables such as age, sex, previous history and/or aneurysm characteristics. Nowadays, the increasing use of electronic charts in clinical practice may lead to automatic generation of predictions.

In elective aortic treatment, it is a challenge in clinical practice to determine which of the treatments will benefit the patient most: OR, EVAR, or conservative therapy. A lower risk of short-term death after EVAR has to be balanced with a lower risk of long-term complications after OR. Prediction models can support clinical decision making for elective aortic surgery. For example, OR may be preferable in a young and relatively healthy patient in order to prevent the intensive yearly follow-up which is required after EVAR. Even so, if a model were to accurately predict a low risk of short-term death after OR and a high risk of reintervention and complications after EVAR, it would support the choice for OR. On the other hand, in the elderly patient with severe comorbidity conservative therapy could be chosen, even where aortic anatomy is friendly. Lastly, if in an elderly patient with severe comorbidity a model is able to accurately predict a low risk of short-term death, reintervention and complications after EVAR, an endovascular graft would be the most reasonable treatment option. In **Chapter 2**, the external validation of the EVAR Risk Assessment (ERA) model predicting survival, reintervention and endograft-related complications after EVAR is described. In **Chapter 3** the external validation of the Medicare, the BAR and the VGNW models predicting the short-term death rate after both EVAR and OR is discussed.

In **Chapters 4 to 10**, care for patients with an RAAA is discussed. In patients with an RAAA, the decision to initiate or withhold surgical intervention is

based on a fast evaluation of the patient's clinical condition, the surgeon's past experience and the wishes of the patient. A prediction model is a more objective way to evaluate the chances of successful intervention and might be helpful in these moments of vital choices. In **Chapter 4** the external validation of models predicting the short-term death rate after surgical intervention for an RAAA is described.

Chapter 5 is somewhat different regarding personalized care as no prediction models are discussed but the association between acute kidney injury (AKI), as defined by the RIFLE criteria, and death. AKI is a serious complication of RAAA repair. Recently, new multidisciplinary diagnostic criteria (the RIFLE criteria) for AKI were introduced by nephrologists and intensive care specialists. The RIFLE criteria do not estimate a precise risk of dying or of other complications, but can be used to identify high-risk patients. AKI is associated with an increased risk of short-term death[14] and with a poorer long-term survival[15]. So far, only two smaller retrospective studies have applied the RIFLE criteria to patients with an RAAA.

Towards centralized care

The Amsterdam Acute Aneurysm (AJAX) trial, a large RCT comparing EVAR and OR for patients with an RAAA, was conducted in the Amsterdam ambulance region between 2004 and 2011. During the inclusion period of the AJAX trial, all hospitals in the Amsterdam ambulance region agreed to centralize care in three vascular centers; the Academic Medical Center, the VU University Medical Center and the Onze Lieve Vrouwe Gasthuis Hospital. All patients suspected of having an RAAA by ambulance staff, a general practitioner or a surgeon in a referring hospital were to be transported to the vascular center on call. A cohort of all 539 consecutive RAAA patients in the ten hospitals of the Amsterdam ambulance region was assembled. In **Chapter 6**, the effect of this unique cooperative effort on regional survival is discussed.

An important aspect of the regional cooperation was the transport of patients with an RAAA from a regional hospital to the vascular center on call. The safety of delaying therapy for these patients is controversial because time is limited. In **Chapter 7**, the duration of in-hospital survival in patients with an RAAA who did not undergo surgical intervention is described.

Towards endovascular care

As mentioned before, vast experience with elective EVAR has led to the increasing use of this technique in an emergency setting. Despite this, high-quality evidence considering the comparison between EVAR and OR for RAAAs is still limited. Moreover, close monitoring of outcomes after EVAR is needed to identify the pitfalls of this relatively new technique. In **Chapters 8 to 10** several aspects of outcomes after EVAR versus OR are discussed.

Although many observational studies have reported a lower death rate after EVAR than after OR, two large RCTs were completed just recently.[16, 17] **Chapter 8** offers a systematic review in which all published studies comparing the short-term death rate of EVAR and OR are discussed.

As in Chapter 8, the majority of studies comparing EVAR and OR in RAAA focus on short-term outcomes. In elective aortic surgery, the midterm risk of reintervention is higher after EVAR than after OR. In **Chapter 9** the midterm reintervention and survival rates after EVAR and OR in patients with an RAAA in the Amsterdam ambulance region are described. These outcomes may provide new insights into what would be the best intervention in patients with an RAAA, and offer guidance on post-intervention surveillance strategies.

In **Chapter 10** the effect of aortoiliac anatomy on outcomes after open repair is discussed. Specifically, we compared the outcomes between patients with aortoiliac anatomy suitable for EVAR ('friendly anatomy') and patients with aortoiliac anatomy unsuitable for EVAR ('hostile anatomy'). Previous studies have shown that outcomes are worse in patients with hostile anatomy. Because patients are selected by aortoiliac anatomy for either intervention, this might be an important confounder in studies comparing EVAR and OR.

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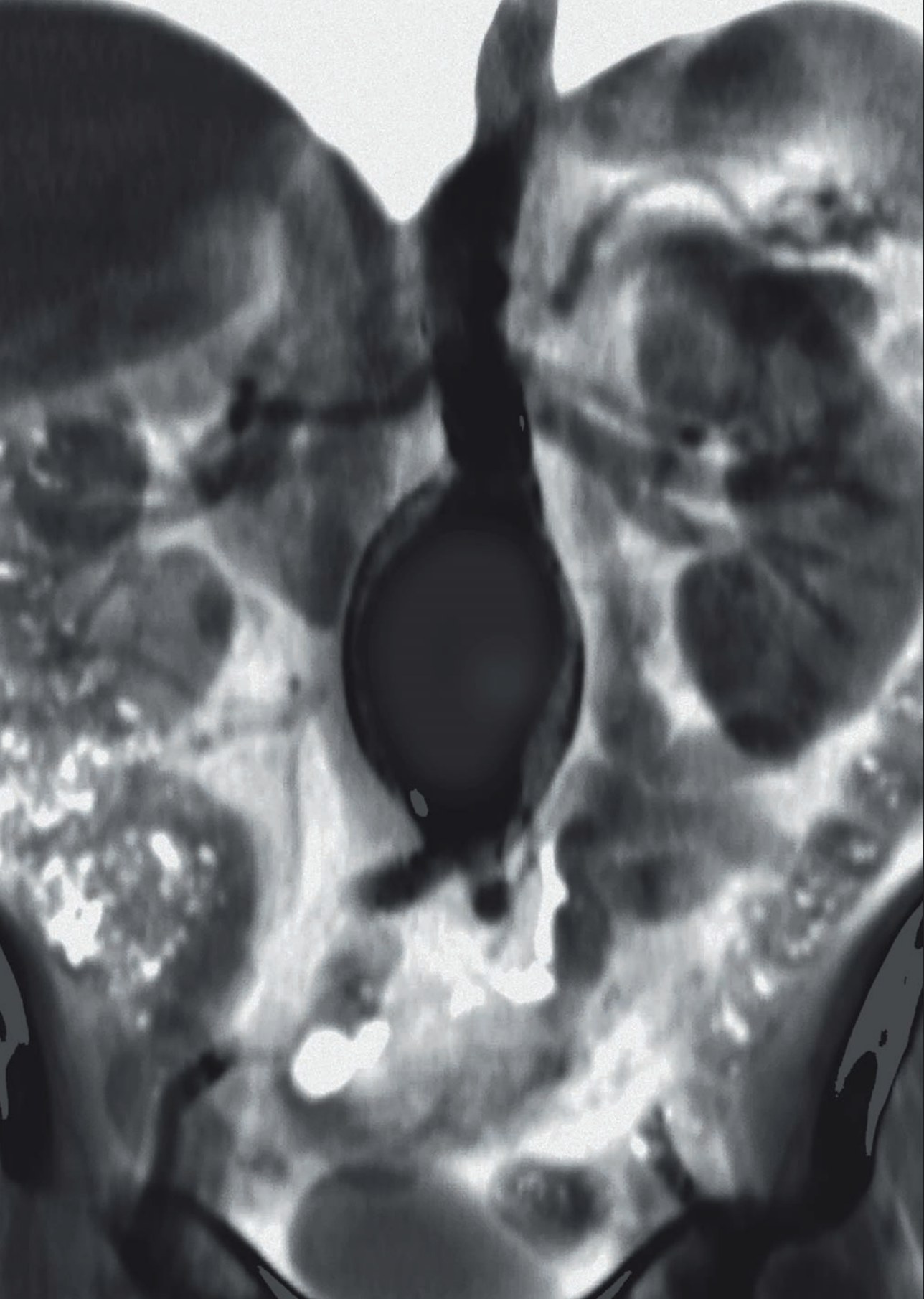
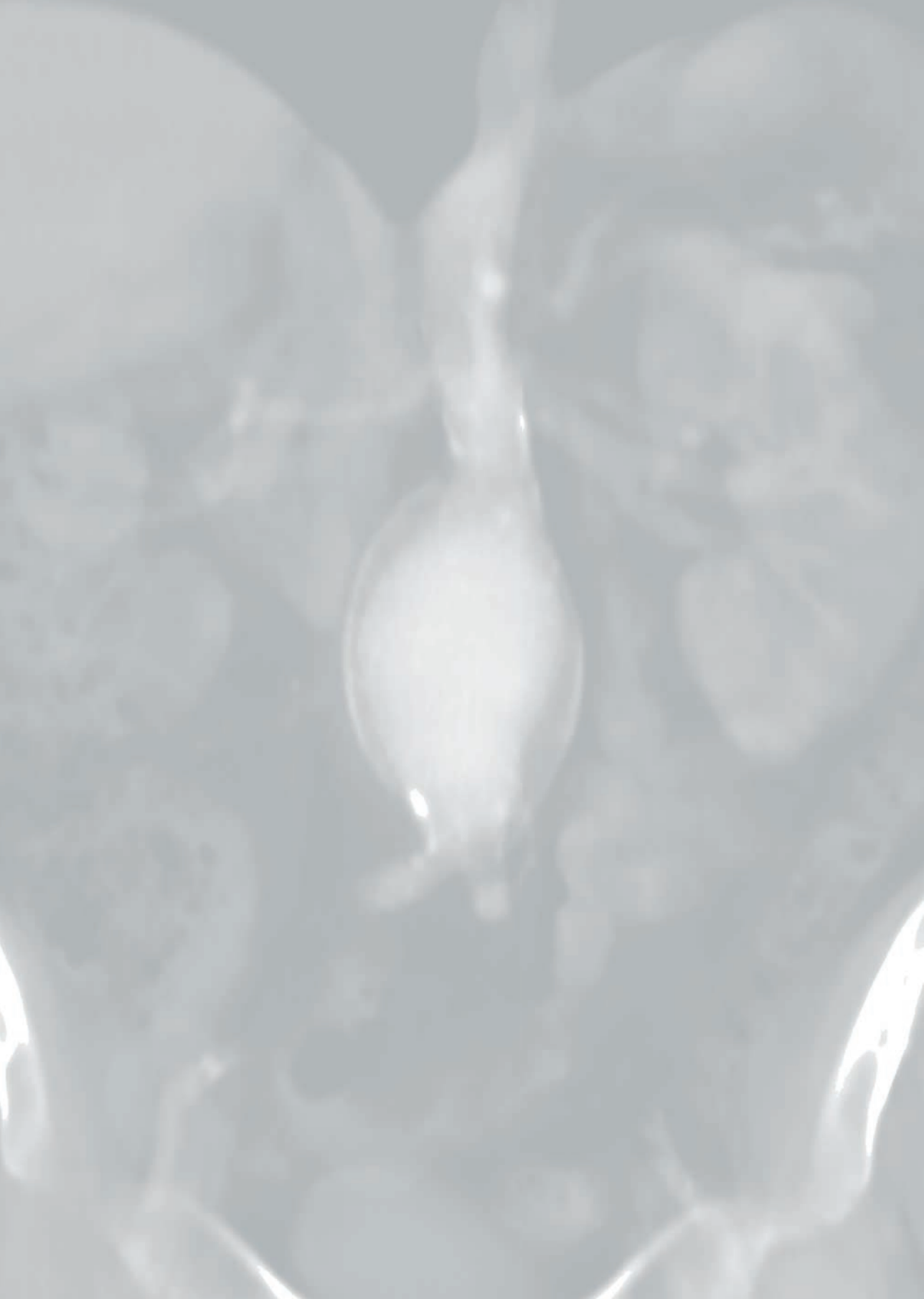


Towards personalized care



Chapter 2

External validation of the Endovascular aneurysm repair Risk Assessment model in predicting survival, reinterventions, and endoleaks after endovascular aneurysm repair

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Abstract

Background

The Endovascular aneurysm repair Risk Assessment (ERA) model predicts survival (early death, 3-year survival, and 5-year survival), reinterventions, and endoleaks after elective endovascular aneurysm repair. We externally validated the ERA model in our cohort of patients.

Methods

This was a retrospective validation study of 433 consecutive patients with an asymptomatic abdominal aortic aneurysm treated with endovascular aneurysm repair in three hospitals (Amsterdam, The Netherlands) between 1997 and 2010. The area under the receiver operating characteristic curve was used as measure of accuracy (>0.70 was considered as sufficiently accurate).

Results

The early death rate was 1% (3/433, 95% confidence interval (CI) 0 to 2%), the 5-year survival rate was 65% (95% CI 61 to 70%), the 5-year reintervention rate was 18% (95% CI 14 to 78%), and the 5-year rate of type I, II, or III endoleak was 25% (95% CI 20 to 29%). The areas under the curve varied between 0.64 and 0.66 for predictions of survival and between 0.47 and 0.61 for reinterventions and endoleaks.

Conclusion

The predictions of survival, reinterventions, and endoleaks made by the ERA model were not sufficiently accurate to be used in our clinical practice.

Introduction

During the past two decades, the treatment of abdominal aortic aneurysms (AAAs) has been subject to change. Conventional open repair (OR) has been partially substituted by endovascular aneurysm repair (EVAR). Recent clinical trials have shown that 30-day mortality is lower after EVAR than after OR.[1-3] However, the incidence of reinterventions and endograft-related complications is higher after EVAR than after OR. A challenge in current clinical practice is to determine which of the treatments will benefit the patient most: OR, EVAR, or nonoperative therapy. Prediction models are helpful in assessing individual outcomes after intervention and can support clinical decision making for elective aortic surgery. A promising prediction model is the EVAR Risk Assessment (ERA) model. The ERA model includes only eight preoperative variables (Table 1).[4, 5]

Table 1. Baseline characteristics and the preoperative variables included in the EVAR Risk Assessment (ERA) model.
EVAR = endovascular aneurysm repair, BMI = body mass index, SVS = Society for Vascular Surgery, ISCS = International Society for Cardiovascular Surgery, ASA = American Society of Anesthesiologists, GAS = Glasgow Aneurysm Score

Variable		Value	Variable included in the ERA model?
Age (years)		73.9 ±7.4	Yes
Male : Female		89% : 11% (386 : 47)	Yes
BMI (kg/m^2)		26.1 ±3.8	No
Current smoking		43% (155/359)	No
Cardiac co-morbidity (SVS/ISCS score ≥1)		59% (246/420)	No
Cerebrovascular co-morbidity (SVS/ISCS score ≥1)		13% (57/429)	No
Previous history of malignancy		23% (101/433)	No
ASA score ≥3		60% (261/433)	Yes
GAS		80 ±10	No
Anemia		26% (111/424)	No
Serum creatinine (µmol/L)		88 (75-105)	Yes
Max aneurysm diameter (mm)		62 ±11	Yes
Infrarenal neck (mm)	Length	33 ±13	Yes
	Diameter	24 ±3	Yes
Aneurysm angulation ≥45°		19% (67/349)	Yes
Late generation endograft		55% (220/399)	No
Adjunctive procedure		20% (86/433)	No

Continuous data are presented as mean ±standard deviation or median (inter-quartile range) and categorical data as percentage (number).

The ERA model has been designed to predict survival-related outcomes (30-day death, 3-year and 5-year survival, and aneurysm- related death), the need for reintervention, type I and type II endoleaks, and other complications, including technical success, graft complications, migration, and conversion. In aortic surgery, many models have been developed predicting the 30-day or in-hospital death rate and reinterventions or complications separately. Until now, the ERA model is the only one that predicts all of these outcomes together. These combined predictions are a major advantage that could potentially support decision making. The model was validated on three occasions: internally, using bootstrapping in the original Australian cohort and externally in the United Kingdom6 and in Australia.7 The predictions of survival (30-day, 3-year, and 5-year) and type I endoleak (30-day and midterm) were sufficiently accurate. The ERA model is freely available at http://health.adelaide.edu.au/surgery/evar/predictive.html or for a small fee as an iPhone application.

The primary objective of the present study was a third external validation of the ERA model using a Dutch cohort of patients. A secondary objective was the identification of preoperative variables that might improve the ERA model.

Methods

We conducted a retrospective cohort study at the Academic Medical Center (tertiary university hospital), at the Onze Lieve Vrouwe Gasthuis (teaching hospital), and at the VU University Medical Center (tertiary university hospital) in Amsterdam, The Netherlands. Included were all consecutive patients with EVAR for an asymptomatic aneurysm of the infrarenal abdominal aorta between January 1, 1997, and January 1, 2010. Patients with an inflammatory aneurysm were excluded.

All patients had routine follow-up, according to local practice, with yearly computed tomography angiography (CTA) or duplex ultrasound imaging combined with plain abdominal X-ray imaging. Patient follow-up was assessed up to July 1, 2012. Primary end points were death, reinterventions, and type I, II, and III endoleaks. The outcomes of 30-day death, 3-year survival, and 5-year survival will be referred to as the 'survival-related outcomes.' The present study focused on the validation of the predictions of these survival-related outcomes, reinterventions, and endoleaks by the ERA model. Because of a very low number of autopsies, cause of death was considered to be unreliable, and we did not validate

the predictions of aneurysm- related death. Because of the retrospective design, we did not validate the predictions of technical success, graft complications, migration, and conversion.

Data collection

Data were collected from medical records, discharge documents, preoperative anesthesia assessment records, and operative reports. Data were entered by the first author using Office Access 2003 (Microsoft Corp, Redmond, Wash) and included field limits and multivariate checks. Patients were identified from a prospective registry (Academic Medical Center) and from the financial coding administration of interventions (Onze Lieve Vrouwe Gasthuis and VU University Medical Center).

Definitions of preoperative variables[8] and postoperative outcomes[9] were in accordance with the reporting standards of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery (SVS/ISCS) and the article first describing the ERA model.[4] Early death was defined as the 30-day death rate. Reinterventions and endoleaks were assessed twice postoperatively: as defined by the ERA model, 'initial' encompassed the first 30 days, and 'midterm' referred to the period between 30 days and 5 years.

As in the ERA model, conversions to OR were separately analyzed from reinterventions, and type III endoleaks were included as type I in the statistical analysis. Anemia was defined as hemoglobin <134 g/L (<8.4 mmol/L) in men and <117 g/L (<7.3 mmol/L) in women. A previous history of malignancy included all types of cancer except nonmelanoma dermal carcinoma.

Endografts were dichotomized into early generation and late generation. Early generation encompassed the endografts formerly used in daily practice, which were the Lifepath (Edwards Lifesciences, Irvine, Calif) in 6, the Ancure (Endovascular Technologies, Menlo Park, Calif) in 8, the Talent (Medtronic, Minneapolis, Minn) in 100, the AneuRx (Medtronic) in 45, and an investigational Cordis endograft (Johnson & Johnson, New Brunswick, NJ) in 4. The late generation encompassed endografts currently used in daily practice, which are the Zenith (Cook Medical, Bloomington, Ind) in 196, the Endurant (Medtronic) in 24, and the Gore Excluder (W. L. Gore & Associates, Flagstaff, Ariz) in 16.

Aneurysm characteristics were measured in the sagittal, coronal, and axial planes of the preoperative CTA. Date of death was obtained from medical records and general practitioner registers.

Statistical analysis

The statistical analysis was done using SPSS 19.0 software (IBM Inc, Armonk, NY) and R (The R Foundation for Statistical Computing, Boston, Mass). Continuous data are described by the mean with corresponding standard deviation for data normally distributed, and by the median with corresponding inter-quartile range (IQR) for data with a skewed distribution. The 5-year survival, reintervention, and endoleak rates were estimated by Kaplan-Meier survival analyses and compared with use of the log-rank test. Also reported are the actual outcome rates in patients treated before July 1, 2007.

The statistical analysis comprised three steps. First, the accuracy of the ERA model was assessed for discrimination and calibration. Discrimination is the ability of a model to distinguish between an event and no event; for example, between dying and surviving patients. Discrimination was assessed using the area under the receiver operating characteristic curve (AUC), specifically using the Harrell C statistic,[10] which takes into account patients who are censored before the end point. An AUC of >0.70 is generally considered sufficiently accurate. Calibration refers to the agreement between predicted and observed outcomes and was assessed by plotting the predicted outcomes in quintiles with the corresponding observed outcomes. Calibration was assessed for 3-year and 5-year survival and included only patients who had the intervention before July 2009 and July 2007 to ensure sufficient follow-up time.

Second, preoperative variables that might improve the predictions of survival-related outcomes of the ERA model were identified using a Cox proportional hazards model. First, a univariable survival analysis was done including variables identified after a thorough literature search. The variables were:

- Patient-related: age,[11] sex,[12] renal impairment,[11] pulmonary impairment,[13] cardiac impairment,[14] diabetes, hypertension, malignancy,[14] smoking, body mass index (BMI), anemia,[15] and the American Society of Anesthesiologists (ASA) Physical Status Classification score[11];
- Aneurysm-related: maximum aneurysm diameter,[11,16] aortic neck diameter, length, and angulation,[11] and iliac artery calcification; and
- Operation-related: anesthesia,[17] adjuvant surgical procedures,[18] and endograft generation.[12]

Subsequently, the variables with a P value of <.20 in the univariable analysis and <15% missing data were included in the Cox proportional hazards model

(stepwise backward method). The variables of the ERA model were forced into the Cox proportional hazards model to identify variables with additional value. The -2 log likelihood (-2LL) was reported to represent Cox model performance. A lower -2LL represents better fit of a multivariable model. The difference between Cox models was tested with use of the -2LL in a χ^2 distribution.

Third, a sensitivity analysis was done to explore the influence of the use of different endograft generations (early vs late) on the outcomes. The sensitivity analysis included AUC assessment per endograft generation and two multivariable Cox proportional hazard models to assess the association between endograft generation and reinterventions. The first Cox model used the end point reintervention, including conversion, and the variables infrarenal neck angulation, diameter, and length were included to adjust for aortic anatomy-related confounding. In the second Cox model, the outcomes reintervention and dying were combined to a composite end point to prevent bias from a competing risk of dying before a reintervention. The variables age, sex, previous history of malignancy, ASA 3 or 4, year of intervention, AAA diameter, and infernal neck angulation, diameter, and length were included to adjust for survival- and anatomy-related confounding.

Missing values

Of the 434 patients studied, ASA scores were missing in 40 (9%) and were imputed with ASA score 3, and serum creatinine levels were missing in three (1%) and were imputed with the mean serum creatinine of the cohort. The preoperative CTA was available in 80% (349 of 434) of the patients. In the patients without a CTA, the aneurysm diameter was collected from the medical records. In these patients, the infrarenal neck length, diameter, and angulation were missing, and the predictions of reinterventions and endoleaks were excluded from the analysis. Therefore, the predictions of the survival-related outcomes were validated in 433 patients and of the reinterventions and endoleaks in 349 patients. An imputation procedure for the missing data was considered but not done because of the amount of missing data.

Ethics committee approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Medical Ethics Committee determined approval was not required because of the observational design.

Results

A total of 433 patients with an asymptomatic AAA were treated with EVAR. The median follow-up time was 4.8 years (inter-quartile range (IQR) 2.9-5.0 years), 86 of 433 patients (20%) did not reach 5-year follow-up, and eight (2%) were lost to follow-up. Baseline characteristics are reported in Table 1. The early death rate was 1% (3/433, 95% confidence interval (CI) 0 to 2%), the 5-year survival rate was 65% (95% CI 61 to 70%), the 5-year reintervention rate was 18% (95% CI 14 to 22%), and the 5-year rate of type I, II, or III endoleak was 25% (95% CI 20 to 29%, Table 2). The actual outcome rates in patients treated before 2007 were comparable to the estimations by the Kaplan-Meier survival analysis.

Table 2. Outcomes after endovascular aneurysm repair (EVAR).
ERA = EVAR Risk Assessment, CI = Confidence interval, KM = Kaplan-Meier

General cohort outcomes	
Follow-up time (years) [a]	4.8 (2.9-5.0)
Censored before 5-year follow-up	20% (86/433)
Lost to follow-up	2% (8/433)
ERA model outcomes	**percentage (number, 95% CI)**
Early death	1% (3/433, 0 to 2%)
3-year survival KM [b]	80% (87/433, 76 to 83%)
3-year survival actual [c]	80% (81/401, 76 to 83%)
5-year survival KM [b]	65% (137/433, 61 to 70%)
5-year survival actual [d]	65% (107/309, 60 to 70%)
Initial reintervention	4% (19/433, 3 to 7%)
Midterm reintervention	13% (57/433, 10 to 17%)
5-year reintervention KM [b]	18% (69/433, 14 to 22%)
5-year reintervention actual [d]	21% (64/310, 17 to 25%)
Initial endoleak type I	2% (9/433, 1 to 4%)
Midterm endoleak type I	4% (17/433, 2 to 6%)
Initial endoleak type II	11% (48/433, 8 to 14%)
Midterm endoleak type II	7% (31/433, 5 to 10%)
5-year endoleak type I, II, or III KM [b]	25% (108/433, 20 to 29%)
5-year endoleak type I, II, or III actual [d]	23% (71/311, 19 to 28%)
5-year conversion to open repair [d]	9% (28/314, 6 to 13%)

[a] Median (inter-quartile range)
[b] Estimated by Kaplan-Meier survival analysis
[c] Actual rate in patients treated before July 1, 2009
[d] Actual rate in patients treated before July 1, 2007

External validation

The AUC (representing the discrimination of the predictions by the ERA model) was 0.64 (95% CI 0.19 to 1.0) for early death, 0.66 (95% CI 0.60 to 0.72) for 3-year survival, and 0.66 (95% CI 0.61 to 0.71) for 5-year survival (AUCs are shown in Figure 1). The AUC of the predictions for initial reintervention was 0.55 (95% CI 0.42 to 0.68) and for midterm reintervention was 0.60 (95% CI 0.51 to 0.69). The AUC of the predictions for initial type I endoleak was 0.61 (95% CI 0.37 to 0.85) and for midterm type I endoleak was 0.59 (95% CI 0.43 to 0.75). The AUC of the predictions for initial type II endoleak was 0.50 (95% CI 0.41 to 0.59) and for midterm type II endoleak was 0.47 (95% CI 0.36 to 0.58). The calibration plot of 3-year survival showed that the agreement between predicted and observed survival was accurate (Figure 2). The calibration plot of 5-year survival showed an overestimation of survival by the predictions. A predicted 5-year survival of 50%, of 66%, and of 80% corresponded with an observed 5-year survival of 39% (95% CI 28 to 51%), 57% (95% CI 45 to 69%), and 68% (95% CI 55 to 78%), respectively.

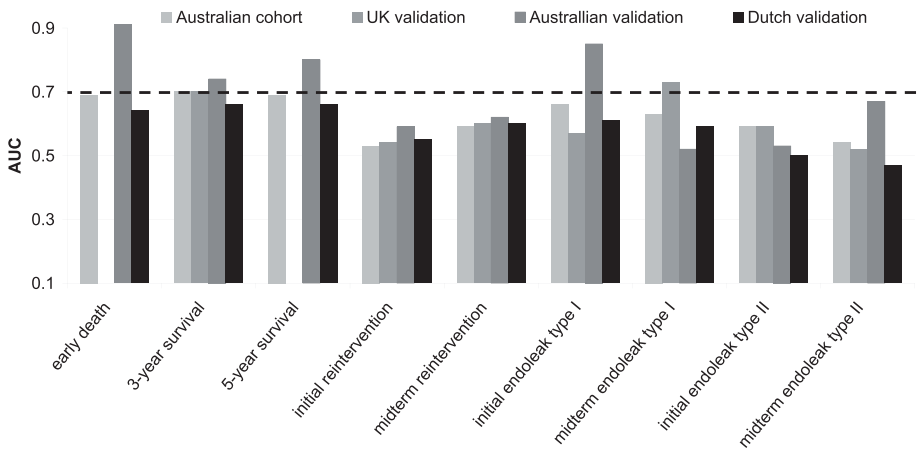

Figure 1. The area under the curve (AUC) (representing discrimination) of the predictions of survival, reinterventions, and endoleaks by the EVAR Risk Assessment (ERA) model in the original Australian audit cohort and in the validations in the United Kingdom (UK), Australia, and The Netherlands. An AUC >0.70 was considered as sufficiently accurate (indicated by the dashed line).
EVAR = endovascular aneurysm repair

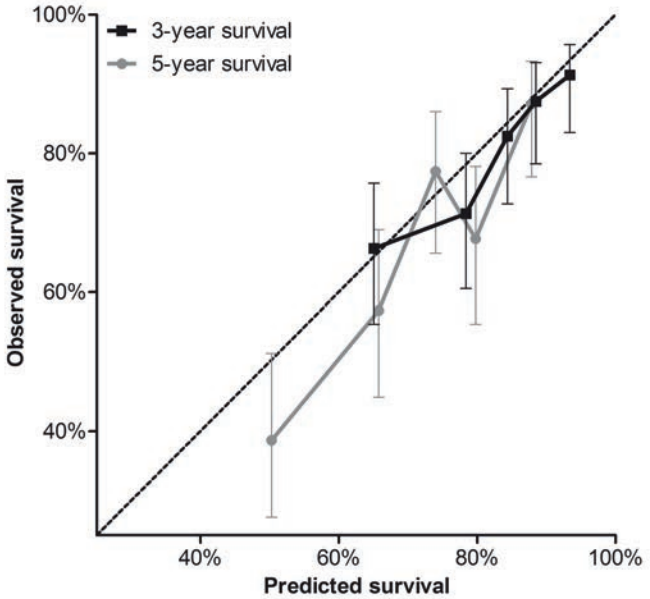

Figure 2. Calibration plots of the predicted 3-year and 5-year survival and the corresponding observed survival. Only patients with an intervention before July 2009 (3-year survival) or July 2007 (5-year survival) were included to ensure sufficient follow-up time. The range bars indicate the 95% confidence interval and the diagonal dashed line corresponds with ideal calibration.

Cox proportional hazards model

Univariable analysis identified sex, age, BMI, cardiac and cerebrovascular co-morbidity, previous history of malignancy, smoking, ASA score, serum creatinine, anemia, aneurysm diameter, length of the infrarenal neck, adjunctive or ancillary procedure during the operation, and endograft generation as possible predictors of death (P<.20, Tables 3 and 4). Smoking, BMI, and length of the infrarenal neck were not included in the Cox proportional hazards model because of >15% missing data. Age and serum creatinine were dichotomized because of nonlinearity. Age, sex, cardiac co-morbidity, previous history of malignancy, ASA score, serum creatinine, and aneurysm diameter were identified as independent predictors of survival (P≤.05, Table 5). The -2LL of the Cox model that included only the ERA variables was 1491. The -2LL of the Cox model that included the ERA variables, cardiac co-morbidity, and previous history of malignancy was 1476 (-2LL difference 12, χ^2 with two degrees of freedom P<.01).

Table 3. Univariable analysis of categorical preoperative patient-related, aneurysm-related, and operation-related characteristics on 5-year survival after endovascular aneurysm repair.
ASA = American Society of Anesthesiologists

Variable		5-year survival	P[a]	Missing data
Sex	Male	67% (386/433)	.17	0
	Female	54% (47/433)		
Cardiac co-morbidity[b]	Yes	60% (246/420)	.02	3% (13/433)
	No	72% (174/420)		
Pulmonary co-morbidity	Yes	63% (120/403)	.36	7% (30/433)
	No	66% (283/403)		
Cerebrovascular co-morbidity[b]	Yes	61% (57/429)	.17	1% (4/433)
	No	66% (372/429)		
Diabetes	Yes	65% (60/425)	.88	2% (8/433)
	No	65% (365/425)		
Hypertension	Yes	66% (157/420)	.89	3% (13/433)
	No	63% (263/420)		
Hypercholesterolemia	Yes	64% (169/418)	.93	3% (15/433)
	No	66% (249/418)		
Previous history of malignancy[b]	Yes	52% (101/433)	<.01	0
	No	69% (332/433)		
Current smoking	Yes	59% (155/359)	.12	17% (74/433)
	No	67% (204/359)		
Use of statin	Yes	60% (203/379)	.12	12% (54/433)
	No	70% (176/379)		
Use of oral anticoagulants[c]	Yes	64% (262/379)	.73	12% (54/433)
	No	65% (117/379)		
Anemia[b]	Yes	56% (111/424)	.01	2% (9/433)
	No	69% (313/424)		
ASA score[b]	1	100% (10/433)	<.01	0
	2	78% (162/433)		
	3	57% (243/433)		
	4	46% (18/433)		
Aneurysm characteristics				
Thrombus or calcification in the infrarenal neck	Yes	67% (202/346)	.52	20% (87/433)
	No	65% (144/346)		
Iliac calcification	Moderate/severe	63% (228/344)	.51	21% (89/433)
	None/mild	69% (116/344)		

Table 3. Continued

Operating characteristics				
Anesthesia	General	66% (353/397)	.81	8% (36/433)
	Locoregional	65% (44/397)		
Graft generation	Early	60% (163/399)	.19	8% (34/433)
	Late	68% (236/399)		
Adjunctive or ancillary procedure [b]	Yes	56% (86/433)	.03	0
	No	68% (347/433)		

[a] Log-rank test
[b] Included in multivariable Cox proportional hazards model (Table 5)
[c] Platelet aggregation inhibitor or vitamin K antagonist

Table 4. Univariable analysis of continuous preoperative patient-related, aneurysm-related, and operation-related characteristics on 5-year survival after endovascular aneurysm repair. BMI = body mass index, AP = anteroposterior

Patient characteristics	Mean	Hazard ratio	P [a]	Missing data
Age [b] (years)	73.9	1.05	<.01	0
BMI (kg/m²)	26.1	0.92	<.01	15% (67/433)
Serum creatinine [b] (µmol/L)	93	1.01	<.01	0
Aneurysm characteristics				
Maximum aneurysm diameter [b] (mm)	62	1.03	<.01	0
Length infrarenal neck (mm)	33	0.99	.05	19% (83/433)
Diameter infrarenal neck (mm)	24	1.02	.61	19% (83/433)
Maximum AP/lateral infrarenal neck angulation (°)	29	1.00	.87	19% (83/433)
Maximum AP/lateral aneurysm angulation (°)	43	1.00	.48	19% (83/433)

[a] Univariable Cox proportional hazards model
[b] Included in multivariable Cox proportional hazards model (Table 5)

Sensitivity analysis

From 2003 onward, more patients were treated with a late-generation endograft than with an early-generation endograft. The median follow-up time was 4.2 years (IQR 1.5-5.0 years) for patients with an early-generation endograft and 3.8 years (IQR 2.0-5.0 years) for those with a late-generation endograft (P=.69). After stratification for endograft generation, the AUCs changed minimally, but the CIs increased (data not shown). The 5-year reintervention rate, including conversions, was 29% (95% CI 21 to 37%) in patients with an early-generation endograft and 16% (95% CI 10 to 21%) in patients with a late-generation

endograft (P<.01). After adjustment for aortic anatomy-related confounders, the risk of reintervention or conversion was lower in patients treated with a late-generation endograft (adjusted hazard ratio 0.49, 95% CI 0.29 to 0.84, Table 6). After adjustment for survival-related and aortic anatomy-related confounders, the risk of reintervention or dying was lower in patients with a late-generation endograft than in patients with an early-generation endograft (adjusted hazard ratio 0.58, 95% CI 0.39 to 0.86, Table 7).

Table 5. Multivariable Cox proportional hazards model (stepwise backward method) for survival after endovascular aneurysm repair.
CI = confidence interval, ASA = American Society of Anesthesiologists

Variable	Hazard ratio (95% CI)
Age ≥79 years	1.60 (1.11 to 2.30)*
Men	0.55 (0.33 to 0.92)*
Cardiac co-morbidity	1.47 (1.01 to 2.15)**
Previous history of malignancy	2.02 (1.39 to 2.93)*
ASA score 3 or 4	2.00 (1.32 to 3.03)*
Serum creatinine >104 µmol/L	1.44 (1.00 to 2.07)**
Aneurysm diameter (per 5 mm)	1.12 (1.04 to 1.21)*

The model included 420 patients and 133 events, -2 log likelihood (LL) = 1476.
* P<.05
** P=.05

Table 6. Multivariable Cox regression model to assess the association between endograft generation (early vs late) and reinterventions, including conversions to open repair.
CI = confidence interval

Variable		Hazard ratio (95% CI)
Infrarenal neck angulation >45°		1.59 (0.86 to 2.93)
Infrarenal neck diameter (mm)	<22 (n = 71)	0.82 (0.35 to 1.91)
	22-26 (n = 170)	1.33 (0.69 to 2.56)
	>26 (n = 85)	Reference category
Infrarenal neck length (mm)	<24 (n = 88)	2.16 (0.97 to 4.81)
	24-43 (n = 160)	1.53 (0.72 to 3.26)
	>43 (n = 78)	Reference category
Late-generation endograft		0.49 (0.29 to 0.84)*

The model included 326 patients and 55 events, -2 log likelihood (LL) = 591.
* P <.05

Table 7. Multivariable Cox regression model to assess the association between endograft generation (early vs late) and a combined end point of death and reinterventions, including conversions to open repair.
CI = confidence interval, ASA = American Society of Anesthesiologists, AAA = abdominal aortic aneurysm

Variable		Hazard ratio (95% CI)
Age (years)	<69 (n = 86)	Reference category
	69-79 (n = 157)	0.99 (0.63 to 1.54)
	>79 (n = 73)	1.36 (0.80 to 2.30)
Women		1.16 (0.68 to 2.00)
Previous history of malignancy		1.66 (1.14 to 2.43)*
ASA 3 or 4		1.39 (0.95 to 2.03)
AAA diameter (mm)	<61 (n = 159)	Reference category
	61-67 (n = 76)	1.18 (0.76 to 1.83)
	>67 (n = 81)	1.49 (0.98 to 2.28)
Infrarenal neck angulation >45°		1.10 (0.72 to 1.69)
Infrarenal neck diameter (mm)	<22 (n = 66)	1.07 (0.62 to 1.84)
	22-26 (n = 167)	1.34 (0.87 to 2.06)
	>26 (n = 83)	Reference category
Infrarenal neck length (mm)	<24 (n = 86)	2.03 (1.22 to 3.37)*
	24-43 (n = 153)	1.40 (0.87 to 2.25)
	>43 (n = 77)	Reference category
Year of intervention	<2004 (n = 95)	Reference category
	2004-2006 (n = 105)	1.15 (0.81 to 1.85)
	>2006 (n = 126)	0.97 (0.62 to 1.54)
Late-generation endograft		0.58 (0.39 to 0.86)*

The model included 316 patients and 139 events, -2 log likelihood (LL) = 1479. * P <.05

Discussion

The present validation study shows that the predictions by the ERA model of survival, reinterventions, and endoleaks after EVAR were not accurate in our cohort of Dutch patients. The study was conducted as a first step toward prospective validation to determine long-term outcomes after treatment allocation with support of the ERA model. In such a prospective validation study, the question can be answered whether our arbitrary AUC cutoff value of 0.70 is sufficiently accurate to support decision making. However, because of our disappointing results, further studies assessing the effect of the present ERA model appear to be futile.

Prediction of survival

Our results for survival-related outcomes conflict with the conclusions of the previous validation studies.[4, 6, 7] An explanation might be the inclusion of relatively healthier patients in our cohort. The proportion of patients with an ASA score 3 or 4 was 60%, compared with 65% to 80% in previous validation studies. The mean preoperative serum creatinine level was 93 µmol/L compared with 106 to 118 µmol/L, respectively. Other preoperative variables, such as age, sex, and aortic anatomy did not differ substantially. Since the United Kingdom EndoVascular Aneurysm Repair 2 trial,[1] we have become less willing to intervene in high-risk patients. However, without data on rejection rates, this explanation is based on reasoning only; moreover, a reliable prediction model should take potentially healthier patients into account.

Another possible explanation for the disappointing accuracy of the ERA model is that the discriminative character of the currently included variables is limited. For this reason, we tried to identify possible additional predictive variables. The Cox proportional hazards model identified 'cardiac co-morbidity' (SVS/ISCS score ≥1) and 'previous history of malignancy' as independent predictors of survival in our cohort. Beside commonly known predictors of survival, 'previous history of malignancy' might be important to consider for long-term survival after EVAR. However, these results have to be interpreted with caution because of limitations that we will discuss later. Future studies should determine the definite role of the variable 'previous history of malignancy'.

For the outcome early death, two new predictions models have been developed recently[19, 20] and have shown sufficiently accurate predictions in external validation studies.[21, 22] Possibly, these two models have more additional value in our clinical practice than the ERA model.

For 3-year and 5-year survival, the ERA model is the most accurate model currently available. The combined interpretation of the AUCs of all validations done so far might be interpreted as sufficiently accurate for 3-year survival (AUCs ranging in all validations between 0.66 and 0.74) and 5-year survival (AUCs in all validations ranging between 0.66 and 0.80).

Prediction of reinterventions and endoleaks

Our results on prediction of reinterventions and endoleaks correspond with the conclusions in the previous validation studies.[4, 6, 7] Combined interpretation of the AUCs of for the reinterventions and endoleaks cannot be interpreted as

sufficiently accurate. A probable explanation is that the ERA model is based on an audit conducted between 1999 and 2001, which is quite some time ago. Clinical practice has changed since the audit, especially in diagnosis and treatment of endoleaks. Moreover, the indication for a reintervention varies between hospitals. Without standardized treatment protocols, any model aiming to predict reinterventions has to overcome this variation.

Clinical practice has changed since the Australian audit also with regard to types of endografts. This might be another reason the predictions of reinterventions and endoleaks were not accurate. Our cohort includes a large number of patients with early-generation endografts. The ERA model aims to predict outcomes after all types of endografts. Our cohort includes seven different types of endografts, which is consistent with that aim. The sensitivity analysis showed that the accuracy of the predictions by the ERA model barely differed stratified for endograft generation. In accordance with recent results, [23] the reintervention rate was higher in early-generation endografts than in late-generation endografts. After adjustment for possible confounders, the risk of dying or reintervention was lower in patients treated with a late-generation endograft. These results indicate that new-generation endografts have improved outcomes.

The ERA model focuses on aortic neck characteristics for the prediction of reinterventions and endoleaks. Next to the Australian audit, the importance of the aortic neck for reinterventions and endoleaks has been reported from the European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) registry[24, 25] and confirmed in more recent studies.[26, 27] This shows that anatomic characteristics associated with these predictions of the ERA might still be valid. However, two other models aiming to predict reinterventions also include other anatomic characteristics of the aortic neck (calcification), of the aneurysm (angulation, branch vessels, diameter, tortuosity), and of the iliac arteries (angulation, calcification, diameter, length, and tortuosity).[28, 29] Possibly, these two models have more additional value in our clinical practice than the ERA model.

The identification of anatomic predictors of reinterventions and endoleaks was not possible in our cohort because of too few adverse events. This problem might be addressed by combining the data sets of all validation studies to the ERA model done so far for a 'meta-regression.' The number of adverse events would be increased, and a multivariable analysis might identify other independent

predictors of outcomes. To increase reproducibility of the measurements of aortic anatomy, an automatically generated central lumen line might be relevant.[30] Current methods of measurement, using sagittal and coronal reconstruction in the CTA, might be too observer-dependent.

Limitations

Despite the high number of patients included in our validation of the ERA model, a limitation was the low event rate for the outcomes of early death and initial type I endoleak. For this reason, the CIs are wide surrounding the AUCs, and the point estimates should be interpreted with caution. All previous validation studies have this limitation, which might be addressed by combining the data sets for a 'meta-validation.'

The retrospective design resulted in missing data. The amount of missing data for the validation of the ERA model was 1% of serum creatinine, 9% of ASA scores, and 20% of CTAs. The reason for the large proportion of missing CTAs was that in one hospital, only images on sheets were available before 2006. Comparing patients with and without a preoperative CTA showed that the 5-year survival rate was 66% (95% CI 60 to 71%) vs 65% (95% CI 55 to 75%, P=.97), the 5-year reintervention rate was 19% (95% CI 14 to 23%) vs 18% (95% CI 9 to 26%, P=.90), and the 5-year endoleak rate was 26% (95% CI 21 to 31%) vs 19% (95% CI 10 to 27%, P=.21), respectively. Because these outcomes are comparable, we expect little effect of the missing CTAs on the conclusions.

The Cox proportional hazards models also suffered from missing data. Possible confounding factors, such as smoking, BMI, and the length of the infrarenal aortic neck, had to be excluded from the Cox model identifying additional predictors of survival after EVAR (Table 3). Another limitation of this model was that our literature search for inclusion of variables might have failed to identify all predictors. For example, the use of medication or a preoperative electrocardiogram[15] might be of importance. A large group of patients (27%) had to be excluded from the Cox models in the sensitivity analysis (Tables 6 and 7). For these reasons, we are reluctant to draw definite conclusions from the results of the Cox models.

In patients in whom decision making is difficult, risk- assessment by a prediction model has the most additional value. For example, EVAR can be more challenging in patients with hostile aortic anatomy, and the risk of reinterventions and endoleaks is higher. OR is a reasonable alternative in these patients, and

risk-assessment with a prediction model might support making the decision. Our validation study was too small to assess the accuracy of the ERA model in a subgroup of patients with hostile anatomy; however, this should be an important consideration in future studies developing or validating prediction models.

The primary objective of a vascular surgeon with EVAR is the prevention of rupture and aneurysm-related death. A final limitation of our study was that we could not objectify this aim by the validation of the predictions of aneurysm-related death. The ERA model predictions of 3-year and 5-year survival only correspond to the population-related survival after EVAR. From a patient's perspective, however, the cause of death is not important and the population-related survival suffices.

Conclusions

This study is the third and largest external validation of the ERA model. The predictions of early death, 3-year survival, 5-year survival, reinterventions, and type I, II, and III endoleaks were not sufficiently accurate to be used in our clinical practice. A multicenter prospective study is underway in Australia that aims to improve the predictive accuracy of the ERA model. We hope the results of this study will produce a model that can support decision making in our clinical practice.

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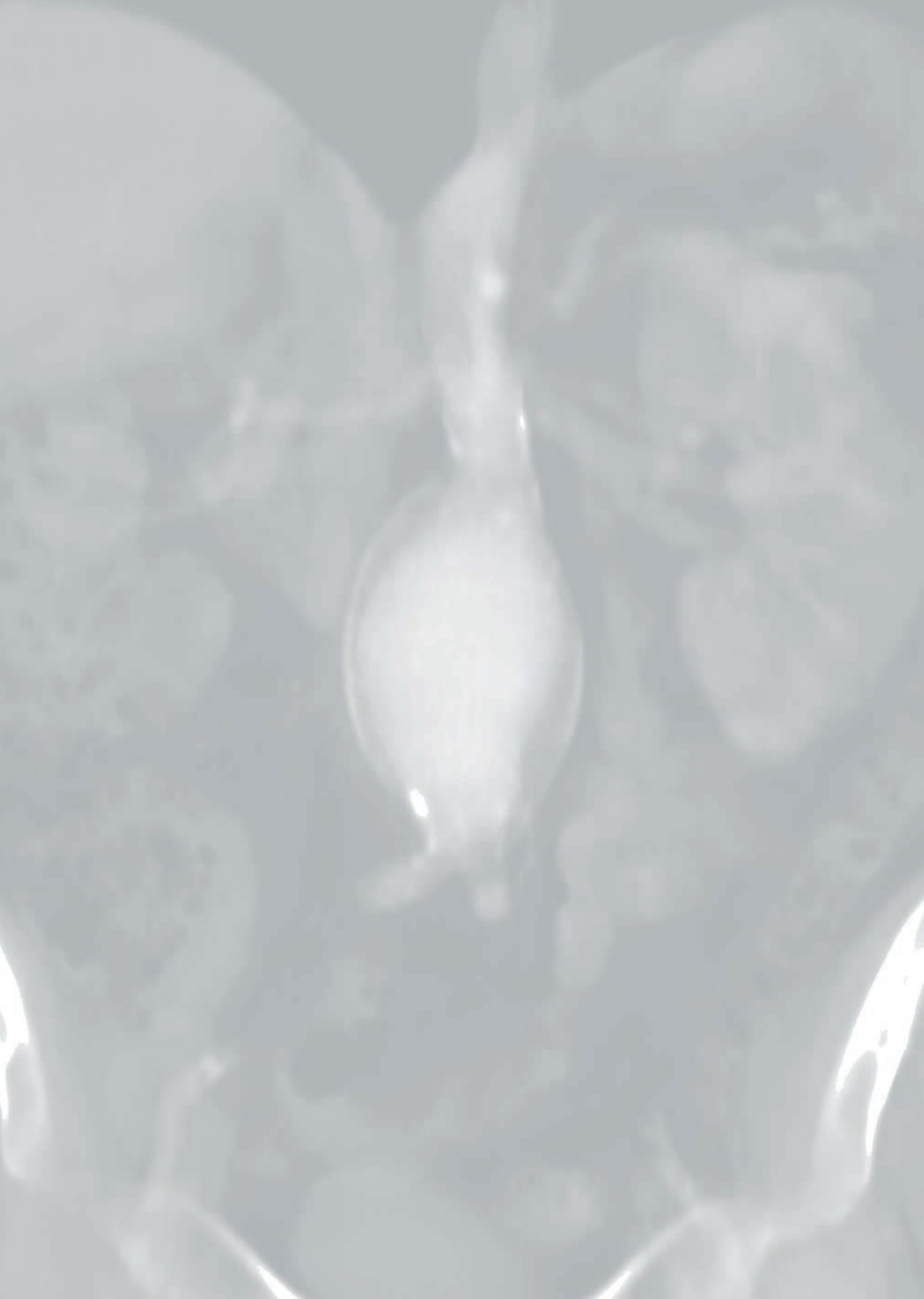

Chapter 3

Validation of three models predicting in-hospital death in patients with an abdominal aortic aneurysm eligible for both endovascular and open repair

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Abstract

Background

The Medicare, the Vascular Governance North West (VGNW), and the British Aneurysm Repair (BAR) models can be used to predict in-hospital death after an intervention for an asymptomatic abdominal aortic aneurysm (AAA). Validation of these models in patients with suitable aortic anatomy for endovascular repair and a general condition fit for open repair is lacking. We validated the Medicare, VGNW, and BAR models in patients from a randomized controlled trial comparing open and endovascular AAA repair.

Methods

A per-protocol analysis was done of 345 Dutch and Belgian patients with in-hospital death as the primary end point. The prediction models were validated taking into account discrimination (the ability to distinguish between death and survival) and calibration (the agreement between predicted and observed death rates). Discrimination was assessed using the area under the receiver-operating characteristics curve (AUC). An AUC >0.70 was considered to be sufficiently accurate. Calibration was assessed using the Hosmer and Lemeshow (HL) test, and P>.05 was considered to be sufficiently accurate.

Results

The AUC was 0.77 (95% confidence interval (CI) 0.64 to 0.90, HL test P=.52) for the Medicare model, 0.88 (95% CI 0.81 to 0.95, HL test P=.31) for the VGNW model, and 0.79 (95% CI 0.67 to 0.91, HL test P=.15) for the BAR model.

Conclusion

In AAA patients eligible for endovascular and open repair, the predictions of in-hospital death by the Medicare, VGNW, and BAR models were sufficiently accurate. Therefore, these models can be used to support deciding between endovascular and open repair.

Introduction

Patients with an abdominal aortic aneurysm (AAA) can be treated with endovascular repair, open repair, or conservatively. When deciding between endovascular and open repair, the clinical decision-making process is predominantly based on estimates of the incidence of mortality, reinterventions, and complications as well as on the expected quality-adjusted life-years.[1] The challenge in current practice is to determine which patients will benefit the most from endovascular repair and which from open repair. Randomized trials have shown long-term survival and quality-adjusted life-years are equal after both interventions.[2-4] However, the incidence of complications and reinterventions is higher after endovascular repair, whereas the incidence of in-hospital death is higher after open repair. Therefore, predicting in-hospital death and long-term reinterventions before the intervention could support clinical decision making.

A prediction model is a standardized and objective way to assess individual outcomes after an intervention. Several models predicting in-hospital death after aortic repair have been developed; for example, the prediction model most frequently used is the well-validated Glasgow Aneurysm Score (GAS), which was developed in 1994.[5] The results of validation studies evaluating the accuracy of the GAS in endovascular repair are conflicting.[6-9] Three new prediction models have recently been developed: the Medicare model in the United States[10] and the Vascular Governance North West (VGNW) and the British Aneurysm Repair (BAR) models in the United Kingdom.[11, 12]

Two validation studies have reported sufficiently accurate predictions of in-hospital death for the Medicare and VGNW models.[7, 13] These validations included patients whose aortic anatomy was unsuitable for endovascular repair and whose general condition was unfit for open repair. As such, these studies included patients where there was no choice between endovascular and open repair. To our knowledge, the BAR model has not yet been validated externally.

To apply the Medicare, VGNW, and BAR models to support the decision between endovascular and open repair in individual patients, validation is needed in patients eligible for both options. Therefore, patients enrolled in randomized trials comparing endovascular and open repair, such as the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, can be used to validate the models.

As well as supporting decision making, prediction models have additional value in improving patient education. In the consulting room, prediction models can be used to advise patients and relatives of the short-term risk of dying after the intervention.

The objective of this study was to validate the Medicare, VGNW, and BAR prediction models in Dutch and Belgian patients with an AAA who were eligible for both open and endovascular repair.

Methods

This study retrospectively analyzed 345 patients included in the DREAM trial.[3] Details of the DREAM trial (registration number clinicaltrials.gov NCT00421330) are described in detail elsewhere.[14] Briefly, the DREAM trial was a multicenter, randomized trial conducted at 26 hospitals in The Netherlands and in four hospitals in Belgium. Inclusion criteria for the DREAM trial were informed consent, an AAA sized at least 5 cm, and suitability for both endovascular and open repair. Excluded were patients with an inflammatory aneurysm, anatomic variations, connective tissue disease, a history of organ transplantation, or a life expectancy of <2 years.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval for the DREAM trial was given by the Institutional Review Board of all hospitals.

Statistical analysis

The analysis was done per-protocol. The primary end point was the combination of 30-day and in-hospital death. Statistical analysis was done using IBM SPSS 19.0 software (IBM, Armonk, New York) and R software (The R Foundation for Statistical Computing, Vienna, Austria). The predictions of death by the Medicare, VGNW, and BAR models were calculated with the formulas presented in Table 1.

The accuracy of the predictions was assessed taking discrimination and calibration into account.[15] Discrimination is the ability of a model to distinguish between those patients who die and those who survive. Discrimination was assessed using the area under the receiver-operating characteristics curve (AUC). An AUC >0.70 is generally considered to be sufficiently accurate. Calibration refers to the agreement between the predicted and observed death rates and was

Table 1. Formula and definitions of the Medicare, the Vascular Governance North West (VGNW), and the British Aneurysm Repair (BAR) prediction models.
ECG = electrocardiogram, AAA = Abdominal aortic aneurysm, ASA = American Society of Anesthesiologist Physical Status Classification, SVS = Society for Vascular Surgery, ISCS = International Society for Cardiovascular Surgery

Model score	Formula
Medicare	-5.02 + age <75 years x 0.15 + age 75-80 years x 0.63 + age >80 years x 1.14 + female sex x 0.42 + chronic renal insufficiency [a] x 0.71 + end-stage renal disease [b] x 0.95 + congestive heart failure [c] x 0.55 + vascular disease [d] x 0.30 + open repair x 1.17
VGNW	-9.3431 + age (years) x 0.0486 + female sex x 0.7322 + diabetes [e] x 0.6620 + creatinine (μmol/L) x 0.0073 + respiratory disease [f] x 0.4718 + antiplatelet medication x 0.7762 + open repair x 1.3130
BAR	-10.9187 + open repair x 1.6466 + age (years) x 0.0568 + female sex x 0.7062 + creatinine >120 μmol/L x 0.5979 + abnormal ECG [g] x 0.3033 + previous aortic surgery or stent x 0.8812 + abnormal white cell count [h] x 0.3697 + abnormal sodium level [i] x 0.3099 + AAA diameter (cm) x 0.1285 + ASA 2 x 0.2292 + ASA 3 x 0.7334 + ASA 4 x 1.6775

[a] SVS/ISCS renal status ≥1 (equal or worse condition, then moderately elevated creatinine level as high as 220 μmol/L)
[b] Need for dialysis
[c] SVS/ISCS cardiac status ≥2 (equal or worse condition, then stable angina, ejection fraction between 25% and 45%, asymptomatic arrhythmia, or history of congestive heart failure)
[d] SVS/ISCS carotid disease ≥2 (equal or worse condition, then transient or temporary stroke), ankle-brachial index <0.90, or previous history of peripheral artery surgery
[e] SVS/ISCS diabetes ≥1 (equal or worse condition, then adult-onset diabetes controlled by diet or oral agents)
[f] SVS/ISCS pulmonary status ≥1 (equal or worse condition, then mild dyspnea on exertion, parenchymal X-ray changes, or pulmonary function tests between 65% and 85% of predicted)
[g] SVS/ISCS cardiac status ≥1 (remote myocardial infarction by history of >6 months, occult myocardial infarction by electrocardiogram, or fixed defect on dipyridamole thallium or similar scan)
[h] White cell count <3.0 x 10^9/L or >11.0 x 10^9/L
[i] Sodium level <135 mmol/L or >145 mmol/L

assessed using a graph plotting the mean predicted death rates in tertiles with the corresponding observed death rates. The tertiles were created by sorting the predictions in ascending order and categorizing the patients in three subgroups of comparable size accordingly. The subgroups included 126, 119, and 100 patients for the calibration of the Medicare model, 114, 116, and 115 patients for the VGNW model, and 106, 118, and 121 patients for the BAR model. The sizes of these subgroups differed slightly because patients with equal predictions were categorized in the same tertile. Calibration was also assessed using the Hosmer and Lemeshow (HL) test. The HL test compares predicted and observed outcomes in a χ^2 distribution. An HL test P value <.05 reflects statistically significant differences between predicted and observed outcomes. Hence, a P value >.05 indicates sufficiently accurate calibration of the model.

In two patients, the preoperative serum creatinine was missing and was imputed as the mean creatinine. The preoperative aneurysm diameter was missing in two other patients and was imputed as the mean diameter. For the BAR model, the white cell count and the sodium level were unknown and assumed to be within normal reference ranges.

Results

In the study, 351 patients were randomized: 173 were assigned to endovascular repair and 178 to open repair. The treatment allocation flowchart is published elsewhere.[16] Six patients were excluded because they did not undergo aneurysm

Table 2. Baseline characteristics of patients included in the per-protocol analysis.
EVAR = endovascular aneurysm repair, OR = open repair, ECG = electrocardiogram, AAA = abdominal aortic aneurysm, ASA = American Society of Anesthesiologist Physical Status Classification

Variable		EVAR n = 175	OR n = 170	Total n = 345
Age (years)		71 (67-75)	70 (66-75)	70 (66-75)
Male : Female		93% : 7% (163 : 12)	90% : 10% (153 : 17)	92% : 8% (316 : 29)
Previous aortic surgery or stent		0 (0/175)	1% (1/170)	1% (1/345)
Congestive heart failure		8% (14/175)	7% (12/170)	8% (26/345)
Cardiac disease		42% (74/175)	46% (78/170)	44% (151/345)
Abnormal ECG		42% (74/175)	45% (77/170)	44% (152/345)
Respiratory disease		27% (47/175)	18% (31/170)	23% (78/345)
Serum creatinine (µmol/L)		96 (83-109)	95 (84-107)	95 (84-108)
Chronic renal insufficiency		7% (13/175)	7% (12/170)	7% (25/345)
End-stage renal disease		0	0	0
Serum creatinine >120 µmol/L		13% (22/175)	12% (20/170)	12% (42/345)
Vascular disease		32% (56/175)	27% (46/170)	30% (102/345)
Diabetes		10% (18/175)	9% (16/170)	10% (34/345)
Antiplatelet medication		40% (70/175)	41% (69/170)	40% (139/345)
AAA diameter (cm)		5.8 (5.5-6.5)	5.8 (5.4-6.4)	5.8 (5.4-6.5)
ASA	2	92% (161/175)	85% (146/170)	89% (307/345)
	3	8% (14/175)	14% (24/170)	11% (38/345)
	4	0	0	0

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).

repair. In the intention-to-treat analysis, 171 patients were included in the endovascular repair group and 174 in the open repair group. One patient randomized to endovascular repair underwent open repair, and five patients randomized to open repair crossed over to endovascular repair. Ultimately, the per-protocol analysis included 175 patients in the endovascular repair group and 170 patients in the open repair group. Three of the patients treated with endovascular repair were converted to open repair perioperatively, and one procedure was aborted. The baseline characteristics of the patients included in the per-protocol analysis are reported in Table 2. The death rate was 1% (2/175, 95% confidence interval (CI) 0 to 4%) after endovascular repair and 5% (8/170, 95% CI 2 to 9%) after open repair.

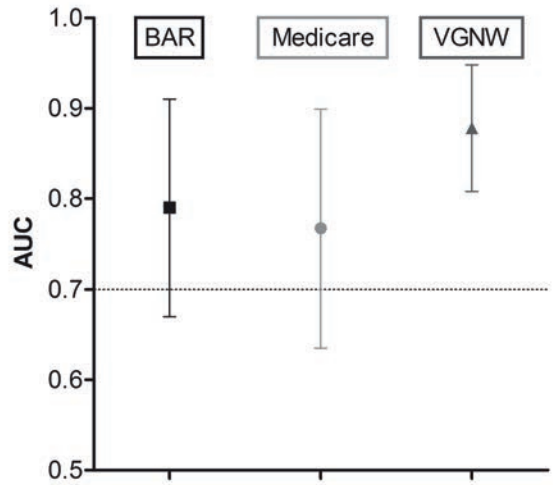

Figure 1. The discrimination of the Medicare, the Vascular Governance North West (VGNW), and the British Aneurysm Repair (BAR) prediction models indicated by the area under curve and the surrounding 95% confidence intervals. An area under the curve >0.70 was considered as sufficiently accurate (indicated by the dashed line).

Medicare model

The median predicted death rate of the Medicare model was 1% (inter-quartile range (IQR) 1-1%, range 1-4%) in patients treated with endovascular repair and 3% (IQR 2-4%, range 2-12%) in patients treated with open repair. The AUC of the predictions was 0.77 (95% CI 0.64 to 0.90, Figure 1). The plot showed close to ideal calibration (Figure 2) and a P=.47 for the HL test. In the tertile of patients with the highest predictions, the mean predicted death rate was 5%, and the corresponding observed death rate was 6% (95% CI 3 to 13%).

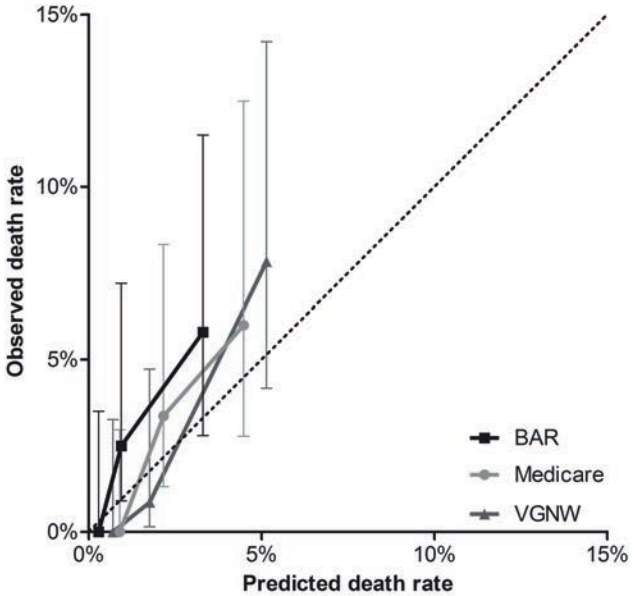

Figure 2. Calibration plots of the Medicare, the Vascular Governance North West (VGNW), and the British Aneurysm Repair (BAR) prediction models. The mean predicted death rates in tertiles are plotted with the corresponding observed death rates. The range bars indicate the 95% confidence interval and the diagonal dashed line corresponds with ideal calibration.

VGNW model

The median predicted death rate of the VGNW model was 1% (IQR 1-2%, range 0-6%) in patients treated with endovascular repair and 4% (IQR 2-5%, range 1-14%) in patients treated with open repair. The AUC of the predictions was 0.88 (95% CI 0.81 to 0.95, Figure 1). The plot showed close to ideal calibration (Figure 2) and a P=.24 for HL test. In the tertile of patients with the highest predictions, the mean predicted death rate was 5%, and the corresponding observed death rate was 8% (95% CI 4 to 14%).

BAR model

The median predicted death rate of the BAR model was 0% (IQR 0-1%, range 0-2%) in patients treated with endovascular repair and 2% (IQR 1-4%, range 0-13%) in patients treated with open repair. The AUC of the predictions was 0.79 (95% CI 0.67 to 0.91, Figure 1). The plot showed close to ideal calibration (Figure 2), with P=.15 for the HL test. In the tertile of patients with the highest predictions, the mean predicted death rate was 3%, and the corresponding observed death rate was 6% (95% CI 3 to 12%).

Discussion

The predictions of death by the Medicare, VGNW, and BAR prediction models were sufficiently accurate in Dutch and Belgian patients with an AAA eligible for both open and endovascular repair.

The discrimination of the Medicare model (AUC=0.77) was comparable with two previous validation studies from the United Kingdom. In these validations, the AUC of the predictions was 0.71 (95% CI 0.69 to 0.74)[7] and 0.79 (95% CI 0.73 to 0.86).[13] The discrimination of the VGNW model (AUC=0.88) was higher than in two previous validations reporting an AUC of 0.71 (95% CI 0.68 to 0.74)[7] and 0.73 (95% CI 0.65 to 0.81).[13] To our knowledge, no previous external validation of the BAR model has been done.

A striking observation was the high accuracy of the VGNW model. First, the AUC (0.88) in our validation was high compared with other surgical prediction models. For example, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a reliable prediction model widely used in daily practice in cardiac surgery. A validation study showed an AUC of 0.79 for the EuroSCORE.[17] Second, the AUC of the predictions by the VGNW model was higher than the AUC of the Medicare and of the BAR models in our validation. This indicates that the predictions by the VGNW model were more accurate. However, given the limitations of our validation and the equivalent AUCs in previous validations, no definite conclusions can be drawn.

From a practical perspective, the Medicare and VGNW models require only a few patient characteristics, and the predictions can be calculated within a minute. The BAR model, however, requires several more patient characteristics and is thereby more complex compared with the Medicare and VGNW models. The BAR model was primarily developed for risk adjustment in mortality outcome analyses in the United Kingdom, which explains the higher complexity.[12] Extra diagnostic assessments are required, including an electrocardiogram, the serum sodium level, and the white cell count. The latter is not routinely measured before intervention in The Netherlands and Belgium. Therefore, the Medicare and VGNW models have a clear practical advantage over the BAR model in our clinical practice.

The variables included in the three models correspond largely, which is suggestive for an accurate representation of a patient's risk profile. Age, female sex, renal comorbidity, generalized atherosclerosis, and open repair increase the

prediction of death. In the Medicare model, atherosclerosis is represented by the variables 'congestive heart failure' and 'vascular disease.' In the VGNW model, 'antiplatelet medication' is used as a surrogate marker for atherosclerosis. In the BAR model, 'cardiac disease,' an 'abnormal electrocardiogram,' and 'previous aortic surgery or stent' are used to represent atherosclerosis.

Decision making

Our validation was done in patients in whom a decision between endovascular and open repair was relevant; that is, patients with aortic anatomy suitable for endovascular repair and in a general condition fit for open repair. Table 3 provides an example of six imaginary patients in whom the models could support decision making. The BAR model was not included in Table 3 because of the previously discussed lower applicability in Dutch clinical practice.

Table 3. Predictions of in-hospital death by the Medicare and Vascular Governance North West (VGNW) prediction model in examples of six imaginary patients.
EVAR = endovascular aneurysm repair, OR = open repair, COPD = Chronic obstructive pulmonary disease, GOLD = Global Initiative for Chronic Obstructive Lung Disease

Patient	Characteristics	Medicare		VGNW	
		EVAR	OR	EVAR	OR
1	66 years, male, previous history of diabetes, creatinine of 100 µmol/L, no antiplatelet medication	1%	2%	1%	3%
2	69 years, male, no previous history, creatinine of 85 µmol/L, no antiplatelet medication	1%	2%	1%	2%
3	71 years, male, previous history of chronic renal insufficiency, heart failure, and peripheral arterial occlusive disorder; creatinine of 190 µmol/L, antiplatelet medication	4%	11%	2%	8%
4	75 years, female, previous history of transient ischemic attack, creatinine of 76 µmol/L, antiplatelet medication	3%	8%	3%	9%
5	81 years, female, previous history of heart failure, diabetes, and peripheral arterial occlusive disorder, creatinine of 100 µmol/L, antiplatelet medication	7%	19%	8%	23%
6	82 years, male, previous history of vascular disease and COPD GOLD II, creatinine of 110 µmol/L, antiplatelet medication	3%	8%	4%	12%

Patients 1 and 2 are relatively young, which means open repair can be considered to prevent intensive yearly follow-up. The models support a choice for open repair by a relatively low predicted in-hospital death rate of between 2% and 3%. Patients 3 and 4 are somewhat older, at 71 and 75 years, and on the basis of their ages, open repair can be considered. However, given the relatively high predicted in-hospital death rate of between 8% and 11% after open repair, this might not be the best choice. Patients 5 and 6 are relatively old and, considering the results of the United Kingdom EndoVascular Aneurysm Repair 2 (EVAR-2) trial,[2] conservative treatment is a reasonable option in these patients. The predicted in-hospital death rate for patient 5 is between 7% and 8% after endovascular repair and could support a choice for conservative treatment. The predicted death rate for patient 6 is between 3% and 4% after endovascular repair, which could justify an intervention.

As mentioned before, the randomized trials have shown that the in-hospital death rate and long-term reintervention rate differ after endovascular and open repair. Our validation shows that the Medicare, VGNW, and BAR models are useful tools to predict in-hospital death and support decision making on this outcome. Other models are needed to predict reinterventions and adverse events, such as aneurysm-related death and endograft-related complications, to further support decision making. An example of such a model is the Endovascular Aneurysm Repair Risk Assessment (ERA) model, which is designed to predict survival, endograft-related complications, and reinterventions after endovascular repair.[18] However, the predictions of adverse events by the ERA model have not been as accurate as hoped.[19, 20] Possibly, a 'meta-regression' of the finalized randomized trials with uniform measurements of aortic anatomy can provide sufficiently accurate predictions of adverse events. An important characteristic of such a model would be the accuracy in patients in whom risk assessment is most needed and might support decision making. For example, the risk of adverse events is higher in patients with hostile aortic anatomy, and open repair might be a reasonable alternative. Moreover, in patients with severe comorbidity (patients 5 and 6 in Table 3), conservative treatment instead of EVAR is defendable based on results of the EVAR-2 trial.[2]

Limitations

An important limitation of the validation of the BAR model was the unknown white cell count and sodium level. The effect on the discrimination is unknown,

and the calibration might be underestimated. However, in the developing cohort of the BAR model, the prevalence of abnormal outcomes of white cell count and sodium level was only 10%. Moreover, the contribution of these variables to the predictions are relatively small compared with the other included variables, shown by the lower coefficients and Wald Z statistics in the model.[12] Therefore, we expect a limited effect of the unknown white cell count and sodium level on our conclusions. However, more studies are needed to confirm the external validity of the BAR model.

The primary end point of our validation was in-hospital death. Originally, the VGNW model was designed to predict 30-day death. We used in-hospital death because from a patient's perspective, dying more than 30 days after the intervention but during the same hospital admission period cannot be considered a success.

Another limitation of our validation is that the DREAM trial excluded patients with severe comorbidity. All three models were developed in cohorts that included patients with severe comorbidity; therefore, we expect that these models take a patient's severe comorbidity into account. Moreover, in previous validation studies, the Medicare and the VGNW models showed accurate predictions.[7, 13] Our study focuses on patients eligible for both interventions. Patients with severe comorbidity are usually not eligible for both interventions; therefore, we expect the exclusion of patients with severe comorbidity had a limited effect on our conclusions.

Another limitation of our validation is the small sample size leading to a low event rate. As a consequence, the calibration plots showed large CIs surrounding the point estimates of the observed death rates (Figure 2).

One final limitation is that the inclusion period of the DREAM trial was about a decade ago, and intensive care unit and anesthetic care have improved since then. Moreover, all patients included in the validation were treated with an early-generation endograft. Although the type of endograft does not seem to have a major effect on the in-hospital death rate, the influence of these differences on the validity of our results in current practice is unknown.

Conclusions

The predictions of in-hospital death by the Medicare, VGNW, and BAR models were sufficiently accurate in patients eligible for both endovascular and open repair. The BAR model is more complex, has limited additional value in Dutch

clinical practice, and needs further external validation. Therefore, the Medicare and VGNW models can be used to support deciding between endovascular and open repair in The Netherlands and Belgium and to advise patients and relatives about the risk of death after the intervention.

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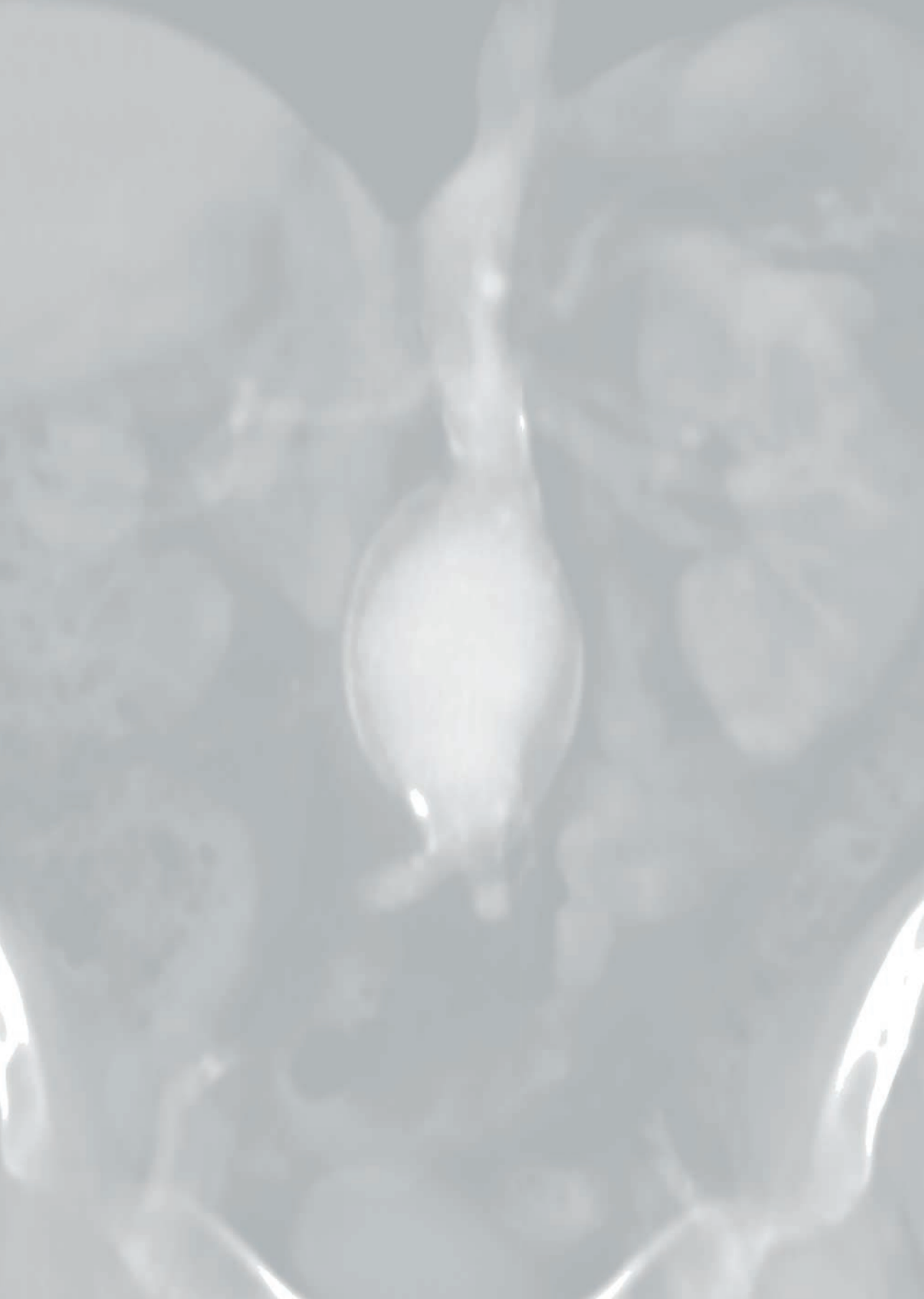

Chapter 4

External validation of models predicting survival after ruptured abdominal aortic aneurysm repair

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Submitted

Abstract

Background

Prediction of survival after intervention for ruptured abdominal aortic aneurysms (RAAA) may support case mix comparison and tailor the prognosis for patients and relatives. The objective of this study was to assess the performance of four prediction models; the updated Glasgow Aneurysm Score (GAS), the Vancouver scoring system, the Edinburgh Ruptured Aneurysm Score (ERAS) and the Hardman index.

Methods

Retrospective study in 449 patients in ten hospitals with an RAAA (intervention between 2004 and 2011). Primary endpoint was combined 30-day or in-hospital death. The accuracy of the prediction models was assessed for discrimination (area under the curve (AUC)). An AUC >0.70 was considered sufficiently accurate. In studies with sufficiently accurate discrimination, correspondence between the predicted and observed outcomes (i.e. calibration) was recalculated.

Results

The AUC of the updated GAS was 0.71 (95% confidence interval (CI) 0.66 to 0.76), of the Vancouver score was 0.72 (95% CI 0.67 to 0.77), and of the ERAS was 0.58 (95% CI 0.52 to 0.65). After recalibration predictions of the updated GAS slightly overestimated the death rate; e.g. predicted death rate 60% vs. observed death rate 54% (95% CI 44 to 64%). After recalibration, predictions of the Vancouver score considerably overestimated the death rate, e.g. predicted death rate 82% vs. observed death rate 62% (95% CI 52 to 71%). Performance of the Hardman index could not be assessed on discrimination and calibration. In 57% of patients electrocardiograms were missing. Where the Hardman index could be applied and where a death rate of 100% was predicted the observed death rate was 50% (95% CI 27 to 73%).

Conclusion

Concerning discrimination and calibration, only the updated GAS predicted death after intervention for an RAAA sufficiently accurately. Performances of the Vancouver score and the ERAS were insufficiently accurate. Because of the large number of missing electrocardiograms, no definite conclusions could be drawn for the Hardman index.

Introduction

The overall death rate in patients with a ruptured aneurysm of the abdominal aorta (RAAA) is approximately 74% (95% confidence interval (CI) 72 to 77%).[1] In patients reaching the hospital and undergoing intervention, the death rate ranges between 24% and 49%.[2-4] Surgeons have proposed distinguishing between those who would potentially benefit from surgery and those in whom it might be better to withhold intervention, after cardiopulmonary resuscitation for example.[5-9] In current clinical practice, the decision to start surgical or conservative treatment is based on a fast evaluation of the patients' clinical condition, the surgeon's experience and the wishes of the patient. It is a subjective interpretation of a harsh reality by the doctor, the patient and the relatives. A prediction model is a more standardized and objective way to evaluate the chances of successful intervention and might be helpful at these moments of vital choices. Further benefits of prediction models lie in case mix comparison between hospitals and a tailored prognosis for patients and relatives.

Several models have been developed to predict death after intervention in patients with an RAAA; the Glasgow Aneurysm Score (GAS)[10], the Vancouver scoring system[11], the Edinburgh Ruptured Aneurysm Score (ERAS)[12] and the Hardman index.[6] These scoring systems were initially designed before the introduction of endovascular aneurysm repair (EVAR). Nowadays, EVAR is being carried out increasingly.[2] Only the GAS has been updated to the era of EVAR by the addition of a variable for type of intervention.[13]

The primary objective of our study was to assess the accuracy of the updated GAS (the model including differentiation between EVAR and OR), the Vancouver score, the ERAS and the Hardman index in predicting death. Only extremely reliable models, those predicting death accurately in more than 95% of cases, may be useful in clinical decision-making. A secondary objective was the assessment of accuracy in patients with a predicted death rate of ≥95% in whom withholding intervention might be considered.

Methods

We conducted a retrospective study in all consecutive surgically treated patients with an RAAA in the Amsterdam ambulance region between May 2004 and

February 2011. The present study was carried out as a sequel of the previously published Amsterdam Acute Aneurysm Trial.[14] Other details and analyses of this cohort have been published previously.[15, 16] None of these previous studies aimed to validate prediction models for patients with an RAAA. The Amsterdam ambulance region covers an area of 1025 km^2 with 1.38 million inhabitants.[17] During the inclusion period, care for patients with an RAAA was centralized in two university hospitals and one teaching hospital in cooperation with seven regional hospitals. All patients with an RAAA in all ten hospitals of the region were registered prospectively and included in the present study. Patients with a previous aortic reconstruction, an RAAA with associated trauma or aortoenteric fistula were excluded. Primary end point was the combined 30-day or in-hospital death rate. Compared to some previous validation studies of the prediction models, we added in-hospital death to the definition; from a patients' perspective the ultimate goal is survival and being discharged. Approval from a medical ethics committee was not needed because of the observational design.

Updated GAS

The updated GAS score was calculated with the formula: age (years) + 7 for cardiac comorbidity (defined as previous history of myocardial infarction, cardiac surgery, angina pectoris or arrhythmia) + 10 for cerebrovascular comorbidity (defined as previous history of stroke or transient ischemic attack) + 17 for shock (defined as an in-hospital systolic blood pressure <80 mmHg) + 14 for renal insufficiency (defined as a pre-operative serum creatinine > 160 μmol/L) + 7 for OR (Figure 1).

$$1 - \frac{1}{1 + (\text{EXP}\,(-5.3 + 0.052 * \text{updated GAS score}))}$$

Figure 1. The formula to calculate the predicted death rate using the updated GAS.

Vancouver score

The Vancouver score was calculated with the formula: age (years) * 0.062 + loss of consciousness (yes = 1 / no = -1) * 1.14 + cardiac arrest (yes = 1 / no = -1) * 0.6 (Figure 2).

$$1 - \frac{1}{1 + (\text{EXP}\ (-3.44 + \text{Vancouver score}))}$$

Figure 2. The formula to calculate the predicted death rate using the Vancouver score.

ERAS

The ERAS score was calculated with the formula: + 1 for best recorded in-hospital Glasgow coma scale (GCS) <15, + 1 for in-hospital systolic blood pressure <90 mmHg, + 1 for pre-operative hemoglobin level <5.6 mmol/L. A score of 0 or 1 corresponded with a predicted death rate of 30%, a score of 2 with a predicted death rate of 50% and a score of 3 with a predicted death rate of 80%.

Hardman index

The Hardman index was calculated with the formula: + 1 for age >76 years, + 1 for in-hospital loss of consciousness, + 1 for a pre-operative serum creatinine > 190 μmol/L, + 1 for pre-operative serum hemoglobin level <5.6 mmol/L, + 1 for electrocardiographic (ECG) ischemia (defined as ST-segment depression greater than 1 millimeter or an associated T-wave change determined by a senior cardiologist (RJGP)). A score of 3 or more corresponded with a predicted death rate of 100%.

Data collection and statistical analysis

Data were collected from the medical records by the first and second authors. Data entry was done using Microsoft Access 2003 (Microsoft Corporation, Redmond, Washington, USA) using field limits, univariate and multivariate checks. A valid way of coping with missing values is by imputation.[18] Missing data was imputed for the variables blood pressure, hemoglobin, creatinine, cardiac comorbidity, cerebrovascular comorbidity, resuscitation, loss of consciousness and GCS. Multiple imputation was done creating ten datasets. Age, sex, renal and pulmonary comorbidity, death and the above mentioned imputed variables were used as predictors in the imputation model. We decided to not impute data for missing ECGs in this way, because of the large number of missing ECGs (>50%). Baseline characteristics and prediction model scores are reported in both the original dataset and in the imputed datasets (Tables 2 and 3).

The statistical analysis and the imputation procedure were done using IBM SPSS Statistics 19.0 (SPSS Inc., Armonk, New York, USA) and R (The R Foundation

for Statistical Computing, Boston, USA). Continuous data were described by the mean with corresponding standard deviation (SD) for data normally distributed, and by the median with corresponding inter-quartile range (IQR) for data with skewed distribution. The statistical analysis comprised four steps. First, the accuracy of the updated GAS, the Vancouver score and the ERAS was determined with regard to the overall performance and the discrimination.[19] Overall performance represents the distance between the predicted outcome and actual outcome statistically and was assessed using the Brier Score. The Brier Score should be as close to 0 as possible and the threshold for a noninformative model was calculated to be at 0.23. Discrimination is the ability of a model to distinguish between dying and surviving patients and was assessed using the area under the receiver operating characteristics curve (AUC). An AUC >0.70 was considered sufficiently accurate. Second, in the models with an AUC >0.70 the calibration of the predictions was determined. Calibration refers to the agreement between the predicted and observed death rate. Calibration was assessed by dividing all patients into five comparable quintiles ranging between 0-20%, >20-40%, >40-60%, >60-80% and >80-100%. Because patients with equal predictions were categorized in the same quintile, the sizes of the quintiles differed slightly between the several prediction models. Subsequently, the mean predicted death rate per quintile was plotted with the corresponding mean observed death rate. In addition, the Hosmer and Lemeshow (HL) chi-square test was done to compare the observed and predicted death rates. The HL test P<.05 reflects a significant difference between the predicted and observed death rate which is a poor calibration. Third, the models with an AUC >0.70 and an HL test P<.05 were recalibrated using the 'calibration intercept method'.[20] Fourth, a subgroup analysis was done in patients with a predicted death rate of ≥95% in order to assess the accuracy in high-risk patients in whom withholding intervention might be considered.

As mentioned above, the Hardman index does not provide a specific predicted death rate for a score <3. For this reason, the accuracy of the Hardman index on overall performance, discrimination and calibration could not be assessed. The accuracy of the Hardman index was assessed by comparing the predicted death rate of 100% (a score of ≥3) with the observed death rate in these patients. Because of the large number of missing ECGs (>50%), a sensitivity analysis was done in which the data for missing ECGs were imputed in accordance with the outcome (death or no death). In this way, a 'best case scenario' for the accuracy of the Hardman index was created.

Results

Of 539 patients with an RAAA in the greater Amsterdam region, 66 did not have an intervention and 24 had to be excluded because of other reasons (Figure 3). The reasons to refrain from intervention were predominantly shock or resuscitation with an expected low chance of survival (n = 20), patient or patient's family decision (n = 17) or unknown (n = 17). The updated GAS, the Vancouver score and the ERAS of these patients without intervention is shown in Table 1. Of 449 patients included in the analysis, the baseline characteristics are shown in Table 2. Sixty-nine patients were treated with EVAR and 380 patients were treated with OR. The death rate was 36% (160/449, CI 31 to 40%).

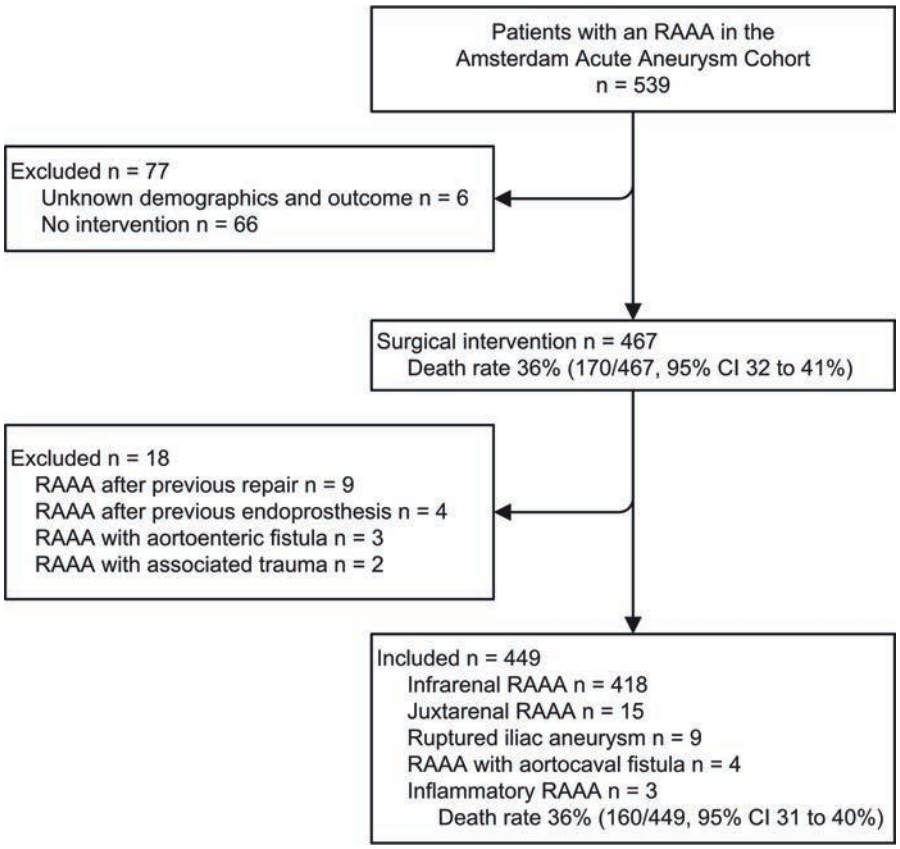

Figure 3. Flowchart of inclusion and exclusion in the analysis.
RAAA = ruptured abdominal aortic aneurysm, CI = confidence interval

Table 1. The updated GAS, the Vancouver score and the ERAS in 66 patients without intervention.
GAS = Glasgow Aneurysm Score, ERAS = Edinburgh Ruptured Aneurysm Score

Prediction model			Missing data
Updated GAS [a]		99 (90-106)	44% (29/66)
Vancouver		3.90 (3.59-6.20)	17% (11/66)
ERAS score	≤1	94% (15/16)	76% (50/66)
	2	0	
	3	6% (1/16)	

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).
[a] Without the variable 'type of intervention'.

Table 2. Baseline pre-operative characteristics.
SBP = systolic blood pressure, CPR = cardiopulmonary resuscitation, GCS = Glasgow coma scale, ER = emergency room, ECG = electrocardiogram, EVAR = endovascular aneurysm repair, OR = open repair

Pre-operative variable	Original data		Imputed data
	Available data	Missing data	
Age (years)	76 (69-80)	0	Not imputed
Male : Female	80% : 20% (360 : 89)	0	Not imputed
Cardiac co-morbidity	42% (184/435)	3% (14/449)	43% (191/449)
Cerebrovascular co-morbidity	15% (67/433)	4% (16/449)	15% (69/449)
Lowest in-hospital SBP (mmHg)	90 (70-125)	11% (48/449)	90 (70-125)
In-hospital CPR	11% (46/429)	4% (20/449)	12% (52/449)
In-hospital loss of consciousness	21% (81/388)	14% (61/449)	21% (96/449)
Best recorded GCS <15	17% (63/372)	17% (77/449)	18% (82/449)
Hemoglobin at ER (mmol/L)	7.0 (5.9-8.0)	1% (5/449)	7.0 (5.9-8.0)
Creatinine at ER (μmol/L)	106 (86-133)	3% (14/449)	107 (87-134)
ECG ischemia	21% (40/192)	57% (257/449)	Not imputed
EVAR : OR	15% : 85% (69 : 380)	0	Not imputed

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).

Updated GAS

The mean updated GAS score was 93 (standard deviation (SD) ±15, Table 3). The Brier Score was 0.21 and the AUC was 0.71 (95% CI 0.66 to 0.76). The calibration plot showed an overestimation of the death rate in patients with a predicted death rate >50% (HL test P=.01, Figure 4). In the quintile of patients with a mean predicted death rate of 66%, the observed death rate was 55% (95% CI 44 to 65%). After recalibration, the plot slightly improved although there was still a

statistically significant deviation between the predicted and observed risks (HL test P=.04, Figure 5). In the quintile of patients with a mean predicted death rate of 60%, the observed death rate was 54% (95% CI 44 to 64%) after recalibration. Subgroup analysis to assess the accuracy in high-risk patients showed that no patients had a predicted death rate ≥95%.

Table 3. The outcomes and distribution in the original dataset and the imputed dataset of the updated GAS, the Vancouver score, the ERAS and the Hardman index.
GAS = Glasgow Aneurysm Score, ERAS = Edinburgh Ruptured Aneurysm Score

Prediction model		Original data		Imputed data
		Available data	Missing data	
Updated GAS		93 (±15)	14% (64/449)	93 (±15)
Vancouver		3.10 (2.66-3.72)	14% (64/449)	3.10 (2.66-3.74)
ERAS score	≤1	79% (274/349)	22% (100/449)	77% (345/449)
	2	17% (61/349)		19% (85/449)
	3	4% (14/349)		4% (19/449)
Hardman index score	0	33% (60/180)	60% (269/449)	32% (62/192)
	1	37% (67/180)		38% (72/192)
	2	23% (42/180)		23% (45/192)
	≥3	6% (11/180)		7% (14/192)

Continuous data are presented as mean ±standard deviation or median (inter-quartile range) and categorical data as percentage (number).

Vancouver score

The median Vancouver score was 3.10 (inter-quartile range 2.66 to 3.72, Table 3). The Brier Score was 0.22 and the AUC was 0.72 (95% CI 0.67 to 0.77). With regard to calibration, in the quintile of patients with a mean predicted death rate of 33%, the observed death rate was 21% (95% CI 14 to 31%), and in the quintile of patients with a mean predicted death rate of 89%, the observed death rate was 62% (95% CI 52 to 71%). Hence, the calibration plot showed an overestimation of death (HL test P<0.01, Figure 6). After recalibration, this overestimation decreased minimally (HL test P<0.01, Figure 7). In high-risk patients there was a significant overestimation of the observed risk by the recalibrated the model. In the quintile of patients with a mean predicted death rate of 82%, the observed death rate was 62% (95% CI 52 to 71%).

Subgroup analysis to assess the accuracy in high-risk patients showed that of 21 patients with a predicted death rate ≥95%, 18 patients died.

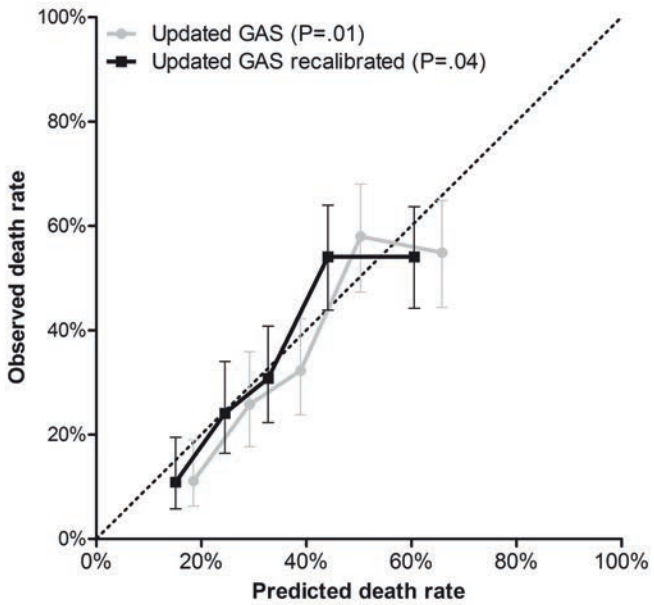

Figure 4. The calibration plots of the updated GAS before and after recalibration. The predicted death rate is plotted with the corresponding death rate and surrounding 95% confidence interval. The interrupted black line indicates ideal calibration. The P corresponds to the Hosmer and Lemeshow test.
GAS = Glasgow Aneurysm Score

$$1 - \frac{1}{1 + (\text{EXP}\ (-5.486 + 0.052 * \text{updated GAS score}))}$$

Figure 5. The formula to calculate the predicted death rate using the updated GAS after recalibration.

ERAS

The distribution of patients per ERAS outcome is shown in Table 3. The Brier Score was 0.23 and the AUC was 0.58 (95% CI 0.52 to 0.64). Calibration was not assessed because of an AUC <0.70.

Subgroup analysis to assess the accuracy in high-risk patients showed that no patients had a predicted death rate ≥95%.

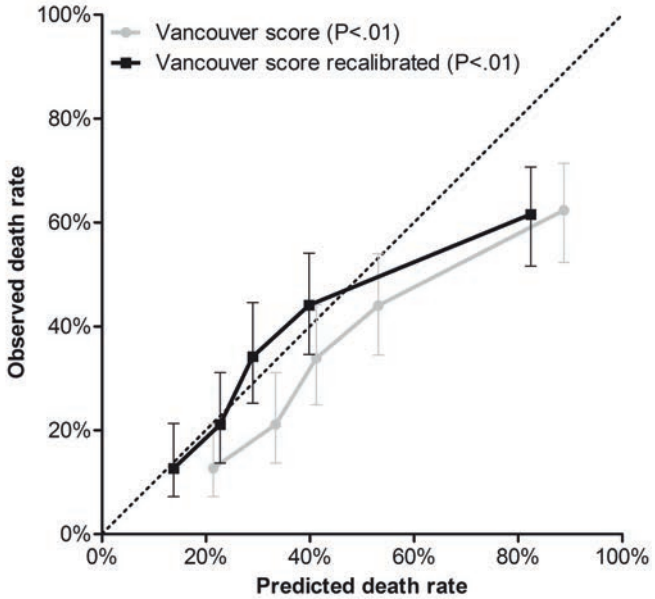

Figure 6. The calibration plots of the Vancouver score before and after recalibration. The predicted death rate is plotted with the corresponding death rate and surrounding 95% confidence interval. The interrupted black line indicates ideal calibration. The P corresponds to the Hosmer and Lemeshow test.

$$1 - \frac{1}{1 + (\text{EXP}\ (-3.973 + \text{Vancouver score}))}$$

Figure 7. The formula to calculate the predicted death rate using the Vancouver score after recalibration.

Hardman index

The distribution of patients per Hardman index outcome is shown in Table 3. In 57% (257/449), the preoperative ECGs was missing. Where the Hardman index could be applied and where a death rate of 100% was predicted the observed death rate was 50% (7/14, 95% CI 27 to 73%, Table 4). In the sensitivity analysis, in patients with a predicted death rate of 100%, the observed death rate was 84% (47/56, 95% CI 72 to 91%).

Table 4. The Hardman index score and corresponding observed 30-day and in-hospital death rate in patients without missing ECGs and in the sensitivity analysis. In the sensitivity analysis, data for missing ECGs were imputed in accordance with the outcome (death or no death).
CI = confidence interval

		Observed death rate (number, 95% CI)
Hardman index score in patients without missing ECGs	0	10% (6/62, 5 to 20%)
	1	32% (23/72, 22 to 43%)
	2	42% (19/45, 29 to 57%)
	≥3	50% (7/14, 27 to 73%)
Hardman index score in the sensitivity analysis	0	5% (6/127, 2 to 10%)
	1	27% (41/152, 21 to 35%)
	2	58% (66/114, 49 to 67%)
	≥3	84% (47/56, 72 to 91%)

Discussion

Our study shows that following intervention for an RAAA the updated GAS predicted death most accurately for both discrimination and calibration. The present study expands on previous studies externally validating the updated GAS, the Vancouver score, the ERAS and the Hardman index in three ways. First, we set a cut-off value of patients in whom withholding intervention might be considered. In this way, we aimed to assess the additional value of the prediction models in clinical practice. Second, the number of patients included (n = 449) was higher than the previous largest study (n = 201).[13] Finally, we recalibrated the updated GAS and Vancouver score to improve accuracy in the era of EVAR.

Decision making

The decision to withhold intervention in patients with an RAAA can be very difficult. Only extremely reliable models can be useful in clinical decision-making and in identifying patients in whom withholding intervention might be considered. For this purpose, we set a cut-off value for the predicted death rate at ≥95%. If the death rate were to be predicted accurately at 95%, the number needed to treat (NNT) would be 20. This cut-off value is arbitrary and could also have been 90% (NNT of 10) or 99% (NNT of 100). Different cut-off values can be used depending on the clinical situation. None of the prediction models met our criterion of identifying patients in whom to withhold intervention.

This disappointing conclusion is in agreement with previous validation studies.[21-23] Currently, the prediction models have insufficient accuracy to evaluate the chances of successful intervention and future studies should focus on improvement towards this aim. The usefulness of current prediction models lies in case mix comparisons between hospitals, and in a tailored prognosis for patients and relatives.

Updated GAS

The updated GAS predicted death most accurately for both discrimination and calibration. Several other studies have validated the GAS.[13, 23-27] In the only previous study including patients treated with EVAR, the AUC was 0.70 (95% CI 0.62 to 0.77).[13] The calibration of the updated GAS was not assessed in this previous study. The strength of the previous validation (201 patients included, multicenter, prospective, including EVAR and OR)[13] confirms our conclusion that the updated GAS is the most accurate in predicting death after intervention for an RAAA. If clinicians consider their patients to be comparable to the ones included in the present study, the model as shown in Figure 5 can be used to predict the risk of dying after intervention.

Vancouver score

The Vancouver score discriminated sufficiently accurately but even after recalibration its predictions still overestimated the death rate considerably. These results are in accordance with previous disappointing results on discrimination[28], but in conflict with previous fairly accurate results on calibration[23]. Therefore, the accuracy of the Vancouver score has not yet been proven and we prefer the updated GAS.

ERAS

The prediction of death by the ERAS were insufficiently accurate. These results are in conflict with one validation study with sufficiently accurate discrimination[25], but in accordance with another validation study with insufficiently accurate discrimination.[23] Concerning calibration, one previous validation reported an observed death rate of 50% in patients with a predicted death rate of 80% (estimated from figure).[23] Because results regarding the ERAS are conflicting, we question its precision.

Hardman index

The accuracy of the Hardman index of the present study is in accordance with previously reported disappointing results.[21, 25, 28] Even after imputation of >50% of the ECGs in accordance with the outcome in the sensitivity analysis, the predicted death rate of 100% corresponded to an observed death rate of only 84% (Table 4). Our statistical analysis of the Hardman index was hampered in two ways. First, overall performance, discrimination and calibration could not be assessed because a score of <3 did not correspond to a specific predicted death rate. Second, 57% of preoperative ECGs missing. Rightfully, one might question our imputation of missing ECGs in the sensitivity analysis. Probably, most ECGs were missing in hemodynamically unstable patients who were operated on as soon as possible. To illustrate, the death rate in patients with and without Hardman index was 29% (95% CI 23 to 35%) and 41% (95% CI 35 to 47%), respectively. Based on these results we are reluctant to draw definite conclusions regarding the accuracy of the Hardman index. The missing ECGs are a drawback of the present study, and also of the scoring system. Most surgical trainees and vascular surgeons do not know how to interpret an ECG with sufficient precision to use it as a variable in a prediction model. From a cardiac perspective, acute ischemia defined by ST segment depression greater than 1 millimeter or an associated T wave change is an oversimplification of the great diagnostic value of an ECG. Based on these considerations we are convinced that in our clinical practice the contribution of a preoperative ECG is limited and, consequently, that the Hardman index is not a useful prediction model.

Limitations

A limitation of the present study was the retrospective data collection. Probably, the variables 'best recorded in-hospital Glasgow coma scale' for the ERAS and 'loss of consciousness' for the Vancouver score contains imprecise data. Another limitation was the amount of missing data (Tables 2 and 3). This is a consequence of the acute character of the disease. Except for the missing ECGs, we coped with this problem by multiple imputation. Death was included as a predictor in the imputation model to correct for the bias that the most missing data was in patients who died. Two other prediction models have been described in the literature, the RAAA-physiological and operative severity score for enumeration of mortality and morbidity (RAAA-POSSUM)[29] and the Vascular Study Group of New England (VSGNE) RAAA score[23]. The RAAA-POSSUM was not included in

the present study because of its complexity including chest X-ray examination, and hence low clinical applicability. The VSGNE RAAA score was not included in the present study because of the use of an intra-operative variable, thereby making predictions prior to the intervention impossible. A final limitation was that a separate analysis in patients treated with EVAR and OR could not be done. Because of a low event rate in patients treated with EVAR (19/69), we were reluctant to draw conclusions regarding the accuracy in patients treated with EVAR and OR separately. Recently published randomized clinical trials reported a comparable death rate after EVAR and OR.[14, 30] This indicates that the risk-profiles are based on the same pre-operative variables and that the accuracy of the prediction models probably do not differ substantially between both interventions.

Conclusions

The updated GAS most accurately predicted death after intervention for an RAAA. However, the updated GAS did not identify patients with a predicted death rate ≥95% and therefore cannot reliably support the decision to withhold intervention.

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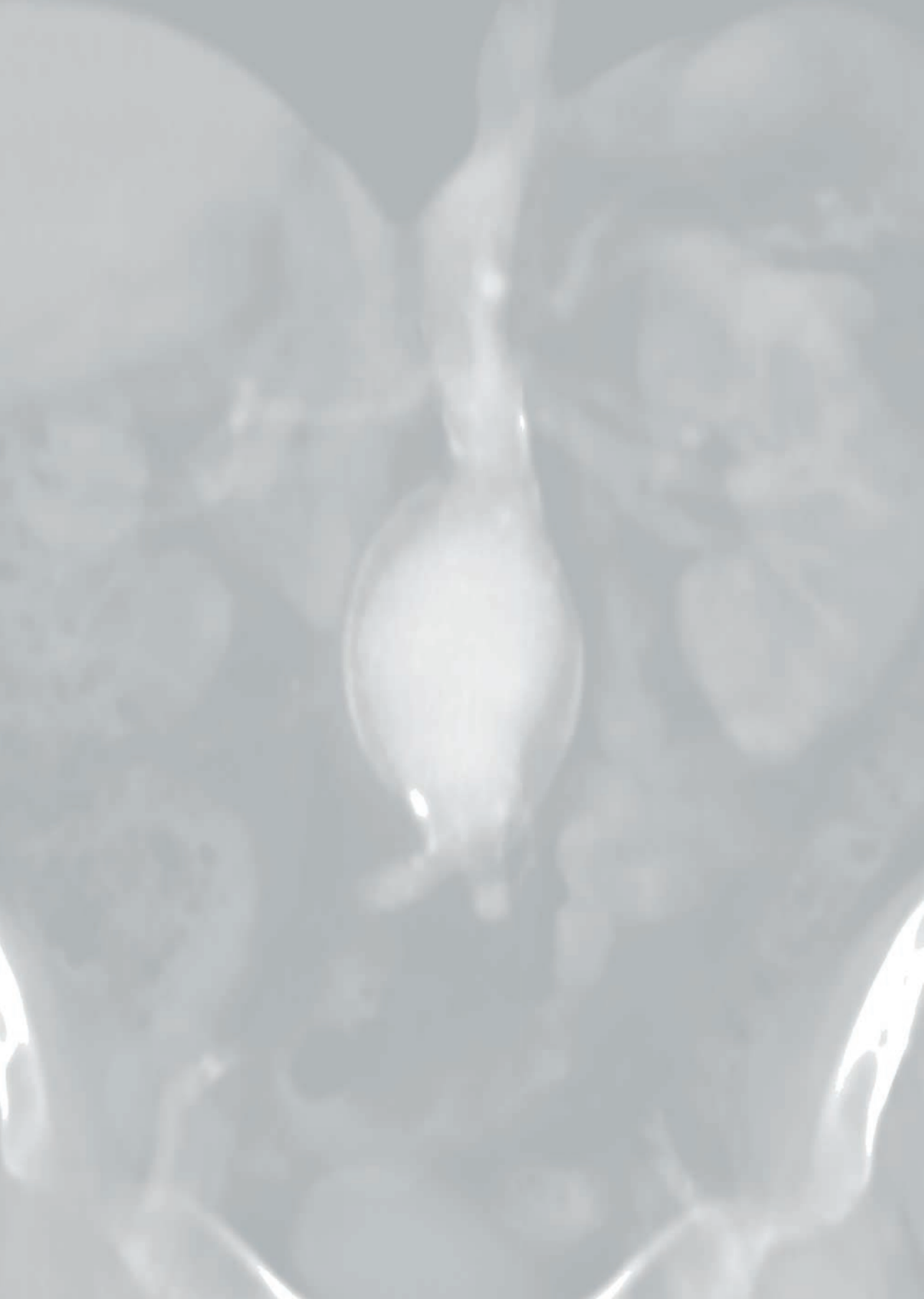

Chapter 5

Acute kidney injury defined according to the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria after repair for a ruptured abdominal aortic aneurysm

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Abstract

Background

Acute kidney injury (AKI) is a serious complication after repair of a ruptured abdominal aortic aneurysm (RAAA). In the present Society for Vascular Surgery (SVS)/International Society for Cardio Vascular Surgery (ISCVS) reporting standards patients are classified as no dialysis (grade I), as temporary dialysis (grade II), and as permanent dialysis or fatal outcome (grade III). However, AKI is a broad clinical syndrome including more than the requirement for renal replacement therapy. The recently introduced 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) classification for AKI comprises three severity categories based on serum creatinine and urine output ('Risk,' 'Injury,' and 'Failure'). The objective of the present study was to assess the incidence of AKI using the RIFLE criteria (AKI_{RIFLE}). Secondary objectives were to assess the incidence of AKI as defined using the SVS/ISCVS reporting standards ($AKI_{SVS/ISCVS}$) and the association between AKI_{RIFLE} and death.

Methods

This was an observational cohort study in 362 consecutive patients with an RAAA in three hospitals in Amsterdam (The Netherlands) between 2004 and 2011. The end points were the incidence of AKI_{RIFLE}, of $AKI_{SVS/ISCVS}$, and the combined 30-day or in-hospital death rate. A multivariable logistic regression model was made to assess the association between AKI_{RIFLE} and death after adjustment for preoperative shock profile (Glasgow Aneurysm Score) and postoperative shock profile (Acute Physiology and Chronic Health Evaluation (APACHE) II score, use of vasopressors, and fluid balance during the first 24 hours after intervention).

Results

AKI_{RIFLE} occurred in 74% (267/362, 95% confidence interval (CI), 69 to 78%), with 27% of these patients categorized as 'Risk' (71/267, 95% CI 22 to 32%), 39% categorized as 'Injury' (104/267, 95% CI 33 to 45%), and 34% categorized as 'Failure' (92/267, 95% CI 29 to 40%). $AKI_{SVS/ISCVS}$ occurred in 48% (175/362, 95% CI 43 to 53%), with 53% of these categorized as 'grade I' (92/175, 95% CI 45 to 60%), 19% as 'grade II' (34/175, 95% CI 14 to 26%), and 28% as 'grade III' (49/175, 95% CI 22 to 35%). After multivariable adjustment for shock profiles the risk of dying in patients categorized as AKI_{RIFLE} 'Failure' was greater than in patients without AKI_{RIFLE} (adjusted odds ratio 6.36, 95% CI 2.23 to 18.13).

Conclusion

The incidence of AKI defined according to the RIFLE criteria (74%) was greater than defined using the SVS/ISCVS reporting standards (48%) and patients categorized as 'Failure' using the RIFLE criteria had a greater risk of dying than patients without AKI. These results indicate that the problem of AKI is much bigger than previously anticipated and that minimizing injury to the kidney could be an important focus of future research on reducing the death rate after RAAA repair.

Introduction

Acute kidney injury (AKI) is a serious complication of repair for a ruptured abdominal aortic aneurysm (RAAA). Previous studies report an incidence of AKI ranging between 20% and 34%.[1-3] AKI after an RAAA is multifactorial and includes acute-on-chronic nephrosclerosis because of age and general atherosclerotic vascular disease, hypovolemic state, aortic cross-clamping, and use of medication and contrast media.[1, 4]

The reporting standards by the Society for Vascular Surgery (SVS)/ International Society for CardioVascular Surgery (ISCVS) define three grades of AKI: 'grade I,' no dialysis; 'grade II,' temporary dialysis; or 'grade III,' permanent dialysis or fatal outcome (Table 1).[5] In RAAA studies, renal replacement therapy (RRT) is often used as an end point based on these SVS/ISCVS reporting standards.[6, 7] However, AKI is a broad clinical syndrome including more than the requirement for RRT. In 2004, the Acute Dialysis Quality Initiative group introduced the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria for AKI based on serum creatinine (SCr) and urine output criteria (Table 1).[8] The aim of this multidisciplinary consensus classification was to standardize the definition of AKI for clinical and research purposes and to reflect the complete spectrum of the disease. The RIFLE classification is the first widely accepted definition for AKI and has been validated in more than half a million patients worldwide.[9-11]Even mild, reversible AKI defined using the RIFLE criteria has important clinical consequences including an increased risk of short-term death[11] and worse long-term survival.[12] Therefore, in daily practice the RIFLE criteria can be used to identify high-risk patients. To date, only two smaller retrospective studies have applied the RIFLE criteria to patients with an RAAA.[13, 14]

The primary objective of the present study was to assess the incidence of AKI in a large cohort of RAAA patients defined using the RIFLE criteria (AKI_{RIFLE}). Secondary objectives were to assess the incidence of AKI defined using the SVS/ISCVS reporting standards ($AKI_{SVS/ISCVS}$), to assess he association between AKI_{RIFLE} and death, and to assess the need for RRT (in-hospital and permanent after discharge).

Table 1. The 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria and the Society for Vascular Surgery/ International Society for CardioVascular Surgery (SVS/ISCVS) reporting standards for acute kidney injury (AKI).
SCr = serum creatinine, GFR = glomerular filtration rate

Category	RIFLE SCr criteria [a]	RIFLE urine output criteria
Risk	Increase ≥1.5 times from baseline or GFR decrease >25%	<0.5 mL/kg/h ≥6 hours
Injury	Increase ≥2 times from baseline or GFR decrease >50%	<0.5 mL/kg/h ≥12 hours
Failure	Increase ≥3 times from baseline or GFR decrease >75% or ≥354 µmol/L with an acute increase ≥44 µmol/L from baseline	<0.3 mL/kg/h ≥24 hours or anuria ≥12 hours
Loss	Complete loss of kidney function >4 weeks	
End-stage	Complete loss of kidney function >3 months	
	SVS/ISCVS reporting standards	**SVS/ISCVS reporting standards in the present study**
I	No dialysis	SCr >159 µmol/L within 7 days after admission
II	Temporary dialysis, prolonged hospitalization, permanently reduced renal function	Temporary dialysis
III	Permanent dialysis, transplant, or fatal outcome	Permanent dialysis or temporary dialysis with fatal outcome

For the RIFLE criteria, only one criterion (SCr or urine output) has to be fulfilled to qualify for a category. Patients are classified based on the criterion that places them in the worst category.
[a] Based on change between two SCr values within 7 days after admission.

Methods

The present study is a sequel to the Amsterdam Acute Aneurysm Trial (registration ISRCTN: 66212637) conducted in the Amsterdam ambulance region between 2004 and 2011. Details of this study have been published previously.[7, 15] In brief, care for patients with an RAAA was centralized at the Academic Medical Center (AMC), the Onze Lieve Vrouwe Gasthuis (OLVG), and the VU University Medical Center (VUMC).

The present study included all prospectively registered consecutive patients with repair for an RAAA at the AMC, the OLVG, and the VUMC. Patients who died during intervention or shortly thereafter and preoperative permanent dialysis patients were excluded from the analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki. No patient consent was needed because of the observational study design.

End points

The end points were the incidence of AKI_{RIFLE}, of $AKI_{SVS/ISCVS}$, the combined 30-day or in-hospital death rate, temporary in-hospital RRT, and permanent dialysis after discharge.

RIFLE criteria

Patients were categorized as 'no AKI,' 'Risk,' 'Injury,' or 'Failure' based on the worst SCr and urine output category during the first week of intensive care unit (ICU) admission (Table 1).[8] The SCr category was assessed by comparing the highest SCr with a baseline SCr. The baseline SCr was defined according to the recommendations of the RIFLE criteria and comprised five steps (Figure 1). The most recent SCr within 1 year before intervention ('premorbid SCr') and the in-hospital SCr before intervention ('preoperative SCr') were collected. An 'estimated SCr' was calculated by solving the modification of diet in renal disease (MDRD) equation.[16] This equation assumes a glomerular filtration rate (GFR) of 75 mL/min/1.73 m^2; SCr = $(75/[186 \times (age^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})])^{-0.887}$. The first step of the baseline SCr approximation was to compare the 'premorbid SCr' with the 'preoperative SCr.' The lowest of these values served as the baseline SCr. The second step was in patients with no renal comorbidity to compare the 'estimated SCr' with the 'preoperative SCr.' Again, the lowest value of these served as the baseline SCr. The third step was in patients with renal comorbidity to use the 'preoperative SCr' as baseline SCr. In three patients no baseline SCr could be created in this way and the 'preoperative SCr' was used (step 4) or was imputed with the median baseline SCr of patients with renal comorbidity (154 µmol/L) (step 5). Renal comorbidity was defined as a previous history of chronic kidney failure. The urine output category was estimated in blocks of 6, 12, and 24 hours and the lowest urine output was used for categorization. In patients treated with RRT, the AKI category before start of RRT was reported.

SVS/ISCVS reporting standards

Patients were categorized as 'no AKI,' 'grade I,' 'grade II,' or 'grade III' (Table 1).[5] Based on a previous study in RAAAs reporting about AKI, patients were categorized as 'grade I' if the highest SCr during the first week of ICU admission was >159 µmol/L (>1.8 mg/dL).[3] The decision to initiate RRT was based on the caregivers' judgment of the severity of illness, the presence of oliguria or fluid overload, the number and type of failed nonrenal factors, and whether the patient was recovering or deteriorating.

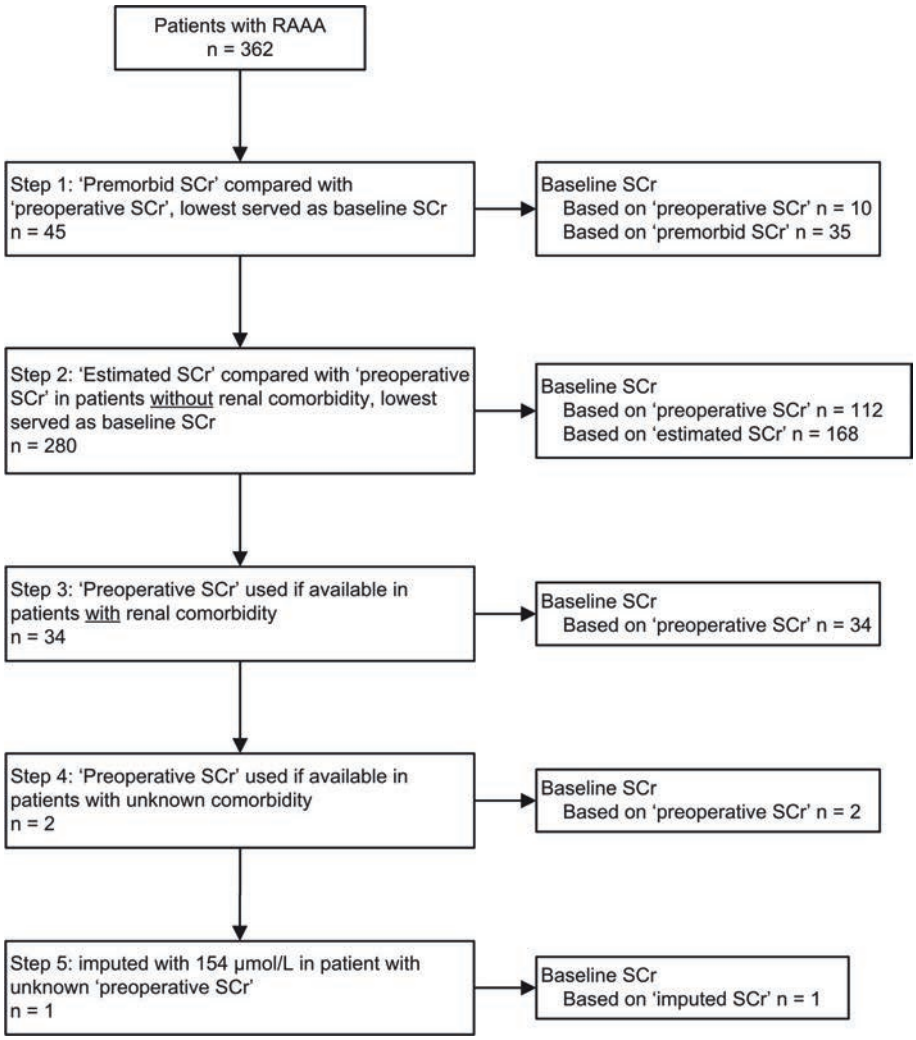

Figure 1. Method of baseline serum creatinine (SCr) approximation. The most recent SCr level within 1 year before the intervention was used as premorbid SCr. The in-hospital SCr level before the ruptured abdominal aortic aneurysm (RAAA) intervention was used as the preoperative SCr. Estimated SCr = assuming a glomerular filtration rate (GFR) of 75 mL/min/1.73 m^2, SCr = $(75/[186 \times (age^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})])^{-0.887}$. The imputed SCr was calculated as the median baseline SCr of patients with renal comorbidity (154 µmol/L).

Data collection

Data were collected retrospectively using Microsoft Office Access 2003 (Microsoft Corporation, Redmond, Wash). Preoperative data were collected from the admission charts and included age (years), sex, comorbidities, body mass

index, lowest in-hospital systolic blood pressure (mmHg) and the application of cardiopulmonary resuscitation. The preoperative variables were defined according to the reporting standards of the SVS/ISCVS.[17] Postoperative data were collected from the electronic charts of the ICU (iMDsoft, MetaVision, Needham, Mass) and included daily SCr, hourly urine output, and the initiation of RRT. The electronic charts showed the exact urine output per hour and were filled in prospectively by ICU staff from the start of ICU admission. All three hospitals used continuous venovenous hemofiltration as temporary RRT. The first 24 hours after intervention the APACHE II score, the use of vasopressors, and the fluid balance were collected. The use of vasopressors was categorized as none (no ICU admission or no vasopressors administered), low dose (noradrenalin <2 μg/min or dopamine <500 μg/min), or high dose (any adrenalin, noradrenalin >2 μg/min, or dopamine >500 μg/min). The fluid balance was categorized by evenly distributing the number of patients in tertiles.

Data on patients requiring RRT after discharge was obtained from the Dutch Renal Replacement Registry, accessed on January 1, 2013 (RENINE, Leiden, The Netherlands).[18]

Statistical analysis

Data were analyzed using IBM SPSS Statistics 20.0 (SPSS Inc., Armonk, NY). Results are presented as mean ± standard deviation for normally distributed data and as median with inter-quartile range (IQR) for data with a skewed distribution. The statistical analysis comprised two steps. First, the incidence of AKI defined using both definitions and corresponding death rates were calculated. Second, a multivariable logistic regression model was made to assess the association between AKI_{RIFLE} and death. The model aimed to adjust for preoperative and postoperative shock profile. The Glasgow Aneurysm Score (GAS) was used as a surrogate marker for preoperative shock profile.[19] The APACHE II score, the use of vasopressors, and the fluid balance during the first 24 hours after intervention were used as markers for postoperative shock profile.

To include all patients in the regression model an imputation procedure was done using logistic and linear regression models whereby 10 datasets were created. The predictors in the imputation model were the baseline characteristics and the level of consciousness, serum hemoglobin, AKI_{RIFLE}, and $AKI_{SVS/ISCVS}$, and death.

Results

Between 2004 and 2011, 457 consecutive patients with an RAAA presented at the AMC, OLVG, and VUMC. Of these patients, 50 did not undergo intervention. Of 407 patients eligible for inclusion, 45 were excluded because of death during the intervention (n = 32), death within 6 hours after the intervention (n = 9), charts could not be retrieved (n = 3), or preoperative permanent dialysis (n = 1). The baseline characteristics of the 362 patients included in the analysis are shown in Table 2. Sixty-eight patients were treated with endovascular aneurysm repair (EVAR) and 294 patients were treated with open repair (OR). The combined 30-day or in-hospital death rate was 27% (97/362, 95% CI 22 to 32%). The baseline SCr was based on the 'estimated SCr' in 168 patients, on the 'preoperative SCr' in 158 patients, on the 'premorbid SCr' in 35 patients, and was imputed in one patient (Figure 1).

AKI defined according to the RIFLE criteria

Seventy-four percent of patients developed AKI_{RIFLE} (267/362, 95% CI 69 to 78%), with 27% categorized as 'Risk' (71/267, 95% CI 22 to 32%), 39% categorized as 'Injury' (104/267, 95% CI 33 to 45%), and 34% categorized as 'Failure' (92/267, 95% CI 29 to 40%, Table 3). Figure 2 shows the death rate per RIFLE category. Multivariable adjustment showed that patients categorized as 'Failure' had a higher risk of dying (adjusted odds ratio 6.36, 95% CI 2.23 to 18.13) than patients without AKI (Table 4).

Table 2. Baseline characteristics of 362 patients with a ruptured abdominal aortic aneurysm.
BMI = body mass index, SBP = systolic blood pressure, SCr = serum creatinine, EVAR = endovascular aneurysm repair, OR = open repair, GAS = Glasgow Aneurysm Score, APACHE = Acute Physiology and Chronic Health Evaluation, GFR = glomerular filtration rate

Variable	Value	Missing data
Age (years)	76 (69-81)	0
Male : Female	81% : 19% (294 : 68)	0
Cardiac co-morbidity	42% (152/360)	1% (2/362)
Pulmonary co-morbidity	23% (83/359)	1% (3/362)
Renal co-morbidity	12% (42/359)	1% (3/362)
Cerebrovascular co-morbidity	16% (58/360)	1% (2/362)
Diabetes	10% (37/356)	2% (6/362)
Hypertension	43% (154/358)	2% (4/362)
BMI (kg/m^2)	25.6 (23.4-27.8)	12% (42/362)
Lowest preoperative in-hospital SBP (mmHg)	98 (74-128)	4% (13/362)
Preoperative cardiopulmonary resuscitation	8% (27/351)	3% (11/362)
Premorbid SCr (available in 45 patients, µmol/L)	84 (64-108)	88% (317/362)
Preoperative SCr (available in 359 patients, µmol/L)	104 (85-132)	1% (3/362)
Estimated SCr (µmol/L)	98 (95-100)	12% (45/362)
Baseline SCr (µmol/L)	96 (74-100)	0
EVAR : OR	19% : 81% (68 : 294)	0
Preoperative GAS	91 (81-103)	4% (16/362)
APACHE II score	19 (15-24)	8% (30/362)
Use of vasopressors 24 hours after intervention		0
None	33% (120/362)	
Low dose	45% (162/362)	
High dose	22% (80/362)	
Fluid balance first 24 hours after intervention		0
<2 L positive	36% (132/362)	
>2 L and <5 L positive	36% (130/362)	
>5 L positive	28% (100/362)	

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).
Premorbid SCr value was derived from the most recent SCr level within 1 year before the intervention. Preoperative SCr was the in-hospital SCr level before the intervention for RAAA. Estimated SCr = assuming a GFR of 75 mL/min/1.73 m^2 and SCr = $(75/[186 \times (age^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})])^{-0.887}$.

Table 3. The incidence of acute kidney injury (AKI) defined according to the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria and according to the Society for Vascular Surgery/International Society for CardioVascular Surgery (SVS/ISCVS) reporting standards.
EVAR = endovascular aneurysm repair, OR = open repair, SCr = serum creatinine, CI = confidence interval

		All patients n = 362	EVAR n = 68	OR n = 294
RIFLE criteria				
Any AKI		74% (267/362, 69 to 78)	63% (43/68, 51 to 74)	76% (224/294, 71 to 81)
AKI category	Risk	27% (71/267, 22 to 32)	33% (14/43, 20 to 47)	25% (57/224, 20 to 32)
	Injury	39% (104/267, 33 to 45)	40% (17/43, 26 to 54)	39% (87/224, 33 to 45)
	Failure	34% (92/267, 29 to 40)	28% (12/43, 17 to 43)	36% (80/224, 30 to 42)
If AKI, reason	Urine output	44% (117/267, 38 to 50)	51% (22/43, 37 to 65)	42% (95/224, 36 to 49)
	SCr	30% (80/267, 25 to 36)	28% (12/43, 17 to 43)	30% (68/224, 25 to 37)
	Urine output and SCr	26% (70/267, 21 to 32)	21% (9/43, 11 to 35)	27% (61/224, 22 to 33)
Days after intervention of AKI category		3 (2-4)	3 (2-4)	3 (2-4)
SVS/ISCVS reporting standards				
Any AKI		48% (175/362, 43 to 53)	40% (27/68, 29 to 52)	50% (148/294, 45 to 56)
AKI category	I	53% (92/175, 45 to 60)	74% (20/27, 55 to 87)	49% (72/148, 41 to 57)
	II	19% (34/175, 14 to 26)	11% (3/27, 4 to 28)	21% (31/148, 15 to 28)
	III	28% (49/175, 22 to 35)	15% (4/27, 6 to 32)	30% (45/148, 24 to 38)
Days after intervention of AKI category		3 (2-4)	3 (2-4)	3 (2-4)

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number, 95% CI).

AKI defined according to the SVS/ISCVS reporting standards

Forty-eight percent of patients developed $AKI_{SVS/ISCVS}$ (175/362, 95% CI 43 to 53%), with 53% of these categorized as 'grade I' (92/175, 95% CI 45 to 60%), 19% as 'grade II' (34/175, 95% CI 14 to 26%), and 28% as 'grade III' (49/175, 95% CI 22 to 35%, Table 3). Figure 2 shows the death rate per SVS/ISCVS reporting standards category.

RRT

The RRT rate during admission was 23% (83/362, 95% CI 19 to 28%). The median duration of RRT was 6 days (IQR 2-14 days). The RRT rate during admission was: after EVAR, 10% (7/68, 95% CI 5 to 20%) and after OR, 26% (76/294, 95% CI 21 to 31%). The permanent RRT rate after discharge was 2% (6/265, 95% CI 1 to 5%).

Table 4. Multivariable logistic regression model to assess the association between acute kidney injury (AKI) defined according to the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria and death.
CI = confidence interval, GAS = Glasgow Aneurysm Score, APACHE = Acute Physiology and Chronic Health Evaluation

Variable		Odds ratio (95% CI)
GAS		1.04 (1.02 to 1.06)*
APACHE II score	5-15 (n = 99)	Reference category
	15-19 (n = 94)	0.55 (0.18 to 1.66)
	19-24 (n = 93)	0.85 (0.26 to 2.77)
	24-44 (n = 76)	0.67 (0.21 to 2.15)
Use of vasopressors	None (n = 120)	Reference category
	Low dose (n = 162)	0.83 (0.37 to 1.83)
	High dose (n = 80)	2.79 (1.17 to 6.68)*
Fluid balance	<2 L (n = 132)	Reference category
	>2 L or <5 L positive (n = 130)	4.65 (1.89 to 11.48)*
	>5 L positive (n = 100)	9.93 (3.66 to 26.90)*
AKI defined according to the RIFLE criteria	No (n = 95)	Reference category
	Risk (n = 71)	0.98 (0.31 to 3.06)
	Injury (n = 104)	1.99 (0.71 to 5.56)
	Failure (n = 92)	6.36 (2.23 to 18.13)*

The model included 362 patients and 97 events: Hosmer and Lemeshow test P=.21-.96 (8 df), AUC 0.87.
* P <.05

Discussion

Most surgically treated RAAA patients develop AKI defined using the RIFLE criteria. The incidence of AKI defined using the RIFLE criteria was much higher (74%) than anticipated according to the SVS/ISCVS reporting standards (48%). A large group of patients (92/362) was categorized as 'Failure' and these patients had a greater risk of dying than patients without AKI. Therefore, in clinical practice the RIFLE criteria can be used to identify high-risk patients.

The RIFLE criteria

A direct comparison between the RIFLE criteria and the SVS/ISCVS reporting standards is inappropriate. The RIFLE criteria can be used to improve risk-stratification for clinical and research purposes and the SVS/ISCVS reporting standards are used to score severe complications for research purposes only.

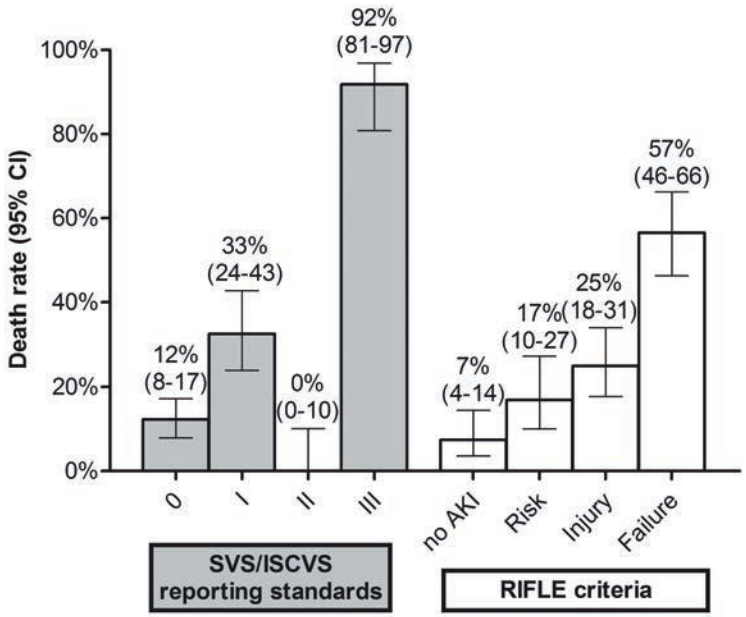

Figure 2. Death rate and surrounding 95% confidence interval (CI) in patients surviving repair stratified according to $AKI_{SVS/ISCVS}$ category and AKI_{RIFLE} category.
AKI = acute kidney injury, SVS = Society for Vascular Surgery, ISCVS = International Society for CardioVascular Surgery, RIFLE = 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage'

Interestingly, in half of the patients (51%, 184/362) the SVS/ISCVS reporting standards either did not diagnose or underestimated the severity of AKI compared with the RIFLE criteria. The patients additionally identified by the RIFLE criteria who were categorized as 'Failure' had a greater risk of dying than patients without AKI after adjustment for shock profiles (adjusted odds ratio 'Failure' vs 'no AKI' 3.04, 95% CI 1.02 to 9.03). This underlines the clinical importance of AKI defined using the RIFLE criteria in addition to the SVS/ISCVS reporting standards. Furthermore, we are convinced that in future studies reporting about AKI after an RAAA the RIFLE criteria should play a central role.

With use of an electronic chart including daily SCr and hourly urine output, patients can be categorized for the RIFLE criteria automatically. A baseline SCr is needed to apply the RIFLE SCr criteria. Although there is debate regarding the optimal methods to approximate the baseline SCr in acute settings,[20] the recommendations of the RIFLE criteria anticipate this issue and we adhered to it accordingly.[8] The baseline SCr has to be a recent measure, either the 'premorbid SCr' or the 'preoperative SCr.' In patients with no renal comorbidity

and no measure of baseline SCr, one can estimate the baseline SCr with use of the 'estimated SCr.' The 'estimated SCr' has been shown to be valid in patients with normal renal function.[16] The RIFLE criteria give no recommendations for baseline SCr approximation in patients with renal comorbidity. We used the 'preoperative SCr' in patients with renal comorbidity. There are several drawbacks of the methods of baseline SCr approximation specifically for our study. The 'premorbid SCr' might have been available in patients recently hospitalized thereby overestimating the baseline SCr. The 'estimated SCr' assumes a GFR of 75 mL/min/1.73 m^2, which might overestimate renal function in patients with atherosclerotic vascular disease. The 'preoperative SCr' was affected by hypovolemia thereby overestimating the baseline SCr. In our cohort of patients the 'premorbid SCr' (median 84 µmol/L, IQR 64-108 µmol/L), the 'estimated SCr' (median 98 µmol/L, IQR 95-100 µmol/L) and the 'preoperative SCr' (median 104 µmol/L, IQR 85-132 µmol/L) barely differed. This confirms that the baseline SCr approximation was accurate by adhering to the recommendations of the RIFLE criteria.

In critically ill patients admitted to the ICU, there is a stepwise increase of death rate per RIFLE category adjusted for multiorgan failure.[11] Figure 2 suggests an increasing death rate per increasing AKI severity in RAAA patients. After multivariable adjustment for shock profiles, this association was not significant for the 'Risk' and 'Injury' categories (Table 4). It might be that after RAAA repair the short-term negative effects of mild AKI are less pronounced. However, another plausible explanation for the lack of statistical significance is our limited sample size.

An advantage of the RIFLE criteria is that they have been validated in other acute conditions. For example, the incidence of AKI defined using the RIFLE criteria in patients with an RAAA is high compared with patients with an acute myocardial infarction (15%, 95% CI 13 to 17%)[9] and comparable with patients with severe burns (62%, 95% CI not available).[10]

In the present study, the MDRD equation was used to estimate baseline GFR and thereby baseline SCr. It has been suggested that estimations of GFR such as the MDRD equation should also be used to estimate GFR for AKI.[21] However, estimations of GFR were only validated in subjects suffering from chronic kidney injury.[22] Current estimations of GFR are invalid in a clinical situation where renal function is rapidly changing, which was underlined by poor performance in sick hospitalized patients[23] and in critically ill patients with early AKI.[24]

Previous studies

One previous study that assessed AKI_{RIFLE} after elective intervention for an asymptomatic abdominal aortic aneurysm reported an incidence of 22% (15/69, 95% CI 14 to 33%).[25] Two previous studies that assessed AKI_{RIFLE} in patients with an RAAA reported an incidence of 80% (16/20, 95% CI 58 to 92%)[14] and of 76% (106/140, 95% CI 66 to 81%),[13] which is comparable with our results. The present study expands on these two previous studies in three ways. First, patients were identified prospectively and consecutively. Second, the number of patients included was considerably larger (362 vs 20[14] and 140[13]). Third, we applied the original RIFLE definition and based AKI severity on SCr and urine output criteria. Kopolovic et al used a modified RIFLE definition based on SCr only.[13] The use of the RIFLE definition without the urine output criteria significantly underestimates the incidence and grade of AKI, significantly delays the diagnosis of AKI, and also results in a higher AKI-related death rate.[26]

The need for RRT after OR of 26% (95% CI 21 to 31%) was comparable with a previously reported RRT rate after OR of 24% (95% CI 17 to 34%).[27] The death rate in patients receiving RRT was 54% (45/83, 95% CI 44 to 65%). This is lower if compared with previous studies reporting a death rate between 75% and 87% after RRT in patients with an RAAA.[27, 28] It is possible that caregivers at the AMC, OLVG, and VUMC had a more liberal policy of starting RRT.

In the Amsterdam Acute Aneurysm Trial, the need for either temporary or permanent dialysis was observed significantly less often after EVAR than after OR.[7] In the present study, the incidence of AKI defined using the RIFLE criteria was lower after EVAR (63%, 95% CI 51 to 74%) than after OR (76%, 95% CI 71 to 81%). Possibly, the problem of AKI is smaller after EVAR than after OR. However, studies powered on the end point AKI are needed to draw definite conclusions on this matter.

Future research

The incidence of AKI was much greater than anticipated. This indicates that minimizing potential injury to the kidney pre-, intra-, and postoperatively could be an important focus of future research on reducing the death rate after RAAA repair. SCr is a late marker of kidney injury. It has been suggested that novel biomarkers including interleukin-18, kidney injury molecule-1, or *N*-acetyl-b-D-glucosaminidase might help to detect AKI earlier and thereby improve AKI diagnostics.[29] Treatment currently suggested for AKI is mostly supportive,

including maintenance of kidney perfusion, treatment of obstruction, nutrition and glycemic control, and avoiding nephrotoxins.[30, 31] Several studies have addressed the balance between fluid administration to maintain renal perfusion and the damage caused by fluid overload. The risk of AKI is decreased with goal-directed therapy for fluid resuscitation,[32] which comprises strictly monitored early aggressive fluid and vasoactive drug administration. For patients with an RAAA, possible future therapies to prevent AKI are mannitol,[33] renal cooling if suprarenal aortic-cross clamping is needed,[34] or the use of carbon dioxide as a contrast agent during EVAR.[35] However, more evidence is required before definite conclusions can be drawn.

The RIFLE criteria have been updated recently.[30] This update recommends classification of patients treated with RRT in the 'Failure' category. Only a few validation studies have been done using these recommendations. For this reason, we focused our study on the original and most widely accepted RIFLE criteria and reported in patients treated with RRT the AKI category before start of RRT. As extra information, patients treated with RRT were put into the 'Failure' category in accordance with the most recent recommendations (Table 5). Future studies could determine the clinical importance of the updated criteria compared with the original RIFLE criteria in patients with an RAAA.

Table 5. The incidence of acute kidney injury (AKI) defined according to the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria when patients treated with renal replacement therapy (RRT) were put into the 'Failure' category.
CI = confidence interval, SCr = serum creatinine

		All patients n = 362
Any AKI		74% (269/362, 70 to 79%)
AKI category	Risk	23% (62/269, 18 to 28%)
	Injury	33% (88/269, 27 to 39%)
	Failure	44% (119/269, 38 to 50%)
If AKI, reason	Urine output	34% (92/269, 29 to 40%)
	SCr	23% (63/269, 19 to 29%)
	Urine output and SCr	15% (40/269, 11 to 20%)
	RRT	28% (74/269, 23 to 33%)

Data are presented as percentage (number, 95% CI).

Limitations

A limitation of the present study was that 60 patients of the Amsterdam ambulance region were not referred to the AMC, OLVG, or VUMC and underwent intervention at a regional hospital.[15] In these patients, the death rate was high (50%, 95% CI 38 to 62%). It is probable that the incidence of AKI and the need for RRT was greater in these patients than in the patients included in the present study. However, data regarding urine output were insufficiently accurate in the regional hospitals, which was the reason these patients were not included.

An exploratory analysis showed that age and blood loss were greater in patients with AKI than in patients without AKI (Table 6). Cardiac comorbidity and suprarenal aortic cross-clamping were more prevalent in patients with AKI than in patients without AKI. The preoperative shock profile represented by the GAS and the postoperative shock profile represented by the APACHE II score, the use of vasopressors and the fluid administration in the first 24 hours after intervention were also worse in patients with AKI. Data collection was retrospective. For this reason, we were reluctant to draw any solid conclusions regarding factors leading to AKI. We consider AKI such a multifactorial syndrome that our statistical methods fell short in the identification of pre-, per-, and postoperative risk factors.

The regression model (Table 4) should be interpreted with some caution. We tried to eliminate effects of confounding factors. We aimed to represent the patients' preoperative shock profile with the GAS and the postoperative shock profile with the APACHE II score, and the use of vasopressors and fluid balance during the first 24 hours after intervention. These representations of shock profiles might not be sufficiently accurate. Moreover, a low event rate meant that we could not include more variables in the logistic regression model. We could not adjust for confounders such as aortic cross-clamping, blood loss during intervention, and administration of medication.

Table 6. Pre-, per-, and postoperative characteristics of patients with and without acute kidney injury (AKI) defined according to the 'Risk,' 'Injury,' 'Failure,' 'Loss,' and 'End-stage' (RIFLE) criteria.
BMI = body mass index, SBP = systolic blood pressure, CPR = cardiopulmonary resuscitation, SCr = serum creatinine, GAS = Glasgow Aneurysm Score, OR = open repair, EVAR = endovascular aneurysm repair, APACHE = Acute Physiology and Chronic Health Evaluation, ICU = intensive care unit,

		No AKI n = 95	AKI n = 267	P	Missing data
Preoperative					
Age (years)		73 (66-78)	76 (70-81)	<.01 [a]	0
Cardiac co-morbidity		32% (30/95)	46% (122/265)	.01 [b]	1% (2/362)
Pulmonary co-morbidity		25% (24/95)	22% (59/264)	.56 [b]	1% (3/362)
Renal co-morbidity		11% (10/95)	12% (32/264)	.68 [b]	1% (3/362)
Cerebrovascular co-morbidity		19% (18/95)	15% (40/265)	.38 [b]	1% (2/362)
Diabetes		11% (10/93)	10% (27/263)	.89 [b]	2% (6/362)
Hypertension		38% (35/93)	45% (119/265)	.22 [b]	1% (4/362)
BMI (kg/m²)		26.0 (23.9-27.8)	25.4 (23.4-27.6)	.62 [a]	39% (141/362)
Lowest in-hospital SBP (mmHg)		110 (80-140)	90 (70-120)	<.01 [a]	4% (13/362)
CPR		5% (5/92)	9% (22/259)	.34 [b]	3% (11/362)
Baseline SCr (µmol/L)		90 (73-100)	96 (74-100)	.09 [a]	0
GAS		83 (75-98)	94 (84-105)	<.01 [a]	4% (16/362)
Peroperative					
If OR, suprarenal aortic cross clamping		26% (18/70)	41% (88/217)	.03 [b]	2% (7/294)
If EVAR, contrast used (mL)		127 (100-233)	180 (120-250)	.21 [a]	60% (41/68)
Duration of intervention [c]		2:53 (2:25-3:25)	2:55 (2:23-3:59)	.21 [a]	10% (35/362)
Blood loss (L)		1.4 (0.5-3.5)	2.9 (1.0-5.7)	<.01 [a]	41% (148/362)
Postoperative					
APACHE II score at ICU admission		15 (12-18)	20 (17-25)	<.01 [a]	8% (30/362)
Use of vasopressors 24 hours after intervention	None	47% (45/95)	28% (75/267)	<.01 [b]	0
	Low dose	50% (47/95)	43% (115/267)		
	High dose	3% (3/95)	29% (77/267)		
Fluid balance first 24 hours after intervention	<2 L positive	59% (56/95)	28% (76/267)	<.01 [b]	0
	>2 L and <5 L positive	34% (32/95)	37% (98/267)		
	>5 L positive	7% (7/95)	35% (93/267)		

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).
[a] Mann-Whitney U test
[b] χ^2 test
[c] Time expressed as hours: minutes

Conclusions

The present study shows that most surgically treated RAAA patients develop AKI defined using the RIFLE criteria. The RIFLE criteria identified a large group of patients with an increased risk of dying after adjustment for shock profile. The RIFLE criteria can thus be used to improve risk stratification in the postoperative period for clinical and research purposes. Finally, these results indicate that the problem of AKI is much larger than previously anticipated and that minimizing potential injury to the kidney could be an important focus of future research on reducing the death rate after RAAA repair.

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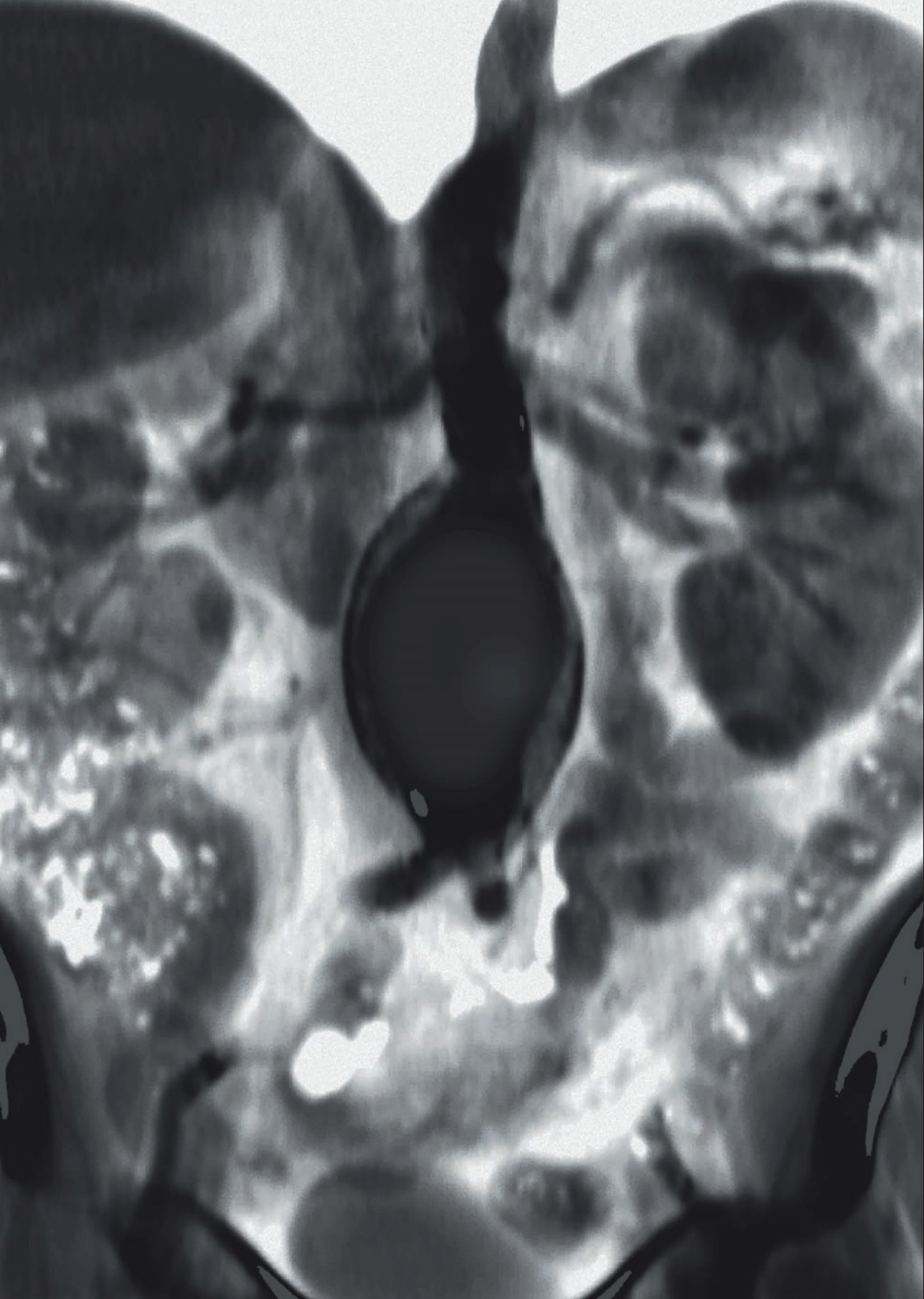
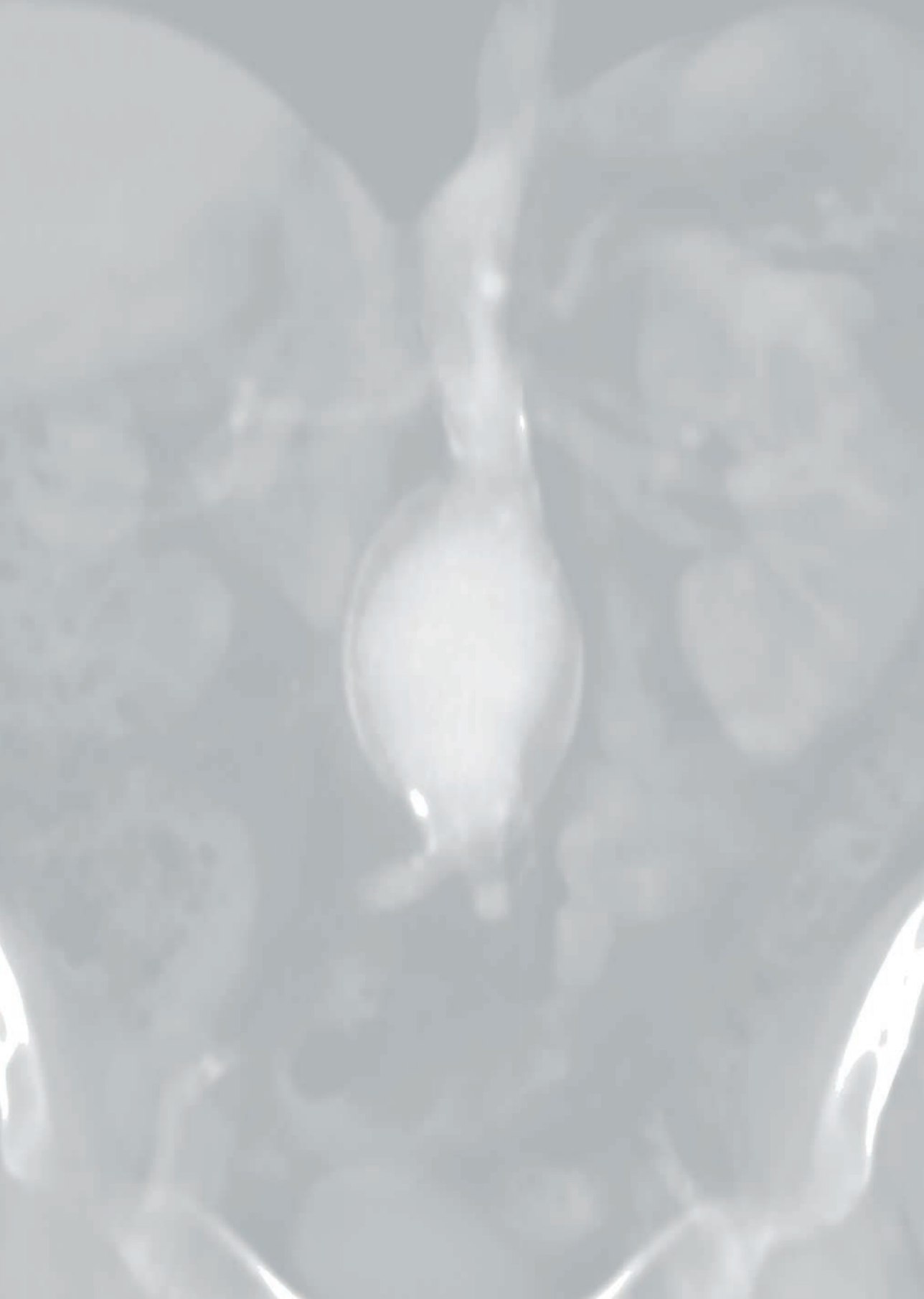


Towards centralized care



Chapter 6

Effect of regional cooperation on outcomes from ruptured abdominal aortic aneurysm

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Abstract

Background

Care for patients with a ruptured abdominal aortic aneurysm (RAAA) in the Amsterdam ambulance region (The Netherlands) was concentrated into vascular centers with a 24-h full emergency vascular service in cooperation with seven referring regional hospitals. Previous population-based survival after RAAA in the Netherlands was 46% (95% confidence interval (CI) 43 to 49%). It was hypothesized that regional cooperation would improve survival.

Methods

This was a prospective observational cohort study carried out simultaneously with the Amsterdam Acute Aneurysm Trial. Consecutive patients with an RAAA between 2004 and 2011 in all ten hospitals in the Amsterdam region were included. The primary outcome was 30-day survival after admission. Multivariable logistic regression, including age, sex, co-morbidity, intervention (endovascular or open repair), preoperative systolic blood pressure, cardiopulmonary resuscitation and year of intervention, was used to assess the influence of hospital setting on survival.

Results

Of 453 patients with RAAA from the Amsterdam ambulance region, 61 did not undergo intervention; 352 patients were treated surgically at a vascular center and 40 at a referring hospital. The regional survival rate was 59% (265/453, 95% CI 54 to 63%). After multivariable adjustment, patients treated at a vascular center had a higher survival rate than patients treated surgically at a referring hospital (adjusted odds ratio 3.18, 95% CI 1.43 to 7.04).

Conclusion

After regional cooperation, overall survival of patients with an RAAA improved. Most patients were treated in a vascular center and in these patients survival rates were optimal.

Abstract: Spanish translation

Antecedentes

El tratamiento de los pacientes con rotura de un aneurisma de la aorta abdominal (ruptured abdominal aortic aneurysm, rAAA) en el área de ambulancias de Amsterdam (Holanda), se concentró en tres hospitales ('centros vasculares') con un servicio vascular de urgencia continuo las 24 horas, en colaboración con siete hospitales regionales que referían a los pacientes. La supervivencia de base poblacional observada previamente en este país era del 46% (intervalo de confianza del 95% [IC 95%] del 43 a 49%). La hipótesis del estudio fue que la cooperación regional mejora la supervivencia.

Métodos

Se llevó a cabo un estudio observacional de cohortes prospectivo simultáneamente con el ensayo de Aneurisma Agudo de Amsterdam (Amsterdam Acute Aneurysm Trial, publicado en 2013). Se incluyeron de forma consecutiva todos los pacientes con RAAA registrados en los diez hospitales de la región sanitaria de Amsterdam entre 2004 y 2011. La variable principal de estudio fue la tasa de supervivencia a los 30 días después del ingreso. Para evaluar la influencia del entorno hospitalario en la supervivencia, se utilizó un modelo de regresión logística multivariable en el que se incluyeron la edad, el género, la patología asociada, la intervención (endovascular o cirugía abierta), la presión arterial sistólica preoperatoria, la reanimación cardiopulmonar y el año de la intervención.

Resultados

De 453 pacientes del la región de ambulancias de Amsterdam, 61 no fueron operados, 352 fueron tratados quirúrgicamente en un centro vascular y 40 en un hospital de procedencia. La tasa de supervivencia regional fue del 59% (265/453, IC 95% 54-63%). En el análisis de regresión logística, los pacientes tratados quirúrgicamente en un centro vascular mostraron una tasa de supervivencia mayor (odds ratio ajustada 3,18, IC 95% 1,43-7,04) que los pacientes tratados quirúrgicamente en un hospital de procedencia.

Conclusión

Después de la cooperación regional, la supervivencia global de los pacientes con rotura de un aneurisma de la aorta abdominal fue mejor de lo que se había anticipado. La mayoría de los pacientes fueron tratados en un centro vascular y en estos pacientes la supervivencia fue incluso mayor.

Introduction

The mortality rate of patients with a ruptured abdominal aortic aneurysm (RAAA) is approximately 80%; it is estimated that one-third of these patients do not reach hospital alive.[1] Patients with an RAAA arriving at hospital require emergency intervention. Several studies[2-4] have indicated that a higher caseload decreases surgical death rates and advocated centralization of care for RAAA.

From 2003, care for patients with RAAA in the Amsterdam ambulance region in the Netherlands was concentrated into three central hospitals. These three vascular centers provided a 24-h full emergency vascular service. All patients suspected of having an RAAA by the ambulance staff or by a general practitioner were transported to a vascular center. The other seven hospitals of the region referred patients with RAAA who were deemed fit for transport. In the present study, it was hypothesized that centralization of care would improve survival after aneurysm rupture. The primary objective was to compare regional survival after RAAA with previous population-based survival from the Netherlands[4,5]. Secondary objectives were to determine the influence of hospital setting (intervention in a vascular center or in a referring hospital), and of patient transfer (from a referring hospital to a center, or not) on survival.

Methods

This was a prospective regional cohort study including consecutive patients with an RAAA presenting at one of the ten hospitals in the Amsterdam ambulance region between April 2004 and February 2011. Patients referred from surrounding ambulance regions, and patients with unknown outcome were excluded from the analysis. The primary outcome was 30-day survival after admission, including both patients rejected for intervention and those in whom an intervention was undertaken; this outcome is referred to as 'the admission survival rate'. The secondary outcome was the combined 30-day or in-hospital survival, including only patients in whom an intervention was started (operative survival rate). These two outcomes were reported to allow comparison with previous population-based studies in the Netherlands.

Patients were identified and registered prospectively by all vascular surgeons in the region. A monthly search of the Amsterdam ambulance

registries and the hospital registries was done to check for patients with a discharge diagnosis of RAAA. The diagnosis of RAAA was based on emergency computed tomographic angiography (CTA), evaluated by a vascular surgeon and a radiologist. Rupture was confirmed by contrast extravasion outside the aorta on CTA. In patients evaluated only by duplex ultrasonography, the diagnosis of RAAA was based on findings at operation or autopsy.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Because of its observational design, written informed consent from patients was not necessary. The present report included all items recommended by the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[6].

Regional and hospital logistics

The Amsterdam ambulance region covers an area of 1025 km^2 with 1.38 million inhabitants[7] and thus has a population density of 1375/km^2. Approximately 280 km^2 is urban and 745 km^2 is rural. The region is served by ten hospitals. All hospitals in this region agreed to centralize care in three vascular centers. The regional referral system for patients with RAAA was introduced in 2003. Two university hospitals and one teaching hospital, experienced in elective and acute endovascular aneurysm repair (EVAR) and open repair of abdominal aortic and thoracic aortic pathology, were appointed as vascular centers. These centers rotated a weekly service in which a vascular surgeon, an interventional radiologist and assisting staff were available around the clock. All patients suspected of having an RAAA by the ambulance staff, by a general practitioner or by a surgeon in a referring hospital were transported to the vascular center on call. Only patients admitted to one of the seven referring hospitals but who were deemed unfit for transfer were treated locally. Fitness for transfer was determined by the local surgeon and was based on clinical judgment of hemodynamic stability. A protocol for permissive hypotension was implemented to optimize conditions during transport and in the emergency room[8].

To confirm the diagnosis and to assess suitability for EVAR, patients were evaluated with CTA on arrival at the hospital. Duplex ultrasonography was used only in patients regarded as too hemodynamically unstable to undergo CTA. The criteria for EVAR were based on the instructions for use of the endograft. Patients with unsuitable aortic anatomy for EVAR underwent open repair. Patients suitable for both EVAR and open repair were consented to be randomized

between the interventions in the Amsterdam Acute Aneurysm Trial (AJAX trial)[9]. Between 2004 and 2011, the AJAX trial was conducted in the three vascular centers to compare the death rate following EVAR and open repair in patients suitable for both interventions. The present study expands on the AJAX trial in two ways. First, it included consecutive patients from the region and not only those eligible for both interventions. Second, it did not aim to compare outcomes after EVAR with those after open repair. The vascular centers had specialized cardiovascular anesthetic care and a closed-format intensive care unit (ICU), with around-the-clock availability of one intensivist for 12 beds, and a minimum of 1500 patient-days of ventilation per year (Dutch level III ICU[10]). Patients from surrounding ambulance regions could also be referred to the vascular centers, but these patients were excluded from the present analysis.

Data collection and statistical analysis

Data were collected on age, sex, co-morbidity (cardiac, pulmonary, renal and cerebrovascular), hemodynamic stability (preoperative lowest in-hospital systolic blood pressure (SBP) measurement and cardiopulmonary resuscitation), hospital setting (vascular center or referring hospital), patient transfer (transport from a referring hospital to a center, or not) and type of intervention (EVAR or open repair). Double data entry was done and data were checked for inconsistency. Inconsistencies were resolved by consulting the original patient charts. Death rates were checked for errors in the communal registry that registers all death certificates in the Netherlands. Data collection and statistical analysis were carried out with use of SPSS version 19.0 (IBM, Armonk, New York, USA). To include all patients in the regression analyses, an imputation procedure was done using logistic and linear regression models, whereby ten data sets were created[11].

The most critically ill patients needed the most urgent decisions and the fewest notes were made. To correct for bias of most missing data in the most critically ill patients, death was included as a predictor in the imputation model. Other predictors were: baseline characteristics, level of consciousness, Glasgow Coma Scale score, and serum hemoglobin and creatinine levels. The statistical analysis was done in the ten separate imputed data sets and the outcomes were pooled.

The regional admission survival rate was calculated by dividing the 30-day survival after admission by all admissions. The regional operative survival rate was calculated by dividing the combined 30-day or in-hospital death rate

after intervention by all interventions. These rates were compared with the only known and most recent Dutch admission and operative survival rates of 46% (95% CI 43 to 49%)[5] and 59% (95% CI 58 to 60%)[4], respectively. Subsequently, the complete cohort was used to assess the association between hospital setting (vascular center or referring hospital) and survival. A subgroup analysis was done in patients treated in a vascular center (center cohort). The center cohort was used to assess the association between patient transfer (transfer from a referring hospital to a vascular center) and survival. Because of the observational design of the present study, the patient risk profiles varied. For example, the regional surgeon's decision to transfer or not meant that relatively more hemodynamically unstable patients were allocated to an intervention in the referring hospitals. A multivariable logistic regression model, a propensity logistic regression model, and a combined multivariable and propensity logistic regression model were developed to adjust for the possible confounders age[12], sex[13], hemodynamic stability[14] (based on SBP and resuscitation), type of intervention (EVAR or open repair) and year of intervention. A further detailed description of the propensity score is provided in Table 5. The χ^2 statistic, the Hosmer and Lemeshow test, and the area under the receiver operating characteristic (ROC) curve were reported to represent model performance. The ranges of the performance measures in the ten imputed data sets were reported.

Results

Between April 2004 and February 2011, a total of 539 patients with an RAAA were admitted to ten hospitals in the Amsterdam region. The incidence rate of in-hospital RAAAs was 5.7 per 100,000 person-years. The in-hospital RAAA repair rate was 4.7 per 100,000 inhabitants. A flow chart showing inclusion and treatment allocation is shown in Figure 1. Of 539 consecutive patients, 80 were excluded from the analysis because they were referred from surrounding ambulance regions, and six were excluded because of unknown demographics and outcome. Only 100 of 453 patients included in the present study were included in the AJAX trial. A total of 399 patients were admitted to the vascular centers, 89 of whom were transferred from a referring hospital. Fifty-four other patients were admitted to the referring hospitals, but not transferred. In total, 61 patients did not undergo intervention, giving a regional rejection rate (non-operative rate)

of 13% (61/453). In the vascular centers the rejection rate was 12% (47/399). In the referring hospitals the rejection rate was 26% (14/54). The baseline characteristics of surgically treated patients are shown in Table 1. Tables 2 and 3 show the data stratified by hospital setting and patient transfer respectively.

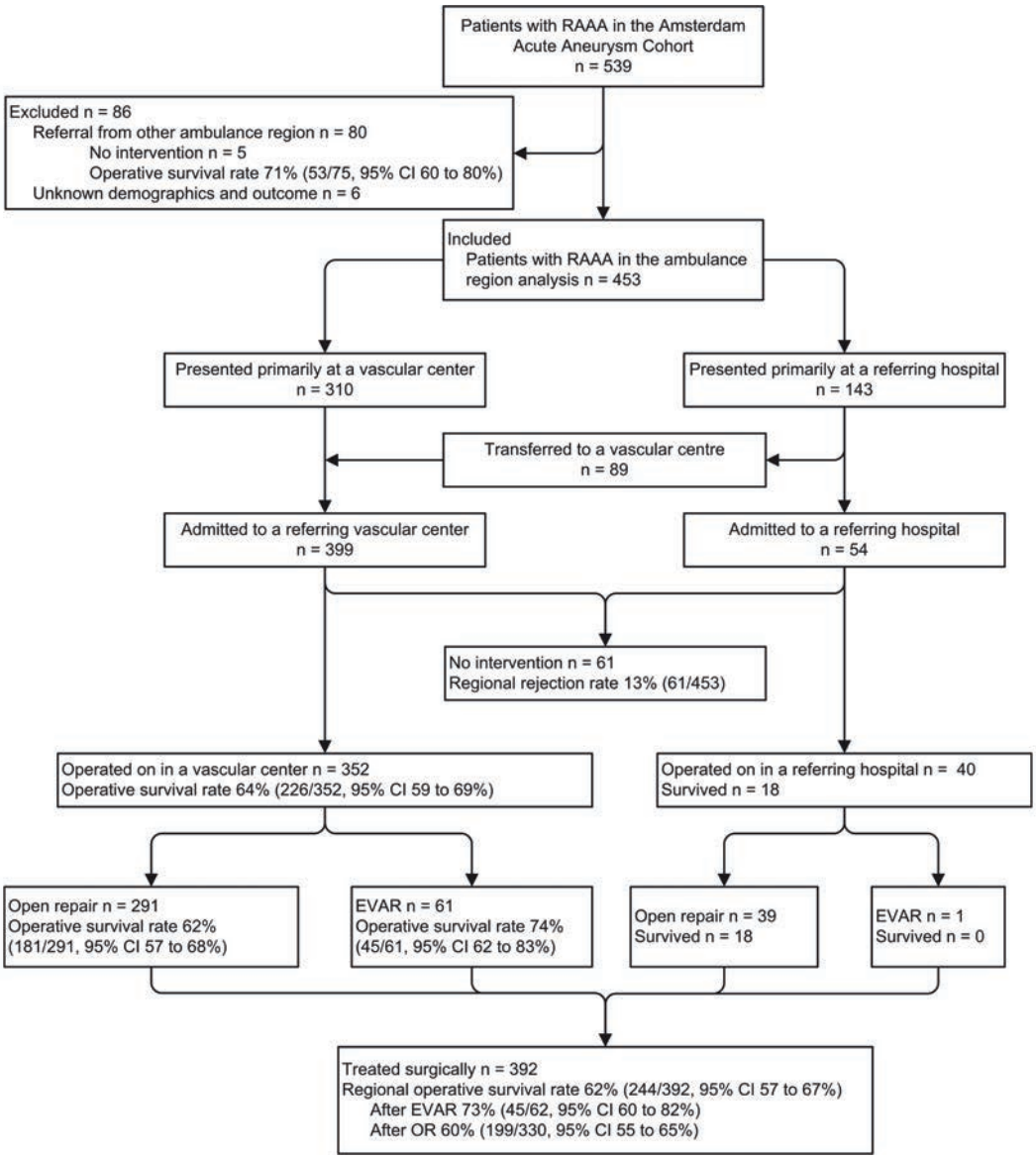

Figure 1. Flow chart showing operative survival; the combined 30-day or in-hospital survival rate included only patients in whom an intervention was started.
CI = confidence interval, EVAR = endovascular aneurysm repair

Survival rate

The overall regional admission survival rate, including both rejected patients and those operated on, was 59% (265/453, 95% CI 54 to 63%). The admission survival rate in the vascular centers was 61% (245/399, 95% CI 567 to 66%) and that in the referring hospitals was 37% (20/54, 95% CI 25 to 50%).

The overall regional operative survival rate was 62% (244/ 392, 95% CI 57 to 67%). It was 64% (226/352, 95% CI 59 to 69%) in the vascular centers, and 18 of 40 patients survived the intervention in the referring hospitals (Figure 1).

Logistic regression

Multivariable adjustment for possible confounders showed that patients treated surgically in a vascular center had a higher survival rate than patients treated in a referring hospital (adjusted odds ratio 3.18, 95% CI 1.43 to 7.04) (Table 4).

Propensity adjustment (odds ratio 2.29, 95% CI 1.16 to 4.52), and combined propensity and multivariable adjustment (odds ratio 2.41, 95% CI 1.19 to 4.87) also showed that patients treated surgically in a vascular center had a higher survival rate (Tables 5 and 6).

Multivariable adjustment for possible confounders showed that, among patients treated surgically in the vascular centers, patient transfer was not associated with survival (adjusted odds ratio 1.07, 95% CI 0.57 to 2.02) (Table 4). Propensity adjustment (odds ratio 0.89, 95% CI 0.50 to 1.60), and combined propensity and multivariable adjustment (odds ratio 1.07, 95% CI 0.58 to 1.98) also showed that patient transfer was not associated with survival (Tables 5 and 6).

Table 1. Baseline characteristics of 392 patients with a ruptured abdominal aortic aneurysm treated surgically in the Amsterdam region in the original data set and the imputed data sets.
SBP = systolic blood pressure, CTA = computed tomographic angiography

	Original data		Imputed data
	Available data	**Missing data**	
Age (years)	74.4 (±8.7)	0	Not imputed
Male : Female	81% : 19% (319 : 73)	0	Not imputed
Cardiac co-morbidity [a]	44% (165/377)	4% (15/392)	44% (172/392)
Pulmonary co-morbidity [b]	19% (71/376)	4% (16/392)	19% (74/392)
Renal co-morbidity [c]	11% (41/376)	4% (16/392)	11% (43/392)
Cerebrovascular co-morbidity [d]	14% (52/376)	4% (16/392)	14% (54/392)
Lowest in-hospital SBP (mmHg)	90 (70-122)	8% (30/392)	90 (70-120)
Cardiopulmonary resuscitation	12% (43/372)	5% (20/392)	13% (49/392)
No CTA	17% (68/392)	0	Not imputed
Year of intervention		0	Not imputed
2004	11% (45/392)		
2005	15% (58/392)		
2006	18% (70/392)		
2007	17% (65/392)		
2008	14% (54/392)		
2009	13% (51/392)		
2010	11% (44/392)		
2011	1% (5/392)		

Continuous data are presented as mean ±standard deviation or median (inter-quartile range) and categorical data as percentage (number).
History of [a] arrhythmia, cardiac surgery or myocardial infarction, [b] chronic obstructive pulmonary disease, [c] chronic kidney failure or dialysis, or [d] transient ischemic attack or stroke.

Table 2. Baseline characteristics of patients in the complete cohort stratified by hospital setting (vascular center or referring hospital).
SBP = systolic blood pressure, CTA = computed tomographic angiography

Variable	Vascular centers n = 352	Referring hospitals n = 40	P
Age (years)	74.6 (±8.6)	72.7 (±10.0)	.20 [e]
Male : Female	82% : 18% (287 : 65)	80% : 20% (32 : 8)	.81 [f]
Cardiac co-morbidity [a]	45% (158/352)	35% (14/40)	.12-.41 [f]
Pulmonary co-morbidity [b]	20% (69/352)	15% (6/40)	.25-.54 [f]
Renal co-morbidity [c]	12% (40/352)	5% (2/40)	.18-.49 [f]
Cerebrovascular co-morbidity [d]	14% (48/352)	15% (6/40)	.47-.85 [f]
Lowest in-hospital SBP (mmHg)	90 (70-120)	90 (55-129)	.26-.96 [g]
Cardiopulmonary resuscitation	13% (45/352)	10% (4/40)	.22-.89 [f]
No CTA	12% (43/352)	63% (25/40)	<.01 [f]
Year of intervention			.04 [h]
2004	12% (41/352)	10% (4/40)	
2005	13% (45/352)	33% (13/40)	
2006	18% (63/352)	18% (7/40)	
2007	17% (60/352)	13% (5/40)	
2008	15% (53/352)	3% (1/40)	
2009	13% (47/352)	10% (4/40)	
2010	11% (39/352)	13% (5/40)	
2011	1% (4/352)	3% (1/40)	

Continuous data are presented as mean ±standard deviation or median (inter-quartile range) and categorical data as percentage (number). Results are shown for the imputed data set.
History of [a] arrhythmia, cardiac surgery or myocardial infarction, [b] chronic obstructive pulmonary disease, [c] chronic kidney failure or dialysis, or [d] transient ischemic attack or stroke.
[e] Unpaired Student's *t* test, [f] range of χ^2 test, [g] range of Mann-Whitney U test and [h] χ^2 test for trend.

Table 3. Baseline characteristics of patients in the center cohort stratified for patient transfer (transport from a referring to a vascular center, or not).
SBP = systolic blood pressure, CTA = computed tomographic angiography

Variable	No transport n = 267	Transport n = 85	P
Age (years)	74.6 (±8.6)	74.4 (±8.4)	.84 [e]
Male : Female	80% : 20% (214 : 53)	86% : 14% (73 : 12)	.24 [f]
Cardiac co-morbidity [a]	43% (115/267)	51% (43/85)	.11-.31 [f]
Pulmonary co-morbidity [b]	18% (47/267)	25% (21/85)	.07-.23 [f]
Renal co-morbidity [c]	9% (24/267)	19% (16/85)	<.01-.02 [f]
Cerebrovascular co-morbidity [d]	12% (32/267)	19% (16/85)	.04-.13 [f]
Lowest in-hospital SBP (mmHg)	86 (68-114)	104 (80-140)	<.01 [g]
Cardiopulmonary resuscitation	15% (41/267)	5% (4/85)	<.01-.03 [f]
No CTA	15% (41/267)	2% (2/85)	<.01 [f]
Year of intervention			.84 [h]
2004	13% (34/267)	8% (7/85)	
2005	12% (33/267)	14% (12/85)	
2006	18% (48/267)	18% (15/85)	
2007	15% (41/267)	22% (19/85)	
2008	15% (41/267)	14% (12/85)	
2009	14% (37/267)	12% (10/85)	
2010	11% (30/267)	11% (9/85)	
2011	1% (3/267)	1% (1/85)	

Continuous data are presented as mean ±standard deviation or median (inter-quartile range) and categorical data as percentage (number). Results are shown for the imputed data set.
History of [a] arrhythmia, cardiac surgery or myocardial infarction, [b] chronic obstructive pulmonary disease, [c] chronic kidney failure or dialysis, or [d] transient ischemic attack or stroke.
[e] Unpaired Student's *t* test, [f] range of χ^2 test, [g] range of Mann-Whitney U test and [h] χ^2 test for trend.

Table 4. Multivariable adjusted logistic regression models.
CI = confidence interval, SBP = systolic blood pressure

Variable	Odds ratio (95% CI)	
	Complete cohort	Center cohort
Age (per year)	0.94 (0.91 to 0.97)*	0.95 (0.92 to 0.98)*
Men	1.32 (0.72 to 2.43)	1.38 (0.72 to 2.63)
Cardiac co-morbidity	0.66 (0.39 to 1.09)	0.68 (0.40 to 1.15)
Pulmonary co-morbidity	0.47 (0.25 to 0.88)*	0.41 (0.21 to 0.78)*
Renal co-morbidity	0.58 (0.28 to 1.24)	0.58 (0.27 to 1.29)
Cerebrovascular co-morbidity	0.71 (0.35 to 1.43)	0.87 (0.41 to 1.85)
Lowest in-hospital SBP (per 10 mmHg)	1.20 (1.12 to 1.29)*	1.21 (1.12 to 1.30)*
Cardiopulmonary resuscitation	0.28 (0.11 to 0.70)*	0.28 (0.11 to 0.70)*
Type of intervention (open repair)	0.73 (0.37 to 1.46)	0.69 (0.34 to 1.40)
Year of intervention (2007 or 2008)	1.43 (0.80 to 2.56)	1.45 (0.79 to 2.65)
Year of intervention (2009 or 2010 or 2011)	2.11 (1.14 to 3.93)*	1.94 (1.01 to 3.74)*
Vascular center*	3.18 (1.43 to 7.04)*	-
Patient transfer	-	1.07 (0.57 to 2.02)

The complete cohort model included all patients to assess the influence of hospital setting (vascular center or referring hospital) on survival. The model included 392 patients and 244 survivors: χ^2 statistic 110.0-119.8 (12 df) P<.01, HL test P=.17-.95, AUC 0.80-0.81.
The center cohort included only patients treated in a vascular center to assess the influence of patient transfer (transport from a referring hospital to a center, or not) on survival. The model included 352 patients and 226 survivors: χ^2 statistic 92.3-102.1 (12 df) P<.01, HL test P=.29-.84, AUC 0.79-0.80.
* P<.05

Table 5. Propensity-adjusted logistic regression models.
CI = confidence interval

	Odds ratio (95% CI)	
	Complete cohort	**Center cohort**
Propensity score (continuous per %)	-	1.12 (1.08 to 1.16)*
Propensity score 1.31-5.85% (n = 98)	Reference category	
Propensity score 5.85-10.16% (n = 99)	1.71 (0.87 to 3.34)	-
Propensity score 10.17-13.54% (n = 95)	1.40 (0.68 to 2.90)	-
Propensity score 13.55-26.93% (n = 100)	1.14 (0.53 to 2.47)	-
Vascular center	2.29 (1.16 to 4.52)*	-
Patient transfer	-	0.89 (0.50 to 1.60)

A propensity score is a single score per patient ranging between 0 and 100%, and is used to adjust for selection by caregivers. In this analysis, the score was calculated with a logistic regression model that included age, systolic blood pressure, resuscitation and year of intervention. Hence the propensity score of a single patient was a weighted summary of these variables.
The complete cohort model included all patients to assess the influence of hospital setting (vascular center or referring hospital) on survival. In the complete cohort the endpoint of the propensity model was 'intervention at a referring hospital' to adjust for allocation of treatment in a referring hospital. The model included 392 patients and 244 survivors: χ^2 statistic 7.2-14.4 (4 df) P=.01-.13, HL test P=.54-.99, AUC 0.56-0.61. The propensity score was categorized because of no linearity in the logit.
The center cohort included only patients treated in a vascular center to assess the influence of patient transfer (transport from a referring hospital to a center, or not) on survival. In the center cohort the endpoint of the propensity model was 'patient transfer' to adjust for transport to a vascular center. The model included 352 patients and 226 survivors: χ^2 statistic 51.6-59.8 (2 df) P<.01, HL test P=.18-.84, AUC 0.72-0.74.
* P<.05

Table 6. Combined multivariable and propensity-adjusted logistic regression models.
CI = confidence interval

	Odds ratio (95% CI)	
	Complete cohort	**Center cohort**
Men	1.36 (0.79 to 2.34)	1.43 (0.77 to 2.65)
Cardiac co-morbidity	0.58 (0.36 to 0.93)*	0.67 (0.40 to 1.12)
Pulmonary co-morbidity	0.58 (0.33 to 1.01)	0.40 (0.21 to 0.75)*
Renal co-morbidity	0.63 (0.31 to 1.28)	0.53 (0.24 to 1.16)
Cerebrovascular co-morbidity	0.65 (0.35 to 1.21)	0.82 (0.40 to 1.71)
Type of intervention (open repair)	0.59 (0.31 to 1.11)	0.64 (0.32 to 1.26)
Propensity score (continuous per %)	-	1.12 (1.08 to 1.17)*
Propensity score 1.31-5.85% (n = 98)	Reference category	-
Propensity score 5.85-10.16% (n = 99)	1.90 (0.93 to 3.89)	-
Propensity score 10.17-13.54% (n = 95)	1.42 (0.66 to 3.08)	-
Propensity score 13.55-26.93% (n = 100)	1.07 (0.48 to 2.36)	-
Vascular center	2.41 (1.19 to 4.87)*	-
Patient transfer	-	1.07 (0.58 to 1.98)

The complete cohort model included all patients to assess the influence of hospital setting (trial center or referring hospital) on survival. The model included 392 patients and 244 survivors: χ^2 statistic 29.5-38.5 (10 df) P<.01-.04, HL test P=.09-.96, AUC 0.65-0.70. The propensity score was categorized because of no linearity in the logit.
The center cohort included only patients treated in a vascular center to assess the influence of patient transfer (transport from a referring hospital to a center or not) on survival. The model included 352 patients and 226 survivors: χ^2 statistic 72.7-81.3 (8 df) P<.01, HL test P=.23-.66, AUC 0.76-0.78.
* P<.05

Table 7. Multivariable logistic regression models to calculate the propensity score.
CI = confidence interval, SBP = systolic blood pressure

	Odds ratio (95% CI)	
	Complete cohort	**Center cohort**
Age (per year)	0.98 (0.95 to 1.02)	0.99 (0.97 to 1.02)
Lowest in-hospital SBP (per 10 mmHg)	0.95 (0.87 to 1.04)	1.09 (1.02 to 1.16)*
Cardiopulmonary resuscitation	1.92 (0.47 to 7.74)	2.01 (0.65 to 6.23)
Year of intervention (2007 or 2008)	0.33 (0.13 to 0.85)*	1.34 (0.75 to 2.39)
Year of intervention (2009, 2010 or 2011)	0.68 (0.31 to 1.50)	0.96 (0.51 to 1.82)

In the complete cohort model, the endpoint was 'intervention in a referring hospital'. The model included 392 patients and 40 interventions in a referral hospital: χ^2 statistic 8.0-10.3 (5 df) P=.07-.16, HL test P=.05-.91, AUC 0.63-0.65.
In the center cohort model, the endpoint was 'patient transfer'. The model included 352 patients and 85 transferred patients: χ^2 statistic 13.1-18.4 (5 df) P=<.01-.02, HL test P=.01-.32, AUC 0.63-0.66.
* P<.05

Discussion

The implementation of a regional referral network with centralized care in hospitals with a 24-h full emergency vascular service improved survival in patients with RAAA. The regional admission survival rate of 59% (95% CI 54 to 63%) was higher than the previous Dutch admission survival rate of 46% (95% CI 43 to 49%)[5]. The regional operative survival rate of 62% (95% CI 57 to 67%) was comparable to the previous Dutch operative survival rate of 59% (95% CI 58 to 60%)[4]. However, compared with this second study[4], the age of the patients and the proportion of women were higher in the Amsterdam region. Both of these factors are likely to influence operative survival rates negatively[4, 5, 12, 13]. An exploratory analysis adjusting the survival rates for age and sex differences confirmed that the outcomes compared favorably with those of the two Dutch studies (data not shown).

The present findings are in agreement with the conclusions of previous studies[2-4,15] that reported an association between an increased annual caseload and improved survival. The present study design and methods differed in three ways from those in these previous studies. First, in the present study all consecutive patients from the region were identified prospectively by the vascular surgeons, resulting in a precise estimate of the survival rates. In the previous studies, patient identification was with use of procedure codes in large administrative databases, which are subject to inaccuracies. Second, detailed preoperative patient data were collected for this study, allowing multivariable adjustment for hemodynamic stability in the statistical analysis. Third, the present study also included data on patients who did not undergo intervention.

From an international perspective, the regional operative survival rate was higher than regional results from the UK between 2005 and 2007 (42%, 95% CI 31 to 54%)[16] and comparable to nationwide results from the USA in 2008 (64%; 95% CI not available)[17]. The regional 30-day survival rate of 68% (265/392, 95% CI 63 to 72%) reported here was lower than nationwide results from Sweden between 2006 and 2010: 72% (95% CI 68 to 75%)[18]. Finally, the regional rejection rate was lower than the reported pooled rejection rate of 26% (95% CI 7 to 51%) in four high-quality studies from different countries since 1990[1]. However, the validity of the comparison with these international results can be questioned because of different age and racial distributions between these countries.

Several studies[17-19] reported an improvement in survival over the years in patients surgically treated for RAAA. The present results are in line with this global trend. The authors of these studies hypothesized that the improvement was attributable to the introduction of EVAR. The results of two trials[9,20] randomizing between EVAR and open repair indicate that the improved survival is probably not attributable to the type of intervention. Logistical aspects of care in treatment protocols have been subject to change alongside the introduction of EVAR[21-23] and this seems a more plausible explanation.

The exact logistical aspects of care that improve survival are difficult to determine. A protocol of permissive hypotension during transport and the availability of a 24-h full emergency vascular service with specialized staff are probably important. CTA was carried out in 324 of 392 patients (83%). Despite some loss of time, the operative survival rate in patients evaluated with CTA was 67% (217/324, 95% CI 62 to 72%). This shows that immediate preoperative CTA is possible in the majority of patients. It can provide important anatomical information before starting open repair. Finally, specialized anesthetic care[24] and level III intensive care were available at the vascular centers.

The majority of patients (352/392, 90%) were treated in the vascular centers. The agreement to refer patients to a center only if deemed fit with regard to hemodynamic stability meant that relatively more unstable patients were allocated to an intervention in the referring hospitals. Although these unstable patients were not expected to survive transfer, almost half of them did survive intervention in a referring hospital (18/40). In the comparison of survival rates between the vascular centers and referring hospitals, the potential problem of confounding was addressed by multivariable and propensity adjustment. After adjustment, the patients treated surgically in the vascular centers had better survival than those treated surgically in the referring hospitals.

Patients with RAAA require emergency intervention. From the perspective of the referring surgeon, it is counterintuitive to postpone intervention by transporting a patient to a vascular center. However, the majority of patients were referred to a vascular center (89/143, 62%), and all patients survived transport. Some adverse events occurred among the referred patients; 4% (4/89) died after the decision to refrain from intervention, 4% (3/82, 3 unknown) required preoperative resuscitation, 5% (4/85) died during the intervention, and 27% (22/81) died after the intervention. The rejection rate of transferred patients was low (4/89, 4%) compared with that of patients presenting primarily

to a vascular center (43/410, 14%). Despite postponement of intervention and these adverse outcomes for individual patients, from a regional perspective the survival of referred patients was comparable to that of patients who presented to the centers.

The most important limitation of the present study is that regional survival was compared with that of two historical control groups. No results were available from a more recent interval in the Netherlands, from a control group in the Amsterdam ambulance region or from a randomized control group. The previous Dutch population-based studies included patients from more than a decade ago. Nowadays there is a trend towards specialization among surgeons and radiologists. In the Amsterdam region, open repair was carried out by a team including a vascular surgeon and an interventional radiologist was also present in case of endovascular repair. This is associated with improved survival[19]. Between 1990 and 2000, some RAAAs were treated by general surgeons, which confounds the comparison. However, the fact that a specialized team improved survival underlines the importance of regional cooperation and a 24-h full emergency vascular service. Another potential confounder is the use of massive transfusion protocols, which are discussed in the literature from 2004[25], and may have attenuated the negative effects of massive bleeding.

The incidence rate of hospital admission for RAAA in the Amsterdam region was 5.7 per 100,000 person-years. Based on the estimate that one-third of patients did not reach hospital[1], the total population-based incidence rate was 8.6 per 100,000 person-years. This is a little lower than the most recently published incidence rates of 14.0 per 100,000 person-years from the UK[16] and 10.6 per 100,000 person- years from Sweden[26]. The in-hospital RAAA repair rate of 4.7 per 100,000 was also lower in Amsterdam than the rate of 8.4 per 100,000 in Sweden during the same interval[18]. These differences might be explained by different age and racial distributions or detection by chance of AAAs between countries. Another explanation might be a failure to identify all patients with RAAA, despite the prospective registration by all vascular surgeons, and checks on the ambulance and hospital registries. The impact of these missing patients on the present conclusions is difficult to determine.

Despite the regional agreement that patients were to be referred to a vascular center if deemed fit, lowest in-hospital SBP and resuscitation were not associated with 'intervention in a referring hospital' in the propensity score (Table 7). Possibly, the variables 'lowest in-hospital SBP' and 'resuscitation'

failed to represent hemodynamic stability sufficiently accurately. However, there was a clear association between lowest in-hospital SBP and resuscitation and survival (Table 4). This suggests that these parameters accurately represent hemodynamic stability. Moreover, an analysis including other markers of hemodynamic stability, such as a subjective judgment by a vascular surgeon (unstable, controlled hypotension, or stable), or the first SBP measurement in the emergency room, did not alter the conclusions.

Although statistical methods were used to eliminate differences in observed confounders, another limitation of the present study was that it was not possible to adjust for differences in unobserved confounders such as hypothermia[27], income quintile of the patient[28], after-hours intervention[28] and annual volume of RAAA interventions of the surgeon[28]. Finally, there is an important geographical limitation to the external validity of the conclusions. The Amsterdam region is urban and densely populated, and the conclusions might not be valid for more rural areas.

Although the results presented here should be interpreted within the context of a global trend towards improved outcome of patients with RAAA, regional survival was improved by regional cooperation compared with that reported in two Dutch population-based studies[4, 5]. It was possible to treat the majority of patients in a vascular center where survival was optimal. Furthermore, despite delaying intervention, patient referral was not associated with impaired survival.

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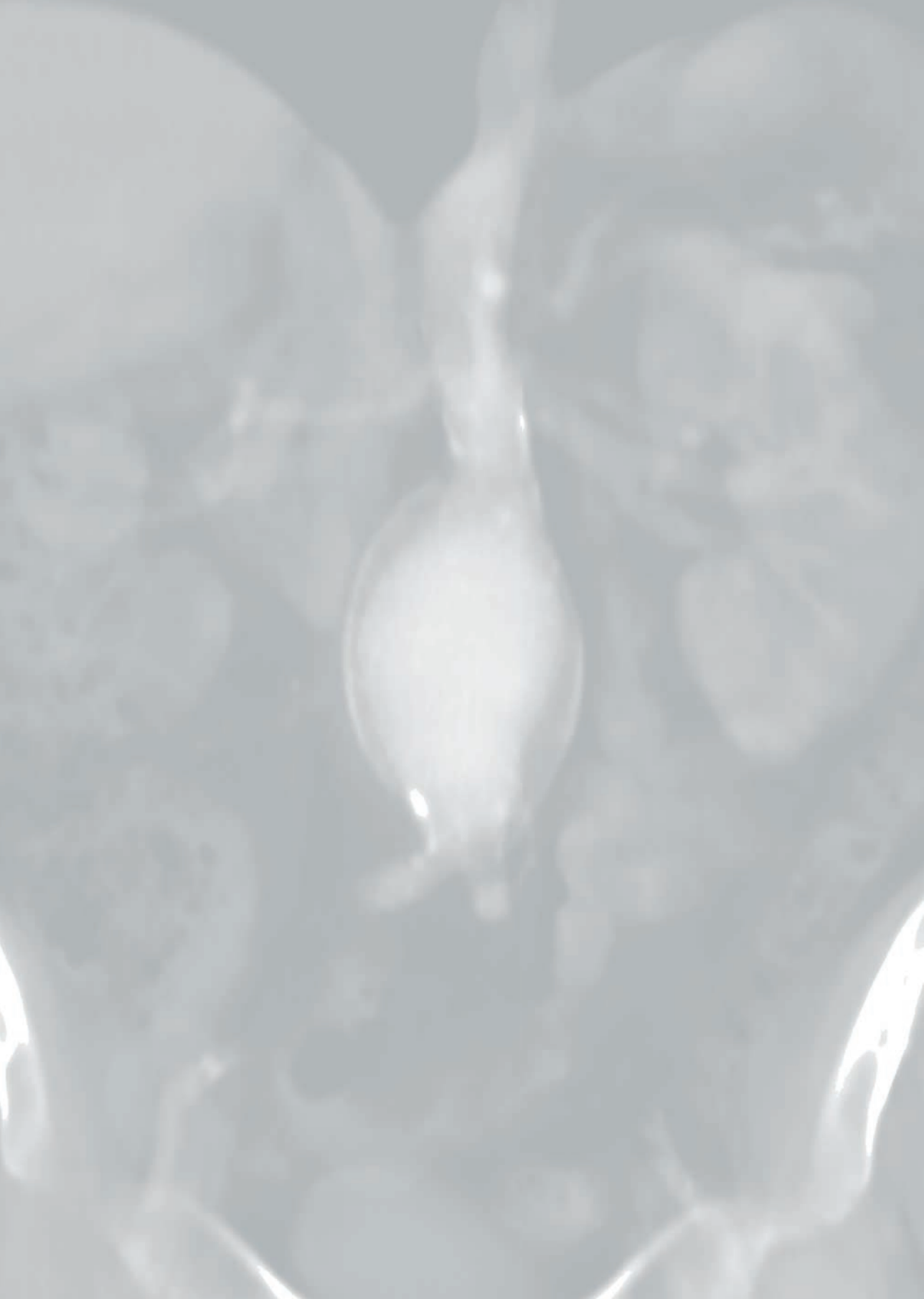

Chapter 7

Fate of patients unwilling or unsuitable to undergo surgical intervention for a ruptured abdominal aortic aneurysm

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Submitted as short report

Abstract

Background

The primary objective was to assess duration of in-hospital survival in 40 patients with a ruptured abdominal aortic aneurysm who did not undergo surgical intervention.

Report

One hour after registration at the emergency room, 95% (95% confidence interval (CI) 88 to 100%) of patients were still alive. After two hours, 80% (95% CI 67 to 92%) of patients were still alive. The median survival was 13 hours (inter-quartile range 2-45 hours).

Conclusion

In patients with an RAAA without surgical intervention, the median duration of survival is 13 hours and the majority of patients survive the first hours after arrival at the emergency room.

Introduction

Rupture of an abdominal aortic aneurysm (RAAA) without surgical intervention almost invariably results in death. Although the outcome is virtually certain, little is known about the duration of survival. Walker et al. (1983) reported a median survival of 8 hours after confirmation of diagnosis.[1] Lloyd et al. (2004) reported that 12% of patients died within 2 hours and median survival was over 10 hours.[2] These findings have important implications for the discussion about the use of a computed tomographic angiography (CTA) to assess suitability for endovascular aneurysm repair, and about patient referral from regional hospitals to specialized tertiary hospitals.

The objective of this study was to assess the duration of survival in patients with an RAAA who did not undergo surgical intervention.

Report

We conducted a retrospective cohort study in patients with an RAAA, confirmed by CTA or autopsy, who did not undergo surgical intervention. Patients were identified from a prospectively assembled cohort of 539 consecutive RAAA patients between 2004 and 2011 in the Amsterdam ambulance region, The Netherlands.[3, 4] Sixty-six patients did not undergo intervention. To facilitate comparison with the group of surgically treated patients, seventeen patients were excluded because of pre-hospital cardiopulmonary resuscitation (CPR). Another nine patients were excluded because demographics or time of registration at the emergency room (ER) were unknown, leaving forty RAAA patients to be included in the analysis. The reasons to refrain from intervention were decision by patient or patient's family (n = 15), cardiac arrest or shock (n = 7), unknown (n = 7), severe comorbidity (n = 6), age (n = 3) or aortic anatomical considerations (n = 2). Patients were allocated to two subgroups based on the reasons to refrain from intervention; subgroup 1 included patients not treated due to patient decision, comorbidity, age or aortic anatomical considerations (n = 26), and subgroup 2 included patients not treated due to shock (n = 7). Baseline characteristics are shown in Table 1. The primary endpoint was the duration of survival in hours after registration at the ER. If the primary endpoint was not retrieved from the record, the patients were censored at the last known time of survival. One hour after registration at the emergency room,

95% (95% confidence interval (CI) 88 to 100%) of patients were still alive (Figure 1). After two hours, 80% (95% CI 67 to 92%) of patients were still alive. Median survival was 13 hours (inter-quartile range 2-45 hours). In subgroup 1 survival after two hours was 96% (95% CI 89 to 100%) and in subgroup 2 29% (95% CI 0 to 62%).

Table 1. Baseline characteristics of patients with an RAAA in the Amsterdam ambulance region undergoing surgical intervention versus patients not undergoing surgical intervention.
RAAA = ruptured abdominal aortic aneurysm, SBP = systolic blood pressure, ER = emergency room

	No surgical intervention n = 40	**Surgical intervention n = 467**
Age (years)	86 (78-89)	76 (69-80)
Male : Female	72% : 28% (29 : 11)	81% : 19% (378 : 89)
Cardiac co-morbidity	51% (20/39)	43% (200/467)
Cerebrovascular co-morbidity	13% (5/39)	15% (72/467)
Cardiopulmonary resuscitation	15% (6/40)	12% (54/467)
Lowest in-hospital SBP (mmHg)	110 (85-126)	106 (80-133)
Hemoglobin at ER (mmol/L)	7 (5.9-7.7)	7 (5.9-8.0)
Serum creatinine at ER (μmol/L)	130 (90-190)	108 (87-134)

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).

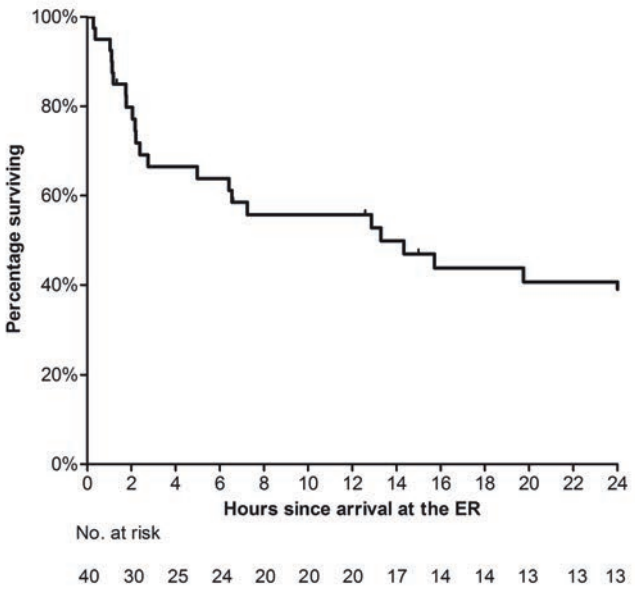

Figure 1. Survival analysis of 40 patients with an RAAA not undergoing surgical intervention and without pre-hospital cardiopulmonary resuscitation.
RAAA = ruptured abdominal aortic aneurysm, ER = emergency room

Discussion

The extrapolation of our outcomes to patients who are prepared for surgical intervention is hampered by several potential biases. It is to be expected that patients who did not undergo intervention are less hemodynamically stable, and these patients are represented mostly in subgroup 2. Table 1 shows surrogate markers of hemodynamic stability of patients in the Amsterdam ambulance region undergoing versus not undergoing surgical intervention. These markers indicate that the hemodynamic status of patients included in this study was comparable with the hemodynamic status in those who did receive surgical intervention. This applies mostly to patients in subgroup 1. Another potential bias was the inclusion of patients after CTA. We may have missed hemodynamically unstable patients who were diagnosed using duplex ultrasound and did not have an autopsy. However, a CTA was done in 83% (324/392) of patients in the region.[4] Critics could argue that patients may have been alive after one or two hours but in a much worse condition than upon admission. Finally, the rejection rate in the region was only 12% (66/533) limiting the number of patients in this study.

Our results confirm the outcomes of the study by Lloyd et al. that the majority of patients with an RAAA are relatively stable.[2] A recent study from England and the United States reported lower death rates in tertiary hospitals.[5] If the death rate at a specialized tertiary hospital is lower than at a regional referring hospital, an increase in transfer time could be deemed acceptable. Analysis of survival in the Amsterdam ambulance region showed that despite delaying intervention, patient referral was not associated with impaired survival.[4]

The results of this study should be interpreted within the context of these considerations. Although time is limited, the majority of patients arriving at hospital without prior CPR were still alive after one and two hours (95% and 80%, respectively). Survival was even longer (96% after two hours) in the subgroup most comparable to patients who do receive surgical intervention. Therefore, the present study is another indication that a reasonable increase of transfer time in order to reach a specialized hospital is justified.

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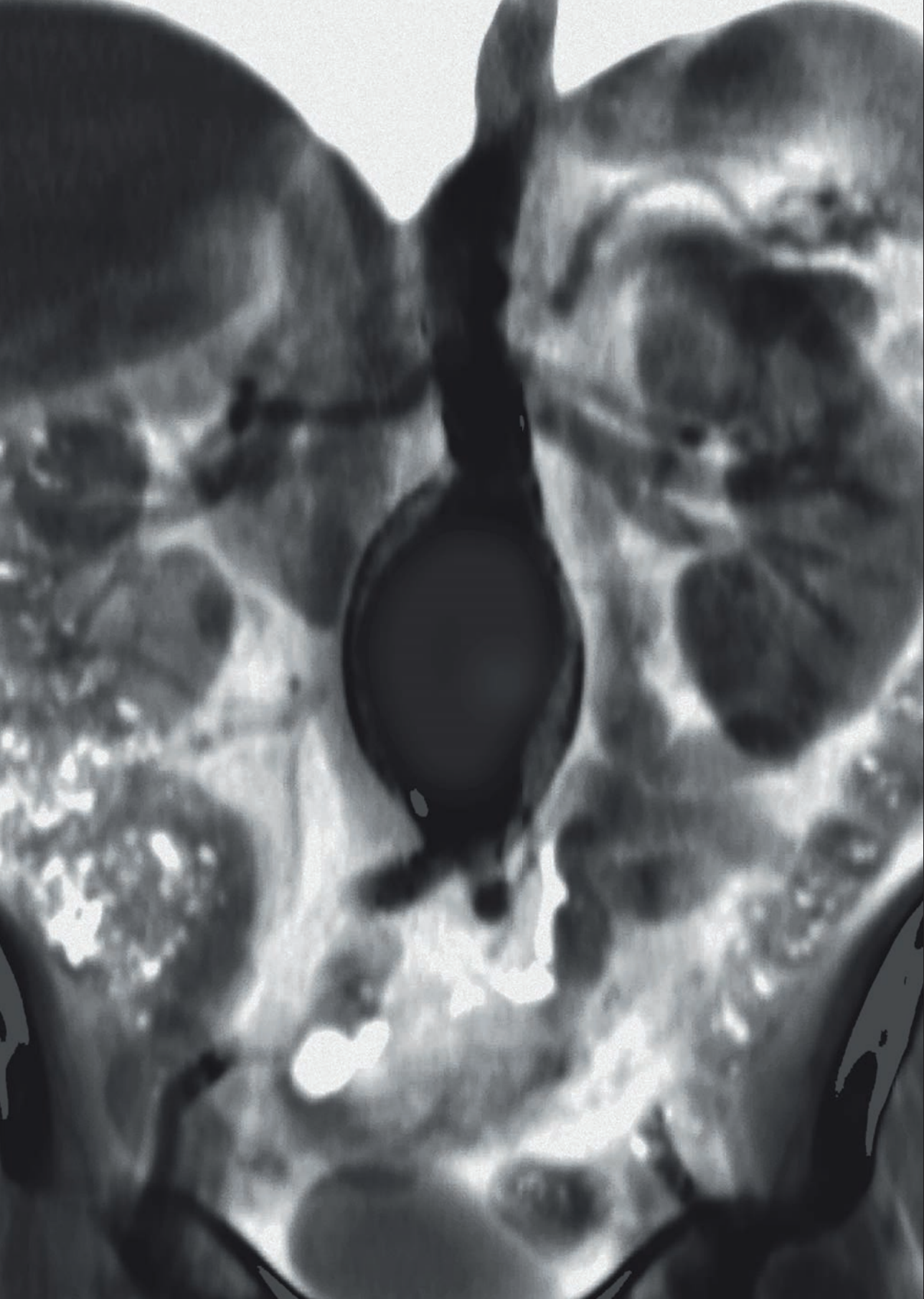
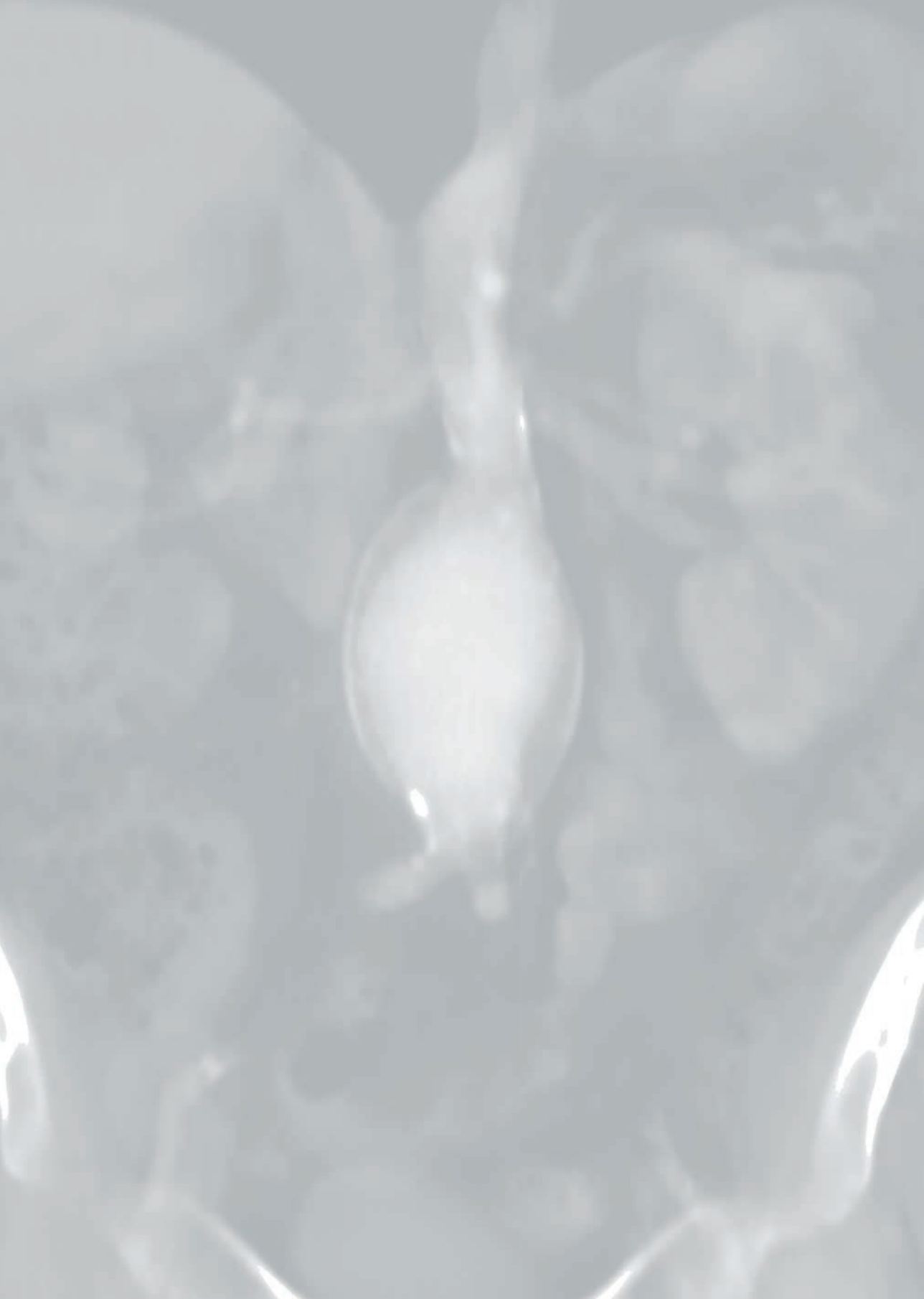


Towards endovascular care



Chapter 8

Endovascular aneurysm repair versus open repair for patients with a ruptured abdominal aortic aneurysm; a systematic review and meta-analysis of short-term survival

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Abstract

Background

There is clinical equipoise between open (OR) and endovascular aneurysm repair (EVAR) for the best treatment of ruptured abdominal aortic aneurysm (RAAA).

Objective

The aim of the study was to perform a systematic review and meta-analysis to estimate the short-term (combined 30-day or in-hospital) survival after EVAR and OR for patients with RAAA. Data sources included Medline, Embase, and the World Health Organization International Clinical Trials Registry until 13 January 2014. All randomized controlled trials (RCTs), observational cohort studies, and administrative registries comparing OR and EVAR of at least 50 patients were included. Articles were full-length and in English.

Methods

Standard PRISMA guidelines were followed. The methodological quality of RCTs was assessed with the Cochrane Collaboration's tool for assessing risk of bias. The quality of observational studies was assessed with a modified Cochrane Collaboration's tool for assessing risk of bias, the Newcastle-Ottawa Scale, and the Methodological Index for Non-Randomized Studies. The results of the RCTs, of the observational studies, and of the administrative registries were pooled separately and analyzed with the use of a random effects model.

Results

From a total of 3,769 articles, three RCTs, 21 observational studies, and eight administrative registries met the inclusion criteria. In the RCTs, the risk of bias was lowest and the pooled odds ratio for death after EVAR versus OR was 0.90 (95% CI 0.65 to 1.24). The majority of the observational studies had a high risk of bias and the pooled odds ratio for death was 0.44 (95% CI 0.37 to 0.53). The majority of the administrative registries had a high risk of bias and the pooled odds ratio for death was 0.54 (95% CI 0.47 to 0.62).

Conclusion

Endovascular aneurysm repair is not inferior to open repair in patients with a ruptured abdominal aortic aneurysm. This supports the use of EVAR in suitable patients and OR as a reasonable alternative.

Introduction

The death rate in all patients with a ruptured abdominal aortic aneurysm (RAAA) is around 80%.[1] One-third of all patients with RAAA do not reach the hospital alive, and one-third do not have an intervention. Of the patients having an intervention, only half survive intervention and admission. The traditional intervention is open surgical repair (OR) with exclusion of the aneurysm with a synthetic tube or bifurcated graft. Endovascular aneurysm repair (EVAR) was developed in the 1990s. The experience with elective EVAR has led to its increasing use in the emergency setting. Between 46% and 64% of patients with RAAA have suitable aortic anatomy for EVAR.[2, 3]

Observational studies have reported improved short-term survival after EVAR compared with OR. Observational studies however have methodological limitations, leading to biased estimates of outcome. Randomized controlled trials are regarded as providing the best evidence for the relative efficacy of interventions. An early trial from the UK did not show any benefit of EVAR in patients with RAAA.[4] Recently, the results of two larger RCTs have been published.[2, 3] These new studies might help to better determine whether EVAR improves short-term survival when compared with open repair, which in turn might help caregivers to decide on the best treatment strategy.

Objective

The aim of this study was to perform a systematic review and meta-analysis to obtain the best estimates of the short-term (combined 30-day or in-hospital) survival after endovascular repair compared with open repair for patients with a RAAA in randomized controlled trials and observational studies.

Methods

The present review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] The objectives, the methodology, and the inclusion criteria were prespecified in a protocol.

Search strategy

A systematic search in Medline through Pubmed and in Embase through Ovid was conducted with the assistance of a clinical librarian. The search strategy was built around the participants, intervention, comparison, outcomes, and study design (PICOS) framework. Additionally, the World Health Organization International Clinical Trials Registry Platform (WHOICTRP) was searched for relevant RCTs. The last search was done on the 13 January 2014. Two authors (SvB, AC) independently screened the titles and abstracts of the identified articles for relevance. Subsequently, the relevant full length articles were assessed by two authors (SvB, AC) to check if they met the inclusion criteria. Disagreements were resolved by discussion with two other authors (MK, RB). The reference list of the included articles was checked for other eligible articles and a cited reference search in the Web of Science was done.

Eligibility criteria

All RCTs comparing OR and EVAR, and all observational studies comparing OR and EVAR that included at least 50 patients were included. Observational studies that included patients based on the International Classification of Diseases (ICD) or other forms of coding were analyzed separately, and are referred to as administrative registries. Studies were included if they were full length and in English. Studies reporting more than once on the same patient population were included only once, based on relevance and size. Studies were excluded if they did not allow extraction of two-by-two contingency tables for the endpoint 30-day or in-hospital death rate.

Assessment of study quality

The methodological quality of the included articles was independently assessed by two authors (SvB, AC). For the RCTs, The Cochrane Collaboration's tool for assessing risk of bias was used (Table 1). For the observational studies and administrative registries, a tool based on the Cochrane Collaboration's tool for assessing risk of bias, the Newcastle-Ottawa Scale, and the Methodological Index for Non-Randomized Studies (MINORS) was used (Table 2). Again, disagreements were resolved by discussion with two other authors.

Table 1. Quality assessment randomized controlled trials.

Domain	Support for judgment	Review authors' judgment
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

The Cochrane Collaboration's tool for assessing risk of bias. Judgment per item high risk, low risk or unclear.

Table 2. Quality assessment observational studies and administrative registries.

Domain	Support for judgment	Review authors' judgment
Representativeness of the cohort	Truly representative of the average and consecutive RAAA in the community. Possible selection in referral patterns of surrounding hospitals and type of hospital (secondary or tertiary)	Selection bias
Selection of patients for the EVAR and OR cohorts	Interventions from the same community and during the same time period and method of treatment allocation.	Selection bias
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received and was effective or check of outcome data was done in a national registry of death certificate.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. Loss to follow up should be less than 5%.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Baseline equivalence of groups	Baseline should be adjusted for at least age, sex and pre-operative hemodynamic stability.	Information bias
Rejection rate reported	Possible selection by not reporting rejection rate.	Selection bias
Other sources of bias	Retrospective patient identification, method of diagnostic confirmation of an RAAA, internal validity and data robustness check in administrative registries.	Bias due to problems not covered elsewhere in the table.

Based on 'the Cochrane Collaboration's tool', 'the Newcastle-Ottawa Scale' and 'the Methodological Index for Non-Randomized Studies'. Judgment per item high risk, low risk or unclear.

Data collection

Data were extracted independently by two authors (SvB, AC) with use of a standardized form in Microsoft Office Access 2003 (Microsoft Corporation, Redmond, WA, USA). The following data were collected: study design (RCT, observational study or administrative registry), study period, study size, country, and rejection rate. For the included RCTs, the number of events and the total number of patients per type of intervention were extracted based on intention-to-treat analysis. For the included observational studies, the number of events and the total number of patients per type of intervention were extracted based on as-treated analysis. Authors were contacted to obtain missing data if necessary. When the authors were unable to provide missing data, the study was excluded from the analysis.

Statistical analysis

The primary endpoint was the combined 30-day and in-hospital death rate. If not reported, the 30-day or in-hospital death rate was used instead. For the observational studies, a secondary endpoint was the odds ratio of EVAR on death rate after adjustment for age, sex, and hemodynamic stability. The statistical analysis was performed using Review Manager 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and Stata/SE 11.0 (StataCorp, College Station, TX, USA). Three meta-analyses were done. The first meta-analysis included all RCTs, the second all observational studies, and the third all administrative registries. Pooled effects of EVAR and OR were presented as odds ratios with 95% CI. Because heterogeneity was expected, the meta-analyses were done a priori with the use of a random effects model. A prespecified sensitivity analysis of observational studies was done by pooling the odds ratios of EVAR versus OR adjusted for at least, age,[6] sex,[7] and hemodynamic stability.[8] Heterogeneity between studies was determined with the I^2 statistic. An I^2 between 30% and 50% was considered moderate heterogeneity and between 60% and 90% as substantial heterogeneity. Funnel plots were created and inspected for the presence of publication bias if more than 10 studies were included.

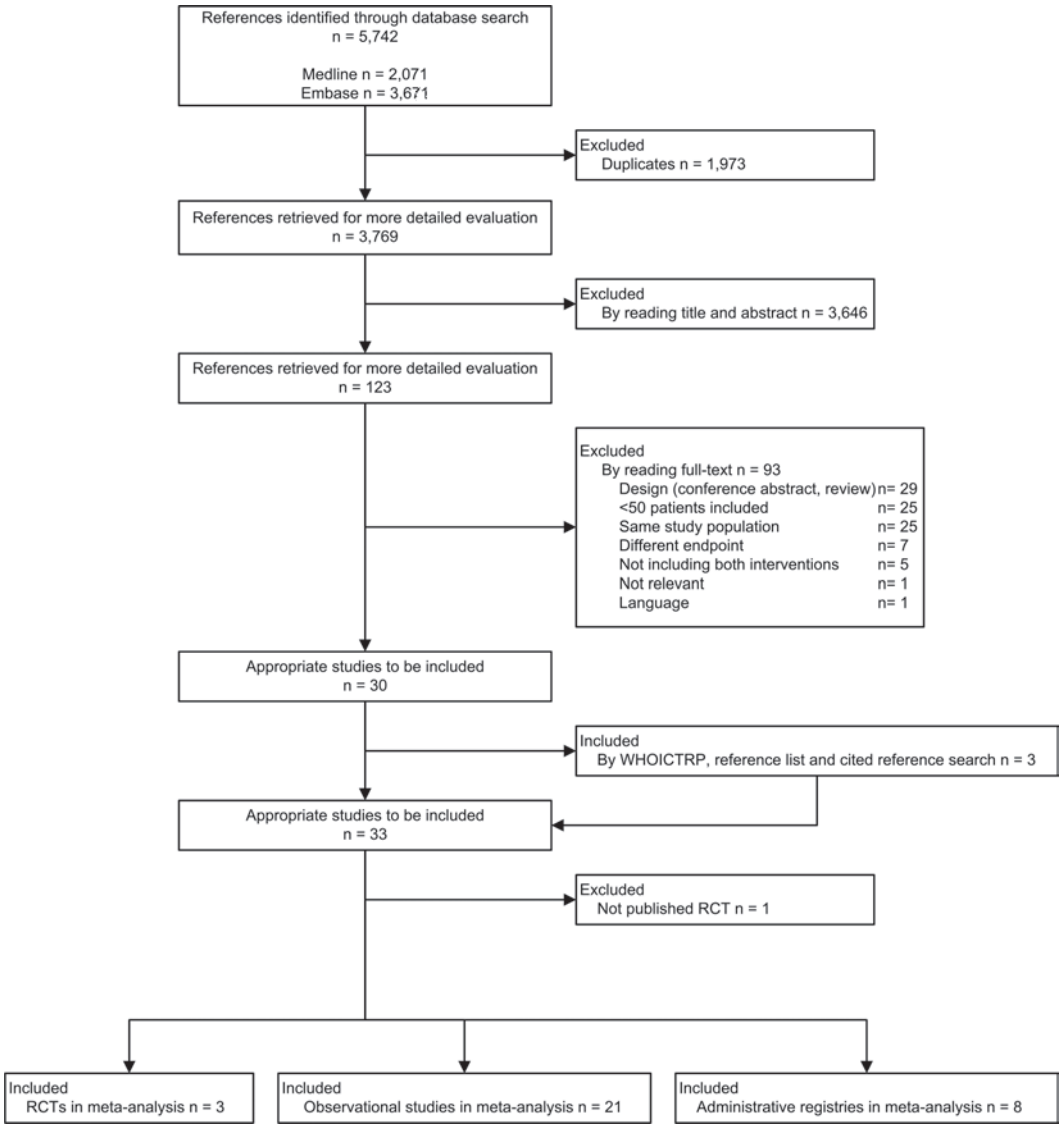

Figure 1. Flowchart of in- and exclusion.
WHOICTRP = World Health Organization International Clinical Trials Registry Platform, RCT = randomized controlled trial

Table 3. Characteristics of studies included in the meta-analyses evaluating the outcome after endovascular (EVAR) and open repair (OR) of a ruptured abdominal aortic aneurysm.

CI = confidence interval, RCT = randomized controlled trial, IH = in-hospital, OS = observational study, USA = United States of America, AR = administrative registry

Study	Country	Study design	Study period	Number of patients	Rejection rate (number)	Type death rate	Death rate EVAR (95% CI)	Death rate OR (95% CI)
Nottingham 2006	United Kingdom	RCT	2002-2004	32	54% (55/103)	30-day	53% (30 to 75)	53% (31 to 74)
AJAX 2013	The Netherlands	RCT	2004-2011	116	9% (46/520)	30-day or IH	28% (18 to 41)	29% (19 to 41)
IMPROVE 2014	United Kingdom	RCT	2009-2013	613	23% (299/1275)	30-day	32% (27 to 37)	35% (30 to 40)
Coppi 2006	Italy	OS	1999-2006	124	Not reported	30-day	30% (17 to 47)	46% (36 to 56)
Peppelenbosch 2006	Multiple[a]	OS	2003-2004	100	Not reported	30-day or IH	35% (23 to 49)	39% (27 to 53)
Acosta 2007	Sweden	OS	2000-2004	162	24% (51/213)	IH	34% (23 to 47)	45% (36 to 55)
Ockert 2007	Germany	OS	2000-2005	58	Not reported	30-day	31% (17 to 49)	31% (17 to 49)
Moore 2007	Canada	OS	2004-2006	56	Not reported	30-day	5% (1 to 24)	25% (14 to 41)
Sharif 2007	United Kingdom	OS	2001-2006	126	10% (14/140)	30-day or IH	33% (22 to 46)	51% (40 to 62)
Lee 2008	USA	OS	2002-2006	52	Not reported	30-day or IH	35% (17 to 59)	63% (46 to 77)
Verhoeven 2009	The Netherlands	OS	2002-2009	159	9% (16/175)	30-day or IH	20% (11 to 34)	35% (27 to 44)
Chagpar 2010	Canada	OS	2003-2008	167	Not reported	30-day	16% (7 to 32)	44% (36 to 52)
Cho 2010	USA	OS	2001-2008	233	Not reported	30-day or IH	20% (7 to 45)	38% (32 to 45)
Sarac 2011	USA	OS	1990-2008	160	Not reported	30-day or IH	31% (18 to 49)	32% (25 to 41)
Van Schaik 2011	The Netherlands	OS	2006-2008	56	3% (2/58)	30-day	27% (11 to 52)	46% (32 to 61)
Bosch 2012	The Netherlands	OS	2002-2008	129	4% (6/135)	30-day	20% (9 to 39)	45% (36 to 55)
Mayer 2012	Multiple[b]	OS	1998-2011	431	10% (42/473)	30-day	18% (14 to 23)	37% (30 to 45)
Noorani 2012	United Kingdom	OS	2006-2010	102	8% (9/111)	IH	12% (5 to 23)	28% (17 to 42)
Rödel 2012	The Netherlands	OS	2006-2010	105	10% (12/117)	30-day	17% (8 to 33)	31% (22 to 43)
Saqib 2012	USA	OS	2001-2011	148	Not reported	30-day or IH	22% (11 to 37)	32% (24 to 41)

Table 3. Continued

Study	Country	Study design	Study period	Number of patients	Rejection rate (number)	Type death rate	Death rate EVAR (95% CI)	Death rate OR (95% CI)
Eefting 2013	The Netherlands	OS	2002-2012	195	Not reported	30-day	24% (16 to 35)	52% (43 to 61)
Mehta 2013	USA	OS	2002-2011	283	Not reported	30-day	24% (17 to 33)	44% (37 to 52)
Mukherjee 2013 [c]	USA	OS	2007-2011	50	Not reported	30-day	27% (15 to 43)	15% (4 to 42)
Wallace 2013	USA	OS	2007-2012	100	15% (18/118) [d]	IH	16% (9 to 28)	46% (32 to 61)
Greco 2006	USA	AR	2000-2003	5,798	Not reported	IH	39% (34 to 45)	48% (46 to 49)
Wanhainen 2008	Sweden	AR	1994-2005	3,516	Not reported	30-day	15% (9 to 24)	36% (35 to 38)
Giles 2009	USA	AR	2005-2007	567	Not reported	30-day	24% (17 to 32)	36% (32 to 41)
Holt 2010	United Kingdom	AR	2003-2008	4,414	Not reported	IH	32% (27 to 37)	47% (46 to 49)
Mani 2011	Multiple [e]	AR	2005-2009	7,040	Not reported	30-day or IH	20% (17 to 23)	33% (31 to 34)
Chen 2013	Taiwan	AR	1998-2009	537	Not reported	IH	44% (29 to 59)	38% (34 to 43)
Mohan 2013	USA	AR	2001-2010	42,126	Not reported	IH	26% (25 to 27)	39% (38 to 40)
Trenner 2013	Germany	AR	1999-2010	4,859	Not reported	IH	23% (20 to 26)	41% (40 to 43)

[a] Belgium, Canada, Finland, Italy, Netherlands and Northern Ireland
[b] Sweden, Switzerland
[c] Patients treated with hybrid repair included in open repair group
[d] 10 patients died during unknown intervention
[e] Australia, Denmark, Finland, Hungary, Italy, Norway, Sweden, Switzerland, United

Results

Literature search

3,769 unique articles were identified from Medline and Embase, of which 123 were retrieved for more detailed evaluation and 30 met the inclusion criteria (Figure 1). Two additional RCTs[2, 9] were identified from the WHOICTRP, of which one was published[2] and included. One additional administrative registry[10] was identified from the cited reference search. Of 32 included studies, three articles were RCTs,[2-4] 21 were observational studies,[6, 11-30] and eight were administrative registries.[10, 31-38] Table 3 summarizes their main characteristics.

Study quality

The quality assessment of the included studies is summarized in Figures 2 to 7. The risk of bias was lowest in the RCTs, whereas the observational studies suffered from all forms of bias. In >75% of observational studies the representativeness of the cohort, the blinding of outcome assessment and the baseline equivalence of groups was considered to have a high risk of bias. In all observational studies, patient selection for EVAR and OR was considered to have a high risk of bias because treatment was based on the preference of caregivers or a clinical algorithm. The administrative registries also suffered from all forms of bias. In more than 50% of the registries the representativeness of the cohort was considered to have a high risk of bias, mostly because of lack of information about the type of hospitals (secondary, tertiary) included.

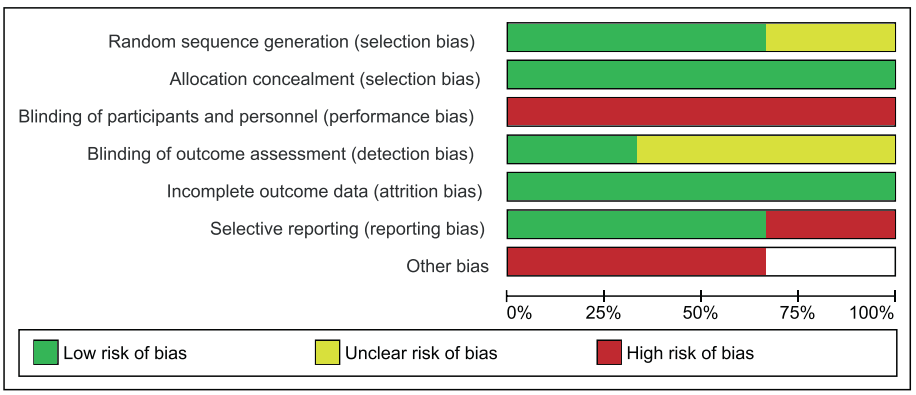

Figure 2. Risk of bias randomized controlled trials.

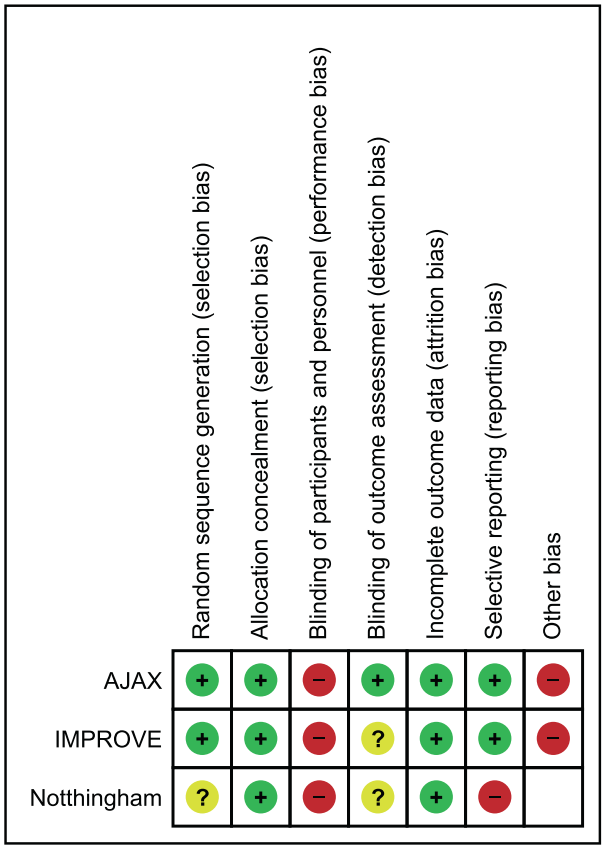

Figure 3. Risk of bias within randomized controlled trials.

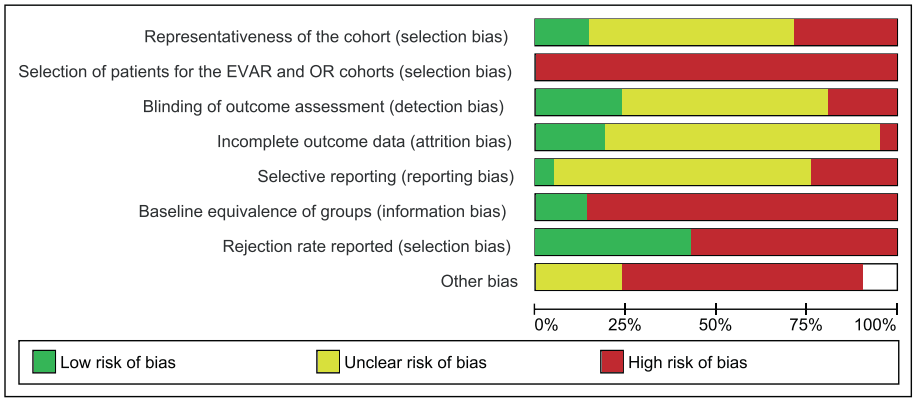

Figure 4. Risk of bias observational studies.

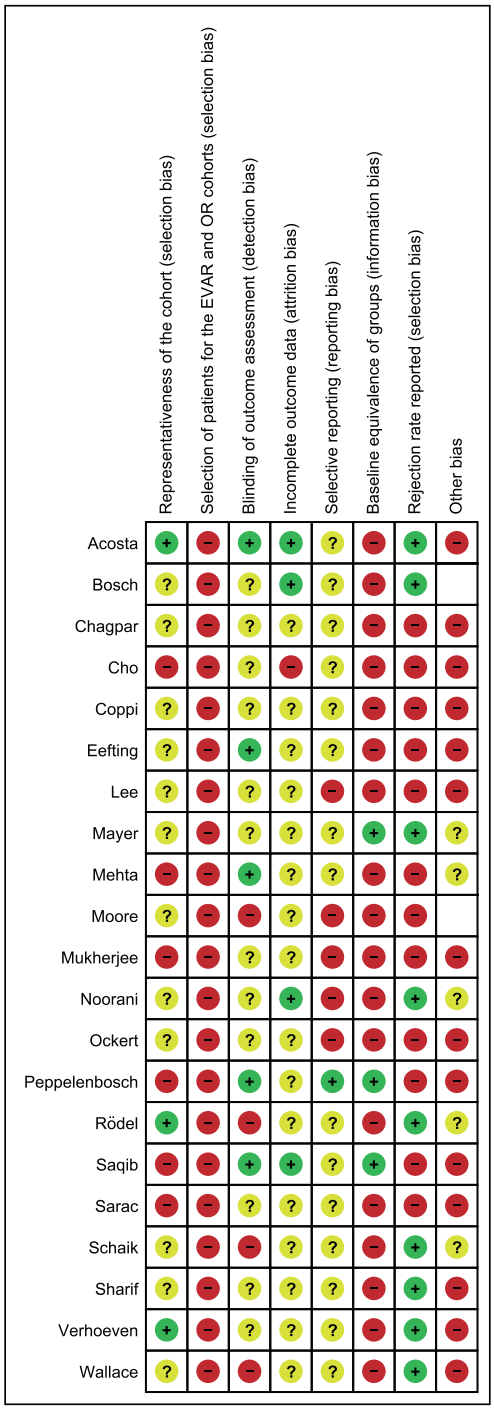

Figure 5. Risk of bias within observational studies.

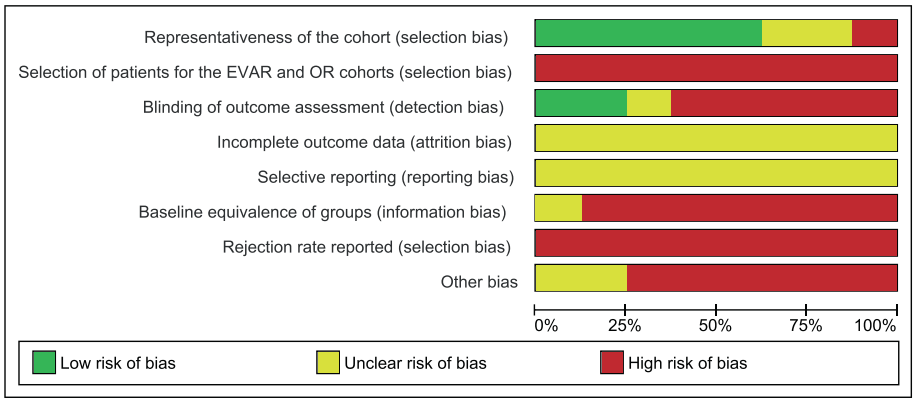

Figure 6. Risk of bias administrative registries.

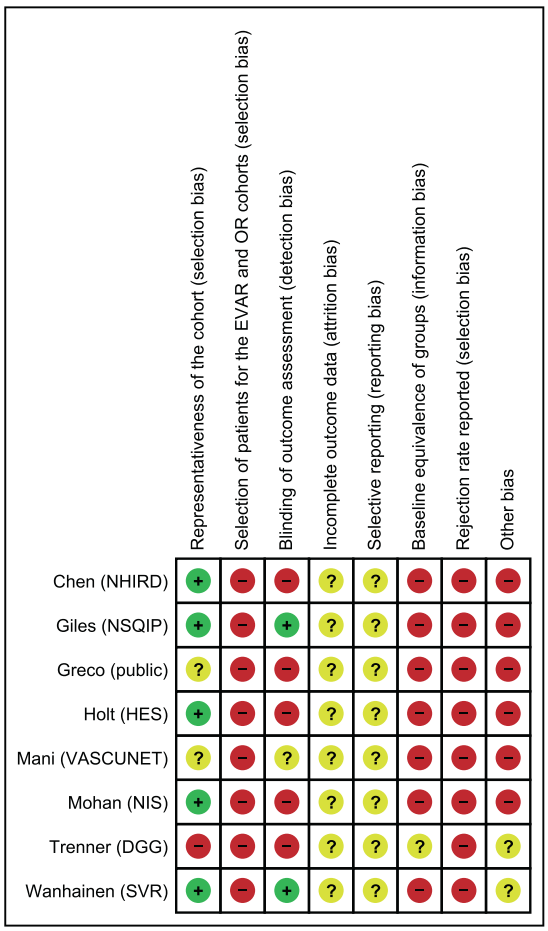

Figure 7. Risk of bias within administrative registries.

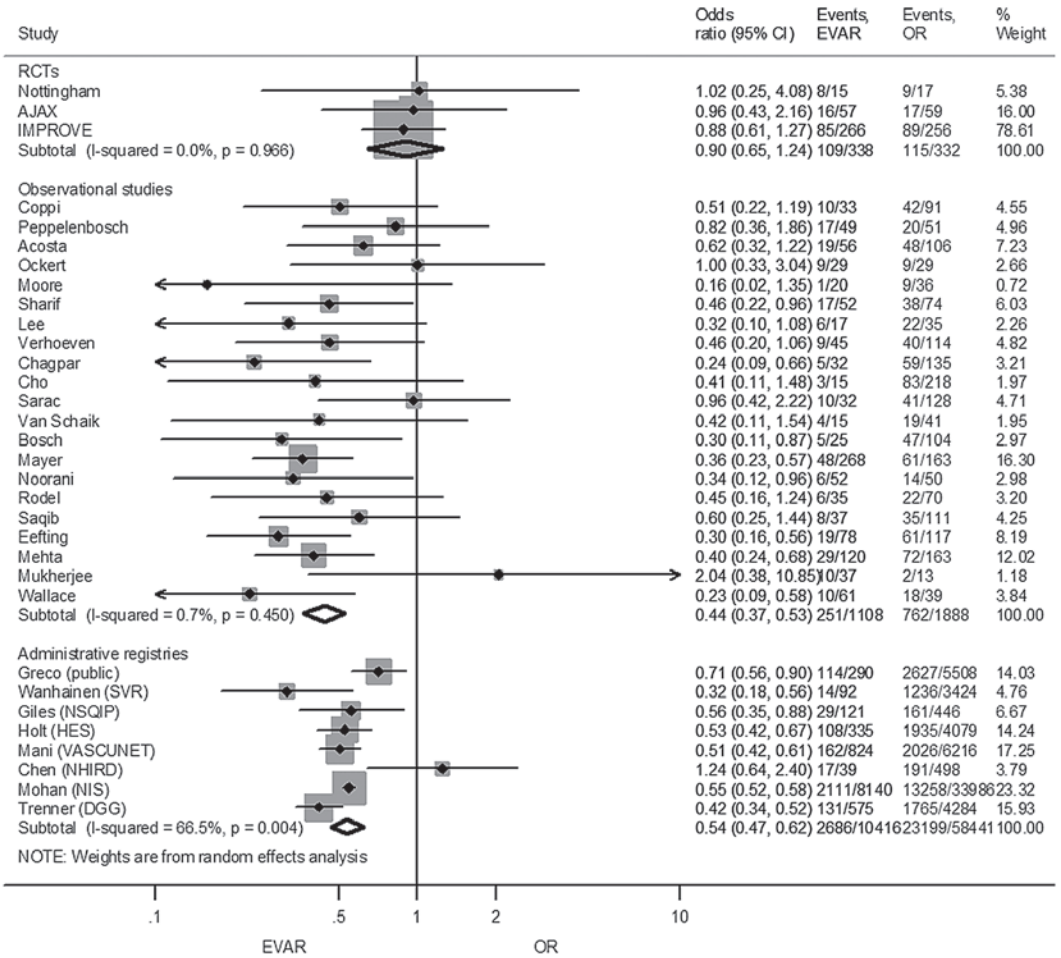

Figure 8. Forest plot showing the pooled odds ratios of the randomized controlled trials, observational studies, and administrative registries comparing endovascular (EVAR) versus open repair (OR) in patients with a ruptured abdominal aortic aneurysm.
SVR = Swedish Vascular Registry, NSQIP = American College of Surgeons National Surgical Quality Improvement Program, HES = Hospital Episode Statistics, NHIRD = National Health Insurance Research Database, NIS = Nationwide Inpatient Sample, DGG = German Vascular Society.

Pooled outcomes

In the RCTs, the reported death rates ranged between 28% and 53% after EVAR and between 29% and 53% after OR. The pooled odds ratio for death after EVAR versus OR was 1.90 (95% CI 0.65 to 1.24) (Figure 8). No funnel plot was created because of the low number of included RCTs.

In the observational studies, the death rates after EVAR ranged between 5% and 35% and between 15% and 63% after OR. The pooled odds ratio for death after EVAR versus OR was 0.44 (95% CI 0.37 to 0.53) (Figure 8). There were no signs of asymmetry in the funnel plot (Figure 9). In the sensitivity analysis of observational studies adjusting for age, sex, and haemodynamic stability, the pooled adjusted odds ratio of EVAR versus OR was 0.53 (95% CI 0.29 to 0.98) with moderate heterogeneity among the studies (I^2 = 34%) (Figure 10).

In the administrative registries, the death rates after EVAR ranged between 15% and 39% and between 33% and 48% after OR. The pooled odds ratio for death after EVAR versus OR was 0.54 (95% CI 0.47 to 0.62) (Figure 8). There was moderate heterogeneity in outcomes among the administrative registries (I^2 = 67%). No funnel plots were created because of the low number of included administrative registries.

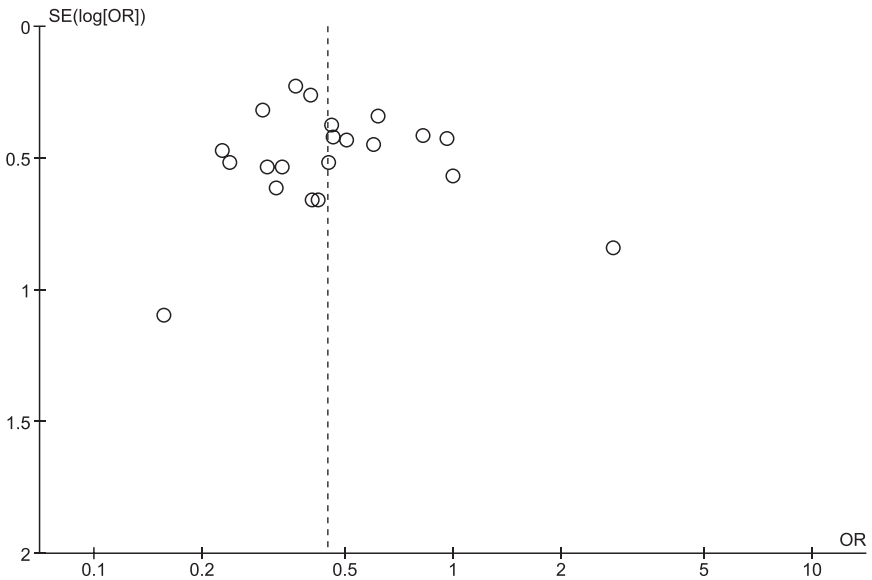

Figure 9. Funnel plot for the meta-analysis in observational studies. Only studies with a sample size of at least 50 patients were included.
SE = standard error, OR = odds ratio

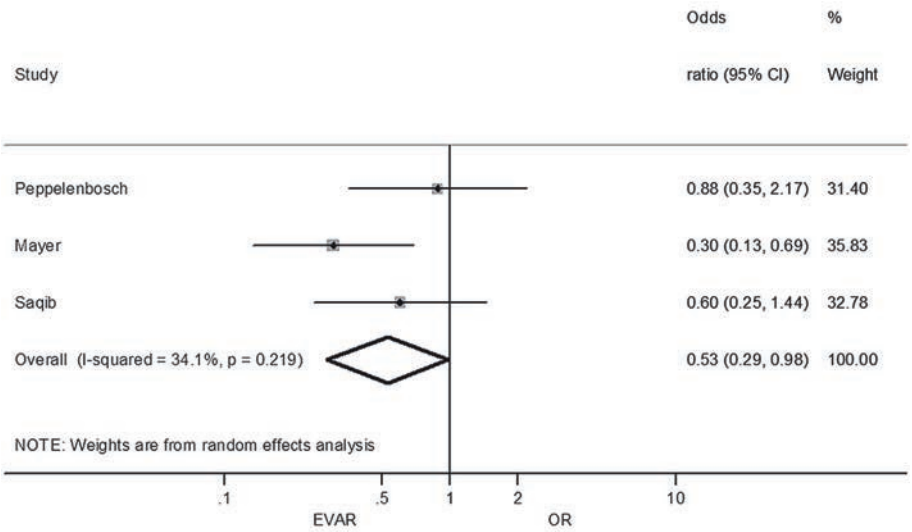

Figure 10. Sensitivity analysis of observational studies comparing endovascular vs. open repair after adjustment for at least age, sex, and hemodynamic stability.

Discussion

The present systematic review expands upon previous reviews[39-48] considering EVAR versus OR for patients with RAAA in two ways. First, this is the first to include three RCTs. Second, only one previous systematic review also included a thorough study quality assessment. The results of the meta-analyses presented here indicate that EVAR is not inferior to OR with regard to short-term survival after RAAA. This supports the use of EVAR in suitable patients and OR as reasonable alternative.

Study quality

There was a conspicuous contradiction between the pooled results of the RCTs, the observational cohort studies and the administrative registries. The pooled results of the observational studies and administrative registries show that EVAR improves short-term survival. However, in the pooled results of the RCTs these results were not confirmed. For this reason, we are reluctant to draw the conclusion that short-term survival is lower after EVAR than after OR.

The disparate results are most likely explained by study quality and selection bias. The study quality assessment clearly showed that the RCTs had the least risk

of bias for the comparison of EVAR and OR. Treatment allocation by caregivers and thereby selection of patients for either intervention is the most important risk of bias in observational studies. Treatment algorithms and surgeon's decisions resulted directly in OR in hemodynamically unstable patients and in preoperative computed tomographic angiography and subsequent EVAR in hemodynamically stable patients. By this selection, patients with a low-risk profile for survival were treated with OR and with a high-risk profile for survival with EVAR. In only three[17, 23, 25] of 21 observational studies was the outcome adjusted for the most important confounders age, sex, and hemodynamic stability. The improved short-term survival after EVAR persisted in the sensitivity analysis of the observational studies adjusting for these confounders (odds ratio 0.53, 95% CI 0.29 to 0.98). Contrary to our expectations, these pooled results did not mimic the outcomes of the RCTs. The multivariate analyses may have been affected by residual confounding, which means that statistical methods could not eliminate all differences in observed and unobserved confounders. On the other hand, the RCTs might have been affected by selection bias before enrolment of patients, thereby hampering comparison with daily practice.

The administrative registries with a low risk of bias described their data quality checks and represented both secondary and tertiary hospitals. These registries reflect the daily practice of EVAR and OR over a longer time period and are state-, nation-, or continent-wide. An advantage is that referral patterns are automatically incorporated in the results. However, rejection rates and detailed patient characteristics are scarcely available which are essential elements of the direct comparison between EVAR and OR. Moreover, accuracy of patient identification with use of ICD coding can be questioned.

Preferred intervention

The present review considers short-term survival. Although this is the most important outcome for patients with RAAA, other arguments might support either EVAR or OR. In general, it might be argued that non-inferiority suffices for a minimally invasive surgical technique compared with the open equivalent. In the RCTs there appears to be a benefit for EVAR with regard to secondary outcomes like reduction of intensive care unit and hospital stay, need for mechanical ventilation, and blood loss.[2, 3] The number of in-hospital reinterventions appears to be comparable.[2, 3] In the direct comparison of costs after 30 days between EVAR and OR in the AJAX trial, EVAR was €5,306 more expensive (95% CI €1,854 to

€12,659).[49] In the comparison of costs after 30 days between the endovascular and open strategy in the IMPROVE trial, the endovascular strategy was €1,435 cheaper (95% CI €756 to €3,626).[2] These seemingly contradictory outcomes can be explained in the IMPROVE trial by the 112/275 patients treated by open surgery in the endovascular strategy group, by shorter stay in the intensive care unit and hospital, and by a cheaper endograft. Yet, the results are not contradictory if it is argued that EVAR is more expensive than OR but that a treatment strategy offering both EVAR and OR is not more expensive than a treatment strategy including only OR. Although it is of importance in decision-making, few data are available on surgeons and patient preferences. Finally, in elective aortic surgery, the long-term risk of reinterventions and aneurysm rupture is higher after EVAR than after OR.[50] A recent observational study in patients with RAAA reported a higher late reintervention rate after EVAR (16/62, median follow-up 42 months with an inter-quartile range 4-76 months) than after OR (4/85, median follow-up 39 months with an inter-quartile range 2-75 months) (P=.01).[51] More data are needed before definite conclusions can be drawn with regard to long-term outcomes. However, one might question whether long-term risks should impact decision-making in the acute clinical setting and EVAR for RAAAs could be considered a damage control intervention.

Future directions

What are the future directions after the present review? Currently, there is still one RCT underway aiming to compare EVAR versus OR,[9] which might change the pooled results. Based on the results from the currently available RCTs that show small differences in short-term survival, it seems unlikely that a new RCT will show marked differences. To our current knowledge the clinical equipoise on short-term survival will remain and the differences between EVAR and OR should be found in the secondary and long-term outcomes. The aggregated results from the RCTs, the observational studies and administrative registries guide us to the conclusion that EVAR is a good choice in patients that are anatomically and clinically fit for endovascular repair. In other patients OR is a reasonable alternative.

Specific patient groups could be studied: EVAR might be more beneficial in women[2] and OR might be more beneficial in patients with hostile aortic anatomy. Although a detailed description runs beyond the scope of the present review, several studies gave other future directions of care for patients with

RAAA. Centralization of care in high-volume hospitals was suggested in four of 30 studies.[3, 19, 33, 34] Two studies proposed 'EVAR-first' or hybrid repair comprising rapid proximal aortic balloon occlusion in all patients and subsequently EVAR or OR.[20, 30] Another study suggested an 'EVAR-only' approach and treated 70 of 73 consecutive RAAA patients with EVAR.[17] These suggestions are promising, but much research needs to be done before definite conclusions can be drawn.

Finally, the most important benefit of EVAR might be that patients who were considered unfit for open surgical repair earlier might be considered eligible for endovascular intervention nowadays. This leads to an increase in the number of treated patients, which might explain the improved population-based survival that was found in a recent systematic review.[1] Another indication of a reduction of rejection rates is a trend towards older patients being treated for RAAAs in administrative registries[35, 37] However, meta-regression of the study midpoint dates and rejection rates showed no significant trend over time (data not shown). Therefore, more high-quality data are needed before definite conclusions can be drawn and the present systematic review cannot answer the question of a reduction in rejection rates. Moreover, a reduction in rejection rates might be caused by EVAR but also by permissive hypotension during transport, massive transfusion protocols, specialized cardiovascular anesthetic care, and improvements in the intensive care unit.

Limitations

An important limitation of this systematic review is that it might have been affected by publication bias. No funnel plots of the RCTs or administrative registries could be created because of the low number of studies. Data might have been missed since one eligible study was excluded because of language restrictions and one because data were missing and could not be provided by the corresponding author. The impact of publication bias on the conclusions is difficult to assess. In general, publication bias leads to an overestimation of treatment effect.

An important limitation of the meta-analysis of the RCTs is that it included only 761 patients. The low number of patients limits the external validity of outcomes for the general RAAA population. It is concluded that EVAR is not inferior to OR. Based on an expected survival rate after EVAR of 68% and after OR of 65% and assuming an α of 5% and a β of 80%, the sample size needed for a hypothetical non-inferiority trial would be 680 patients for a margin of 6% and

860 patients for a margin of 5%. Assuming a survival rate of 65% after OR, the margin of this non-inferiority conclusion includes a survival after EVAR of at least 59% (65 minus 6%). It could be argued that this margin is too wide and more patients are needed to decrease the margin. However, given the pooled results of EVAR from the RCTs, observational studies, and administrative registries it is considered highly unlikely that the survival of EVAR is worse than 59%. The inclusion of the IMPROVE trial troubled our statistical analysis. From this RCT, only the surgically treated RAAA patients were included, and this violated the intention-to-treat principle to reduce bias from patients with no RAAA and patients without treatment. Inclusion of non-surgically treated RAAA patients (n = 36) and patients with other diseases (n = 55) was considered inappropriate. Noteworthy, after including all patients from the IMPROVE trial the pooled odds ratio of the RCTs barely differed (0.93, 95% CI 0.69 to 1.25).

Conclusion

The results of the present systematic review, meta-analyses, and study quality assessment indicate that EVAR is not inferior to OR in patients with a ruptured abdominal aortic aneurysm with regard to short-term survival. This supports the use of EVAR in suitable patients and OR as reasonable alternative.

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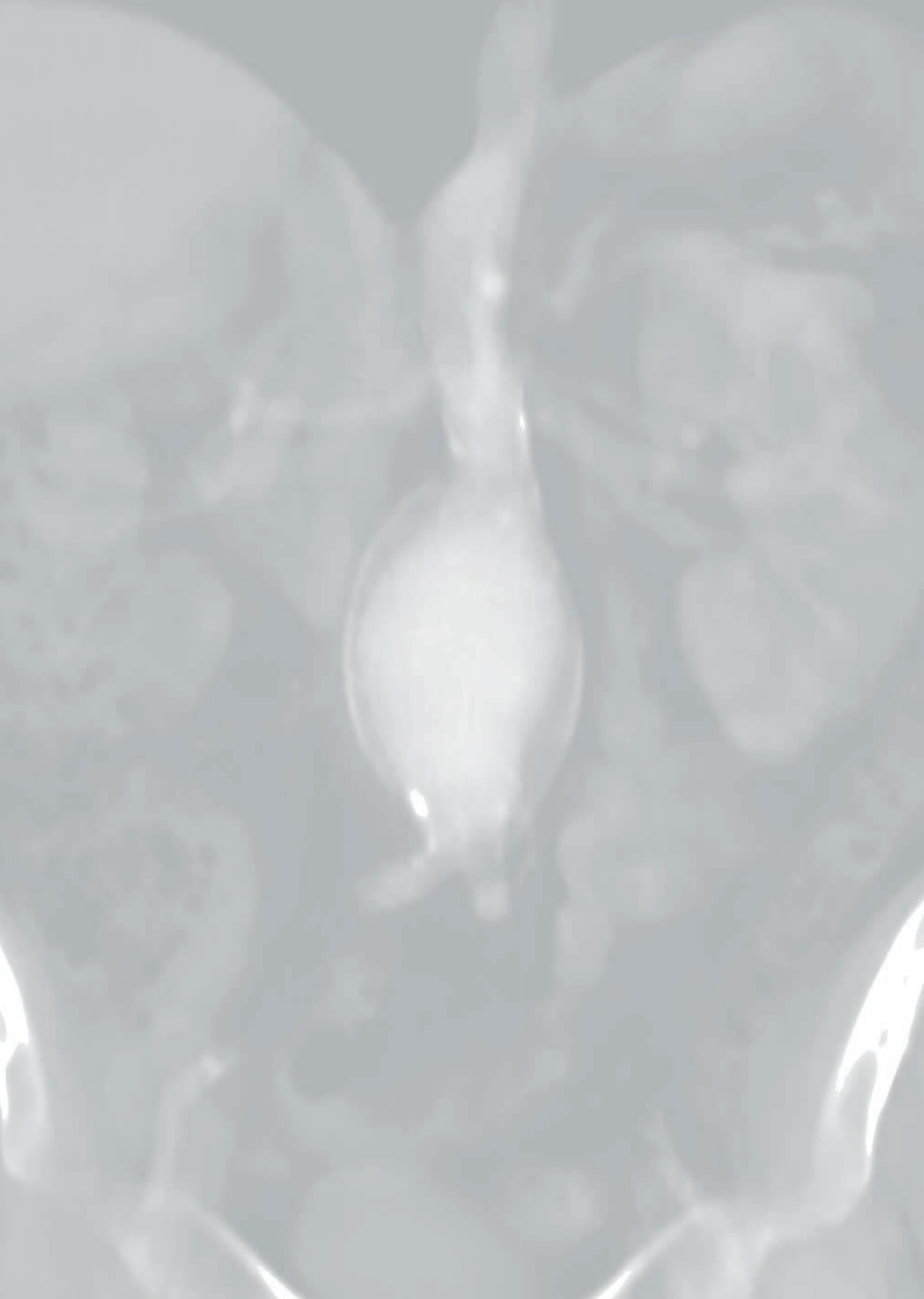

Chapter 9

Midterm reinterventions and survival after endovascular versus open repair for a ruptured abdominal aortic aneurysm

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Submitted

Abstract

Background

In elective aortic surgery, the midterm risk of reintervention is higher after endovascular aneurysm repair (EVAR) than after open repair (OR). In the present study we compared the reintervention and survival rates after EVAR and OR for ruptured abdominal aortic aneurysms (RAAA).

Methods

An observational cohort study was carried out including all consecutive surgically treated RAAA patients between 2004 and 2011 in ten hospitals in the Amsterdam ambulance region. The primary end points were reinterventions and death within five years after the primary intervention. The outcomes were estimated by Kaplan-Meier survival analyses and compared with use of the logrank test. Outcomes were estimated in all patients and in patients who survived their hospital stay.

Results

Of 467 patients with an RAAA, 73 were treated with EVAR and 394 with OR. Five years after primary intervention, the rates of freedom from reintervention were 49% for EVAR (30/73, 95% confidence interval (CI) 36 to 63%) and 60% for OR (128/394, 95% CI 55 to 66%, P=.31). The survival rates were 36% for EVAR (45/73, 95% CI 24 to 47%) and 38% for OR (235/394, 95% CI 33 to 43%, P=.83). In 297 patients who survived their hospital stay, the rates of freedom from reintervention were 66% for EVAR (15/54, 95% CI 52 to 81%) and 90% for OR (20/243, 95% CI 86 to 95%, P<.01). In these patients, the survival rates were 48% (26/54, 95% CI 34 to 62%) for EVAR and 62% for OR (84/243, 95% CI 56 to 69%, P=.04).

Conclusion

Five years after the primary intervention, endovascular and open repair for a ruptured abdominal aortic aneurysm resulted in similar reintervention and survival rates. However, in patients who survived their hospital stay the reintervention rate was higher for EVAR than for OR.

Introduction

Patients with a ruptured aneurysm of the abdominal aorta (RAAA) can be treated with endovascular (EVAR) or open repair (OR). So far no significant difference in the 30-day death rate between these interventions has been reported in randomized controlled trials.[1-3] For this reason midterm outcomes are starting to be of interest in the debate on whether EVAR or OR is to be preferred for patients with an RAAA.[2,4,5] Midterm encompasses the period between the primary intervention and five years thereafter. In elective aortic surgery, the midterm risk of reintervention and aneurysm rupture is higher after EVAR than after OR.[6] Midterm outcomes after acute intervention may also differ. Therefore, midterm outcomes may give new insights into the preferred intervention in patients with an RAAA or guide post-intervention surveillance strategies. In the present study we compared the reintervention and survival rates five years after EVAR and OR for an RAAA.

Methods

The present study was an observational cohort study and reports follow-up data from the previously published Amsterdam Acute Aneurysm (AJAX) trial which was conducted in the Amsterdam ambulance region which comprises ten hospitals and 1.38 million inhabitants.[3,7] Between April 2004 and February 2011, all consecutive patients with an RAAA in the region were registered prospectively and of these, all who underwent surgical treatment were included in the present study. Only patients whose demographics or short-term outcome were unknown were excluded. Patients suitable for both EVAR and OR were randomized to either intervention in the AJAX trial. Details of patient identification, the randomization procedure and the informed consent procedure have been published previously.[3,7] After discharge patients had routine follow-up according to local practice. EVAR follow-up included either yearly computed-tomographic angiography (CTA) or duplex ultrasound combined with plain abdominal x-ray.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the present report includes all items recommended by the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.[8]

End point

The primary end points were reinterventions and death within five years after the primary intervention. Reinterventions were defined according to the reporting standards.[9] Indications for reinterventions were categorized as abdominal compartment syndrome, access site infection, anastomosis aneurysms, re-bleeding, bowel ischemia, endograft migration, endoleaks (type I – IV), false aneurysms, graft thrombosis or obstruction, graft infection, incisional hernia, ischemia of lower limbs, secondary aneurysm rupture, secondary symptomatic aneurysm and symptomatic adhesions.

Data collection

Data were collected up to January 2014 using Microsoft Office Access 2003 (Microsoft Corporation, Redmond, Washington, USA) and included field limits and multivariate checks. Dates of death were obtained stepwise from the hospital registries (1), from the registry of the general practitioner (2) or from the communal registry of death certificates (3). Data regarding reinterventions and their indications were collected from hospital medical records and the general practitioners were asked for information on reinterventions in other hospitals. Patients whose follow-up was unknown were censored in the analysis at the last point of contact. The data collection was done in the same way in patients treated with EVAR and OR.

Statistical analysis

Continuous data were described by the mean with corresponding standard deviation (SD) for data normally distributed, and by the median with corresponding inter-quartile range for data with a skewed distribution. Baseline characteristics were compared using the chi-square test and the Mann-Whitney U test (two-sided; $\alpha = .05$). The reintervention and survival rates were estimated by Kaplan-Meier survival analyses and EVAR and OR compared using the logrank test. Reintervention rates were reported as freedom from reintervention with corresponding events and surrounding 95% confidence interval (CI). In the Kaplan-Meier survival analyses of the reintervention rates, patients who died were censored.

Two subgroup analyses were conducted. The first subgroup included patients who survived their hospital stay and the first 30 days after the primary intervention. The second subgroup included patients from the AJAX trial in whom

treatment allocation was done using randomization. This subgroup analysis was done according to the intention-to-treat principle.

Results

Between 2004 and 2011, 539 patients with an RAAA were admitted to one of the ten hospitals in the Amsterdam ambulance region. Six patients whose demographics or outcome were unknown and 66 patients without surgical intervention were excluded from the analysis (Figure 1). The baseline characteristics of 467 patients included in the analysis are shown per type of intervention in Table 1. Patients treated with EVAR showed a tendency towards higher preoperative systolic blood pressure (P=.07), and required less preoperative cardiopulmonary resuscitation (P=.05). Five years after the primary intervention, the overall survival rate was 38% (280/467, 95% CI 33 to 43%) and the median follow-up was 2.2 years (interquartile range 0.0-5.0 years). Eighteen patients (3 for EVAR, 15 for OR) were lost to follow-up and censored at the last point of contact.

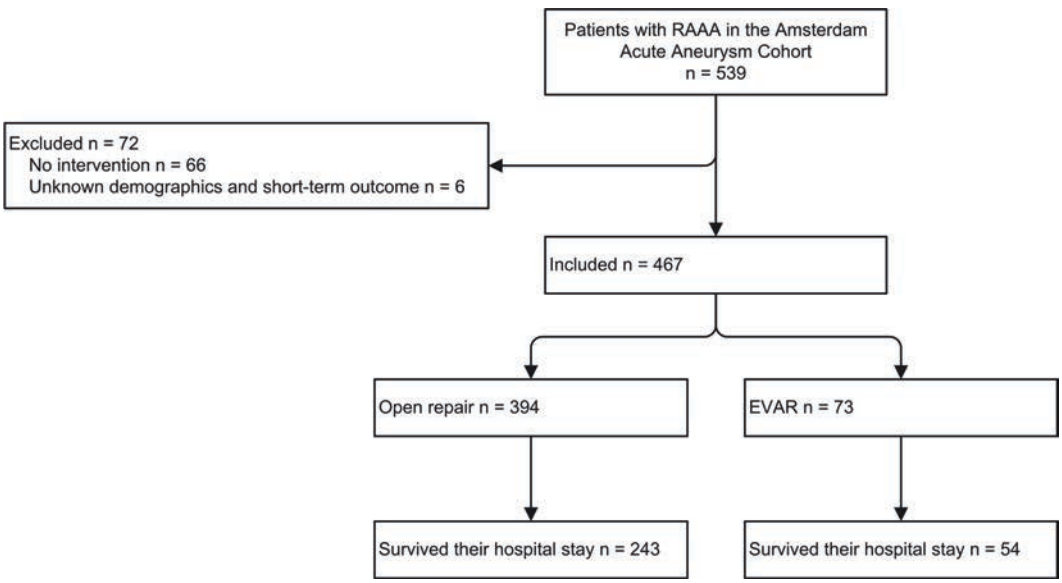

Figure 1. Flowchart of inclusion.
EVAR = endovascular aneurysm repair

Table 1. Baseline characteristics.
CPR = cardiopulmonary resuscitation, SBP = systolic blood pressure

Variable	EVAR n = 73	OR n = 394	P	Missing data
Age (years)	76 (69-80)	76 (69-82)	.70 [a]	0
Male : Female	82% : 12% (64 : 9)	80% : 20% (314 : 80)	.11 [b]	0
Cardiac co-morbidity	48% (35/73)	42% (158/379)	.32 [b]	3% (15/467)
Pulmonary co-morbidity	27% (20/73)	20% (76/376)	.17 [b]	4% (18/467)
Renal co-morbidity	10% (7/73)	12% (45/377)	.57 [b]	4% (17/467)
Cerebrovascular co-morbidity	15% (11/73)	15% (58/378)	.95 [b]	3% (16/467)
CPR	4% (3/73)	12% (45/374)	.05 [b]	4% (20/467)
Lowest in-hospital SBP (mmHg)	90 (75-129)	90 (69-125)	.07 [a]	11% (50/467)

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number).
[a] Mann-Whitney Test
[b] Chi-squared statistic

All patients

Five years after the primary intervention, the rates of freedom from reintervention were 49% for EVAR (30/73, 95% CI 36 to 63%) and 60% for OR (128/394, 95% CI 55 to 66%, P=.31) (Figure 2A). The indications for the first reinterventions are shown in Table 2. The survival rates after five years were 36% for EVAR (45/73, 95% CI 24 to 47%) and 38% for OR (235/394, 95% CI 33 to 43%, P=.83) (Figure 3A).

Discharged patients

In 297 patients who survived their hospital stay, the rates of freedom from reintervention were 66% for EVAR (15/54, 95% CI 52 to 81%), and 90% for OR (20/243, 95% CI 86 to 95%, P<.01) (Figure 2B). In these patients, the survival rates were 48% for EVAR (26/54, 95% CI 34 to 62%) and 62% for OR (84/243, 95% CI 56 to 69%, P=.04) (Figure 3B).

Randomized patients

Of 467 patients included in the analysis, 113 were randomized between EVAR and OR in the AJAX trial and were studied in the subgroup analysis. Because of the intention-to-treat principle, 3 patients with a discharge diagnosis other than RAAA were also included in the AJAX trial and therefore added to the subgroup analysis. In patients who survived their hospital stay, the rates of freedom from reintervention were 63% for EVAR (13/41, 95% CI 47 to 80%) and 81% for OR (7/42,

95% CI 68 to 94%, P=.14) (Table 3). The overall survival rates were 38% for EVAR (34/57, 95% CI 25 to 51%) and 42% for OR (33/59, 95% CI 29 to 55%, P=.81).

Table 2. Indications of the first reintervention after EVAR and OR.
EVAR = endovascular aneurysm repair, OR = open repair

	All patients		Patients who survived their hospital stay	
	EVAR n = 73	**OR n = 394**	**EVAR n = 54**	**OR n = 243**
Abdominal compartment syndrome	1	7	0	0
Access site infection	0	1	0	2
Anastomosis aneurysm	0	0	0	1
Re-bleeding	1	38	0	0
Bowel ischemia	3	28	0	0
Endograft migration	4	0	3	0
Endoleak	12	0	4	0
False aneurysm	1	0	1	0
Graft thrombosis or obstruction	1	2	1	1
Graft infection	5	6	4	4
Incisional hernia	0	9	1	3
Ischemia of lower limbs	2	22	0	2
Secondary ruptured aneurysm	0	0	0	1
Secondary symptomatic aneurysm	0	1	0	1
Symptomatic adhesions	0	5	0	3
Other	0	2	1	2
Unknown	0	6	0	0

Table 3. Subgroup analysis of the AJAX trial with Kaplan–Meier estimates of the freedom from reintervention and of the overall survival rates during five years of follow-up in all patients and in patients who survived their hospital stay.
EVAR = endovascular aneurysm repair, CI = confidence interval, OR = open repair

	EVAR (events, 95% CI)	**OR (events, 95% CI)**	**P**
Freedom from reintervention in all patients	45% (26/57, 30 to 60%)	59% (20/59, 45 to 74%)	.23
Freedom from reintervention in patients who survived their hospital stay	63% (13/41, 47 to 80%)	81% (7/42, 68 to 94%)	.14
Overall survival in all patients	38% (34/57, 25 to 51%)	42% (33/59, 29 to 55%)	.81
Overall survival in patients who survived their hospital stay	53% (18/41, 36 to 69%)	59% (16/42, 43 to 75%)	.62

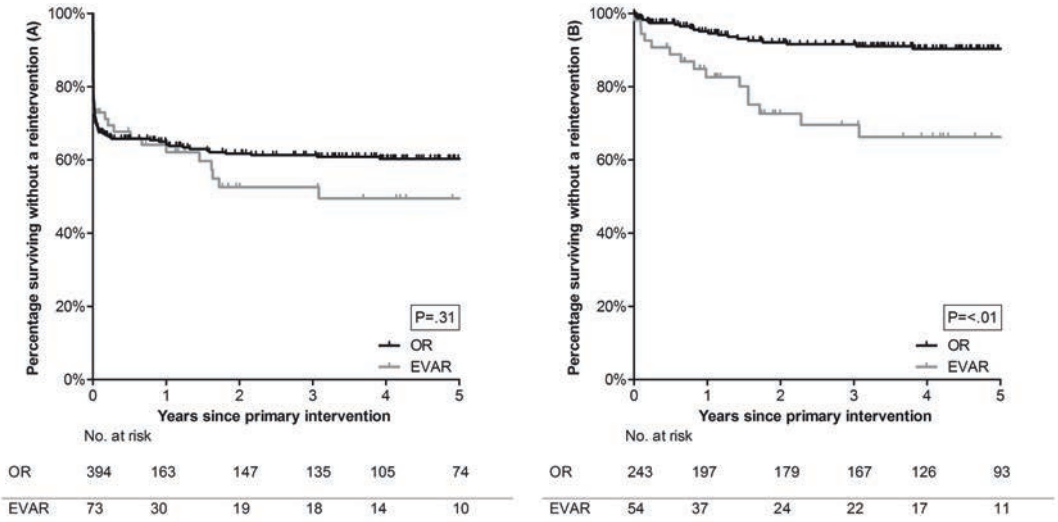

Figure 2. Kaplan–Meier estimates of the freedom from reintervention during five years of follow-up in all patients (A, left) and in patients who survived their hospital stay (B, right).
OR = open repair, EVAR = endovascular aneurysm repair

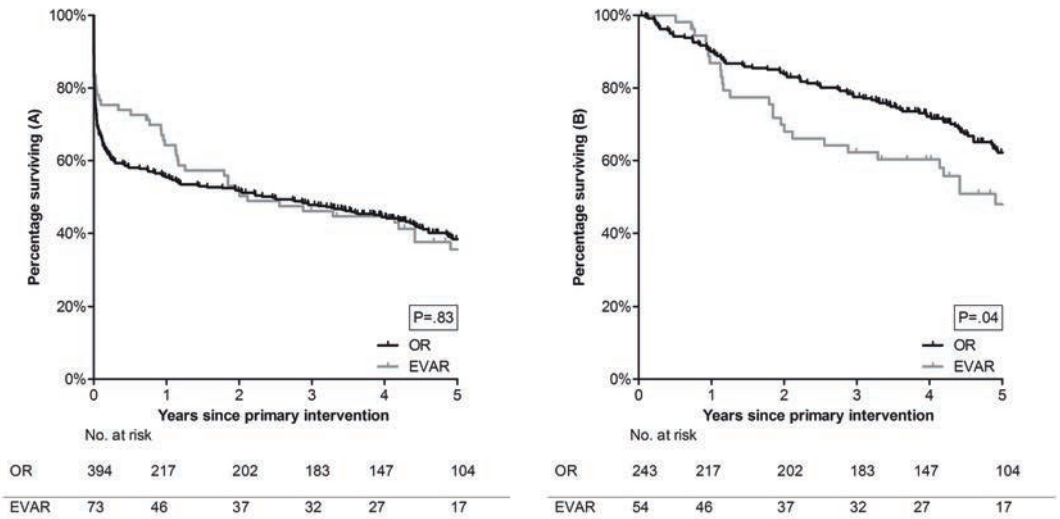

Figure 3. Kaplan–Meier estimates of the overall survival during five years of follow-up in all patients (A, left) and in patients who survived their hospital stay (B, right).
OR = open repair, EVAR = endovascular aneurysm repair

Discussion

The present study in patients with a ruptured abdominal aortic aneurysm shows that five years after the primary intervention the reintervention and survival rates for endovascular and open repair are similar. In patients who survive their hospital stay the reintervention rate for EVAR is higher than for OR.

Midterm outcomes

The majority of studies comparing EVAR and OR for RAAA focus on short-term outcomes and only five studies[10-14] have reported midterm outcomes so far. The present study expands on these studies by the prospective patient identification, by the multi-center design representing ten hospitals from one ambulance region and by the subgroup analysis with randomized treatment allocation. Several conclusions can be drawn by interpreting our results in the light of the previous studies.

It is known that in elective aortic surgery, the midterm risk of reintervention is higher after EVAR than after OR.[6] In agreement with a previous study[13], the present study shows that there is no difference in reintervention rates after an acute intervention. Because our study (n = 73) and the previous study (n = 62) included a limited number of patients treated by EVAR, more data is required before definite conclusions can be drawn. An interesting observation from both these studies is that during the in-hospital period there were fewer reinterventions after EVAR and during follow-up there were fewer reinterventions after OR (Figure 2A).

Our results confirm previous results that in patients who survived their hospital stay the reintervention rate is higher after EVAR than after OR.[10, 13] Although not statistically significant, the large difference with the subgroup analysis in the AJAX trial (63% vs. 81%, respectively) also confirms that the reintervention rate is higher after EVAR than after OR. This conclusion echoes the results after elective aortic surgery.[6] We did not determine if the indications for reintervention were found by routine follow-up or by an acute event. For this reason, no definite conclusions could be drawn about the need for routine follow-up after EVAR for an RAAA.

The overall survival rate of all patients in the present study (38%, 95% CI 34 to 43%) corresponds to a previously reported 5-year survival of 44% (99% CI 40 to 47%).[11] This indicates that the 5-year survival after an RAAA is low; approximately 40%.

In the present study, results regarding the midterm survival after EVAR and OR were conflicting. In all patients, the survival rates five years after the primary intervention were similar for EVAR and for OR (Figure 2A). In patients who survived their hospital stay, there was a conspicuously higher survival rate for OR (Figure 3B). Conversely, the subgroup analysis in the AJAX trial showed similar survival rates for both interventions in all patients and in patients who survived their hospital stay (Table 3). The same conflicting results can be found on assessing the outcomes of previous studies. One study[13] reported similar survival rates, while other studies reported lower survival rates for EVAR.[10-12, 14] It appears probable that patient selection for EVAR significantly influences these midterm survival rates. Because randomized treatment allocation adjusts for this patient selection, the results of the subgroup analysis in the AJAX trial guide us towards the conclusion that the midterm survival rates for EVAR and for OR are comparable.

Preferred intervention

The present study adds to the debate on whether EVAR or OR is to be preferred for patients with an RAAA. The randomized trials reported a similar short-term survival rate for both EVAR and OR.[5] EVAR appears to be beneficial on secondary outcomes such as less blood loss, less need for mechanical ventilation and temporary dialysis, a shorter intensive care and hospital stay, and more patients were discharged home.[2, 3] With the results of the present study in mind, when deciding between EVAR and OR in the acute setting, caregivers have to balance the short-term benefit of secondary outcomes after EVAR with the lower midterm risk of reintervention after discharge for OR.

Limitations

A limitation of the present study was that complications that did not require surgical intervention were not included. For example, an incisional hernia in a patient who was considered to be unfit for reintervention was not included. Hence, the incidence rates of individual complications do not reflect the true incidence of these complications.

There are also some limitations to the external validity of our results. In general, indications for reintervention vary between hospitals and over time. As mentioned before, the number of patients treated with EVAR was low (n = 73). Of those patients evaluated with a CTA in the Amsterdam ambulance region,

only 49% were considered to have aortoiliac anatomy suitable for EVAR.[15] This is rather low compared with the suitability rate of the IMPROVE trial of 64%.[2] Caregivers in the Amsterdam region adhered mostly to the instructions for use (IFU) because few data or guidelines are available on the use of endografts outside the IFU. In elective aortic repair, patients treated outside the IFU have a higher risk of adverse events.[16] For this reason, the midterm reintervention rates in the Amsterdam region were probably low compared with hospitals pushing the anatomical limits of EVAR for RAAAs. In the present study, an aorto-uni-iliac endograft with a contralateral iliac occluding device was to be used for EVAR. Fifty-eight patients received the Talent endograft (Medtronic AVE Europe), seven patients the Endurant endograft (Medtronic BV, Heerlen), and the remaining eight patients received another or unknown endograft. The outcomes for EVAR are therefore predominantly limited to the Talent aorto-uni-iliac endograft. Other and more recent endografts may have better midterm outcomes.

Conclusions

Five years after the primary intervention, endovascular and open repair for a ruptured abdominal aortic aneurysm resulted in similar reintervention and survival rates. However, in patients who survived their hospital stay the reintervention rate was higher for EVAR than for OR.

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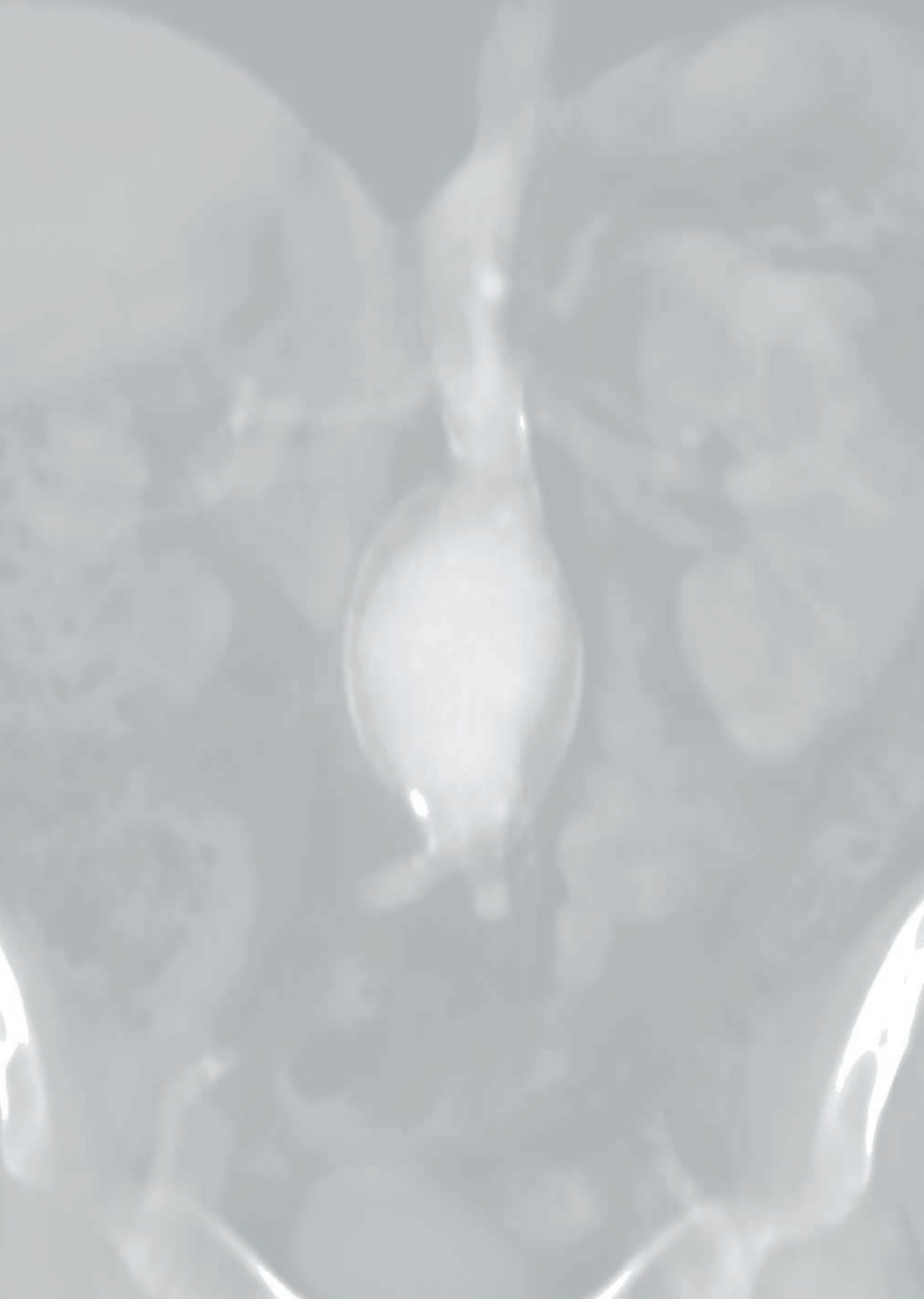

Chapter 10

Outcomes after open repair for ruptured abdominal aortic aneurysms in patients with friendly versus hostile aortoiliac anatomy

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Abstract

Background

In patients with a ruptured abdominal aortic aneurysm (RAAA), anatomic suitability for endovascular aneurysm repair (EVAR) depends on aortic neck and iliac artery characteristics. If the aortoiliac anatomy is unsuitable for EVAR ('hostile anatomy'), open repair (OR) is the next option. We hypothesized that the death rate for OR is higher in patients with hostile anatomy than in patients with friendly anatomy.

Methods

We conducted an observational cohort study in 279 consecutive patients with an RAAA treated with OR between 2004 and 2011. The primary endpoint was 30-day or in-hospital death. Aortoiliac anatomy (friendly vs. hostile) was determined prospectively by the vascular surgeon and the interventional radiologist treating the patient. A multivariable logistic regression analysis was done to assess the risk of dying in patients with hostile anatomy after adjustment for age, sex, comorbidity, and hemodynamic stability.

Results

Aortoiliac anatomy was friendly in 71 patients and hostile in 208 patients. Death rate was 38% (95% confidence interval (CI) 28 to 50%) in patients with friendly anatomy and 30% (95% CI 24 to 37%) in patients with hostile anatomy (P=.23). After multivariable adjustment, the risk of dying was not higher in patients with hostile anatomy (adjusted odds ratio 0.74, 95% CI 0.39 to 1.40).

Conclusion

The death rate after open repair for an RAAA is comparable in patients with friendly and hostile aortoiliac anatomy.

Introduction

Anatomical suitability for endovascular aneurysm repair (EVAR) depends on aortic neck and iliac artery characteristics. The aortoiliac anatomy of patients with a ruptured abdominal aortic aneurysm (RAAA) has been shown to be suitable ('friendly anatomy') for EVAR, in approximately 40% of cases.[1, 2] If the anatomy is unsuitable for EVAR ('hostile anatomy'), open repair (OR) is the next option. Hostile anatomy comprises shorter, wider, or more angulated aortic necks and calcified or tortuous iliac arteries. As the number of patients treated with EVAR is increasing,[1] fewer patients with friendly anatomy are being treated with OR. This leaves the more challenging patients for OR. Previous studies have shown that outcomes are worse after OR in patients with hostile anatomy than in patients with friendly anatomy.[3-5] For this reason, aortoiliac anatomy might be an important confounder in observational and randomized studies comparing OR and EVAR.

In the present study, we hypothesized that after OR for an RAAA, outcomes are worse in patients with hostile anatomy for EVAR than in patients with friendly anatomy for EVAR. The objective was to test this hypothesis with regard to the outcomes of in-hospital death rate, in-hospital complication rate, and long-term survival.

Methods

We conducted an observational cohort study in all consecutive patients with an RAAA treated with OR in the Amsterdam ambulance region between May 2004 and February 2011. Patients who had previously undergone aortic reconstruction, or had an RAAA with an aortoenteric fistula or whose anatomy was not classified, were excluded. Details of the cohort of patients in the Amsterdam ambulance region have been published previously.[6] All patients with an RAAA in the region, comprising 10 hospitals and 1.38 million inhabitants, were registered prospectively. All patients were to be evaluated with computed-tomographic angiography (CTA) on arrival at the hospitals. Patients regarded as too hemodynamically unstable to undergo CTA, immediately underwent OR after confirmation of the diagnosis with duplex ultra- sound. After CTA, aortoiliac anatomy (friendly vs. hostile) was classified by the vascular surgeon and the interventional radiologist

treating the patient in the acute setting. Patients with friendly anatomy who were clinically suitable for both EVAR and OR, were randomized to the Amsterdam Acute Aneurysm Trial.[6] Patients with a hostile anatomy were not randomized and were treated with OR. By this treatment algorithm, a cohort of patients treated with OR with either friendly or hostile anatomy was created for the present study. The criteria of friendly and hostile anatomy were based on the instructions for use (IFU) of an aorto-uni-iliac endograft and are shown in Table 1. OR comprised midline laparotomy and exclusion of the aneurysm by either polyester tube or polyester bifurcated graft.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Because of its observational design, written informed consent from patients was not necessary for the present study.

Table 1. Criteria for friendly and hostile aortoiliac anatomy based on the instructions for use of an aorto-uni-iliac endograft.

Suitable infrarenal anchoring segment
A minimum length of the infrarenal segment of at least 10-15 mm
An infrarenal diameter of 20-32 mm
No obstructing calcifications, tortuosity, or thrombus
Suitable iliac anchoring segment
An ipsilateral iliac diameter of 8-18 mm
A contralateral iliac diameter of 10-20 mm
At least one iliac artery should be able to accommodate an endograft
No obstructing calcifications, tortuosity, or thrombus

Outcomes

The primary endpoint was the combined 30-day or in-hospital death rate. The primary endpoint of included patients was checked for errors in the communal registry of all death certificates in the Netherlands.

The secondary endpoints were severe complications, a composite endpoint of death or complication, long-term survival, length of hospital stay, length of intensive care unit (ICU) stay, and peroperative blood loss. Details of severe complications were collected retrospectively from the medical patient charts by the primary author. Severe complications were defined as cardiac (myocardial infarction including enzymatic changes or severe hemodynamic dysfunction

necessitating resuscitation or with a fatal outcome), renal (requiring temporary or permanent dialysis), gastrointestinal (ischemia necessitating bowel resection, stoma or fatal bowel ischemia), neurological (stroke or spinal cord ischemia), graft related (graft occlusion or infection), major amputation, or the need for acute reoperation in accordance with the reporting standards.[7] Long-term survival was also derived from the communal registry of death certificates (last search October 10, 2013).

Data collection

Data collection and statistical analysis were done with IBM SPSS Statistics 19.0 (SPSS Inc., Armonk, NY, USA). Patient variables collected from the patient charts were age, sex, comorbidity categorized as cardiac disease (previous history of arrhythmia, cardiac surgery or myocardial infarction), pulmonary disease (chronic obstructive pulmonary disorder (COPD)), renal disease (previous history of chronic kidney failure or dialysis), cerebrovascular disease (previous history of transient ischemic attack or stroke), serum hemoglobin (in mmol/L, 1 mmol/L corresponds with 1.61 g/dL), serum creatinine (in μmol/L, 1 μmol/L corresponds with 88.4 mg/dL), and incidence of suprarenal aortic cross clamping. The preoperative lowest in-hospital systolic blood pressure (SBP) and incidence of cardiopulmonary resuscitation (CPR) were used as markers for hemodynamic stability. The pre-operative Glasgow aneurysm score (GAS),[8] a validated score used for case-mix comparison, was calculated. Double data entry was done for the patient variables and data were checked for inconsistencies. Inconsistencies were resolved by consulting the original patient charts. To validate the decision of friendly or hostile anatomy, aneurysm characteristics were measured by the primary author in the sagittal, coronal, and axial planes of the preoperative CTA. The measurements were done blinded for type of anatomy and outcome.

To include all patients in the regression analyses, an imputation procedure was done using logistic and linear regression models whereby ten datasets were created.[9] The most critically ill patients needed the most urgent decisions and the fewest notes were made. To correct for bias of most missing data in the most critically ill patients, we included 'death' as a predictor in the imputation model. Other predictors were the baseline characteristics, level of consciousness, and Glasgow coma scale. The statistical analysis was done in the ten separate imputed datasets and the outcomes were pooled.

Statistical analysis

Continuous data were described by the mean with corresponding standard deviation (SD) for data normally distributed, and by the median with corresponding interquartile range (IQR) for data with skewed distribution. Baseline characteristics and outcomes were compared with Student t test, the chi-square test, the Kruskal-Wallis test and the Mann-Whitney U test (two-sided; α=.05). A P less than .05 was considered statistically significant. The ranges of outcomes of the statistical tests in the ten imputed datasets were reported. Long-term survival was assessed by Kaplan-Meier survival analysis and compared using the log rank test.

Two logistic regression models were made to assess the risk of the outcomes in friendly and hostile anatomy after adjustment for possible confounding baseline characteristics. The first model was of the endpoint death and the second model of the composite endpoint of death or severe complication. If a continuous variable was not linear on the logit scale, it was categorized. The chi-square statistic, the Hosmer and Lemeshow (HL) test, and the area under the receiver operating characteristics curve (AUC) were reported to represent model performance. The ranges of the performance outcomes in the ten imputed datasets were reported.

A sensitivity analysis was done to examine the impact of not including patients without a CTA and treatment with EVAR in our analysis. First, we compared the baseline characteristics of included versus not included patients. Second, patients not included because no CTA was carried out were considered as hostile anatomy and EVAR treated patients were considered as friendly anatomy. Subsequently, a multivariable regression model was made to assess the risk of dying in friendly and hostile anatomy after adjustment for age, sex, comorbidity, SBP, CPR, and type of intervention.

Results

During the inclusion period, 539 consecutive patients with an RAAA were admitted to the hospitals in the Amsterdam ambulance region (Figure 1). Of these patients, 259 were not included in the present study because no CTA was carried out (80), they were treated with EVAR (73), no intervention was done (66), or demographics and outcome were unknown (6). Of 314 patients eligible for inclusion, 35 patients were excluded because of unknown aortoiliac anatomy classification (23), previous

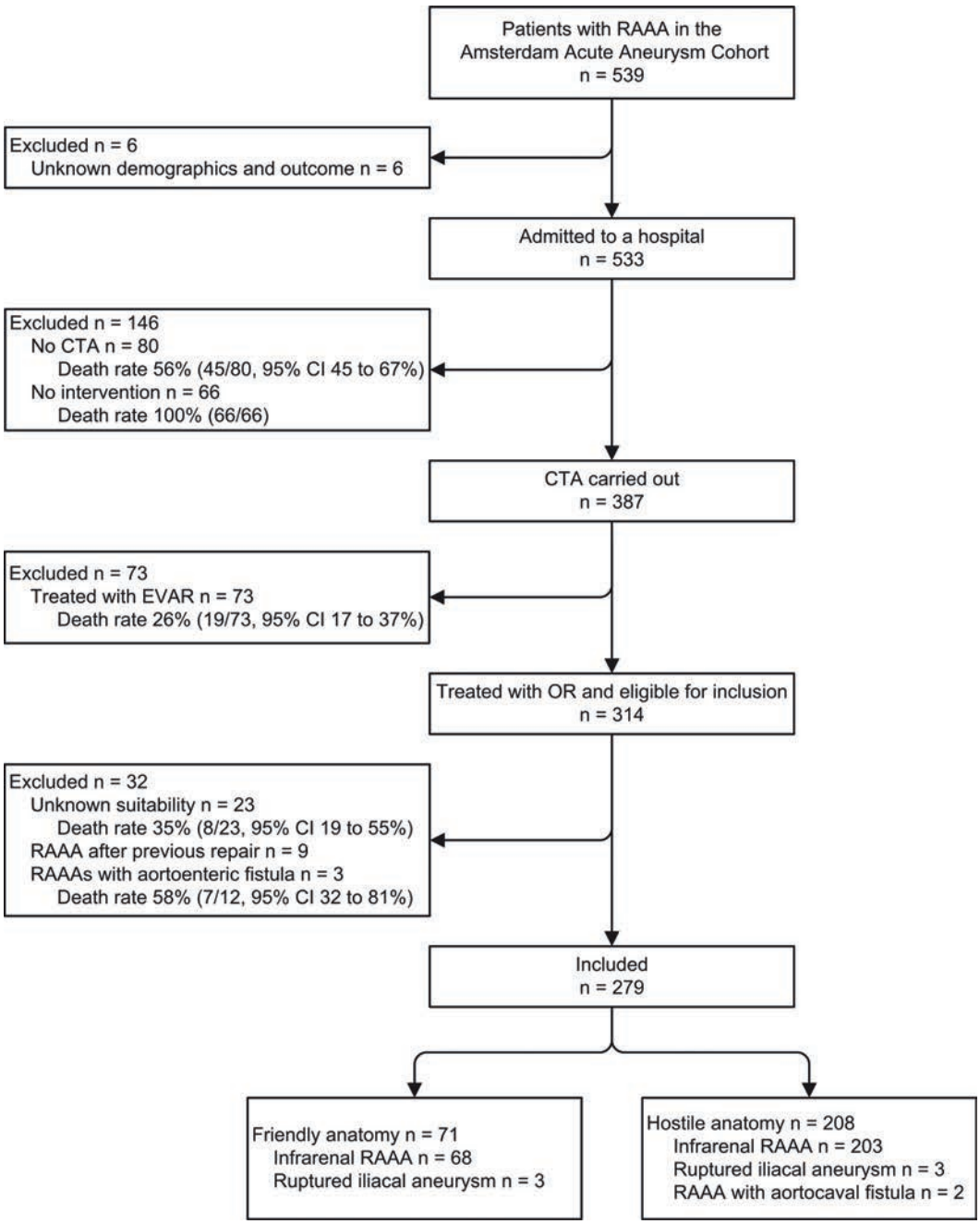


Figure 1. Flowchart of inclusion of 279 patients with friendly and hostile aortoiliac anatomy for EVAR.

RAAA = ruptured abdominal aortic aneurysm, CTA = computed tomographic angiography, EVAR = endovascular aneurysm repair, OR = open repair

aortic reconstruction (9) or an RAAA with aortoenteric fistula (3). In total, 279 patients were included in the analysis, of whom 71 had friendly and 208 had hostile anatomy. The infrarenal aortic segment was hostile for EVAR in 156 cases, the iliac arteries were hostile in 39 cases, and in 13 patients there were other or unknown reasons for hostile anatomy classification. Of 279 patients included in the analysis, 58 were also included in the Amsterdam Acute Aneurysm Trial.

The baseline characteristics are shown in Table 2 and were comparable between patients with friendly and hostile anatomy (P>.05). Suprarenal aortic cross clamping was necessary in 27% of patients with friendly anatomy (19/70, 1 unknown), and in 43% of patients with hostile anatomy (86/201, 7 unknown) (P=.02).

Table 2. Baseline characteristics of patients with friendly and hostile aortoiliac anatomy for endovascular aneurysm repair.
SBP = systolic blood pressure, GAS = Glasgow aneurysm score

Variable	Friendly anatomy n = 71	Hostile anatomy n = 208	P
Age (years)	74.6 (±9.0)	74.3 (±8.2)	.80 [a]
Male : Female	83% : 17% (59 : 12)	77% : 23% (161 : 47)	.40 [b]
Cardiac co-morbidity	47% (33/71)	44% (92/208)	.64-.96 [c]
Pulmonary co-morbidity	20% (14/71)	22% (45/208)	.73-.94 [c]
Renal co-morbidity	13% (9/71)	13% (28/208)	.71-.95 [c]
Cerebrovascular co-morbidity	20% (14/71)	17% (35/208)	.52-.85 [c]
Lowest in-hospital SBP (mmHg)	90 (68-130)	100 (80-126)	.17-.37 [b]
Cardiopulmonary resuscitation	11% (8/71)	7% (14/208)	.04-.51 [c]
Hemoglobin (mmol/L)	7.3 (5.9-8.1)	6.8 (5.9-8.0)	.38-.59 [b]
Creatinine (μmol/L)	108 (90-146)	108 (85-134)	.26-.49 [b]
GAS	90 (80-99)	86 (74-97)	.13-.32 [b]
Suprarenal aortic cross clamping	27% (19/70, 1 unknown)	43% (87/201, 7 unknown)	.02 [c]

Continuous data are presented as mean ±standard deviation or median (inter-quartile range) and categorical data as percentage (number). Results are shown for the imputed data set.
[a] Student t test
[b] Mann-Whitney U test
[c] Chi-squared test

Outcomes

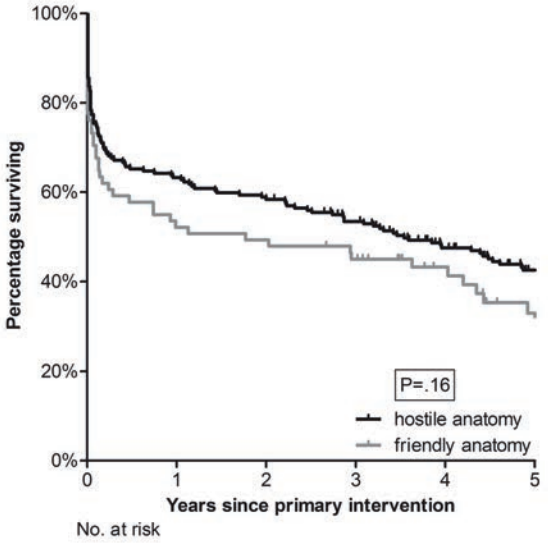
The outcomes are shown in Table 3. The death rate in patients with friendly anatomy was 38% (27/71, 95% CI 28 to 50%) and in patients with hostile anatomy this was 30% (63/208, 95% CI 24 to 37%) (P=.23). The composite death or severe

complication rate in patients with friendly anatomy was 61% (43/71, 95% CI 49 to 71%) versus 60% in patients with hostile anatomy (125/208, 95% CI 53 to 67%) (P=.95). The proportion of any severe complication, length of hospital stay, length of ICU stay, and peroperative blood loss did not differ between the groups (P>.05). The survival analyses are shown in Figure 2. After 2 years, 49% (95% CI 38 to 61%) of patients with friendly anatomy were still alive versus 58% of patients with hostile anatomy (95% CI 52 to 65%) (P=.16).

Table 3. Outcomes of patients with friendly and hostile aortoiliac anatomy for EVAR.
ICU = intensive care unit

	Friendly anatomy n = 71	**Hostile anatomy n = 208**	**P**
Death rate	38% (27/71, 28 to 50%)	30% (63/208, 24 to 37%)	.23 [a]
Severe complication rate [b]	36% (16/44, 24 to 51%)	43% (62/145, 35 to 51%)	.45 [a]
Composite endpoint death or severe complication	61% (43/71, 49 to 71%)	60% (125/208, 53 to 67%)	.95 [a]
Length hospital stay (days) [b]	16 (9-30)	16 (10-30)	.39 [c]
Length ICU stay (days) [b]	2 (1-9)	3 (1-8)	.58 [c]
Estimated blood loss (L)	3.5 (1-5)	3 (1.4-6)	.47 [c]

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number, 95% CI).
[a] Chi-squared test
[b] In discharged patients
[c] Mann-Whitney U test



No. at risk

friendly anatomy	71	37	35	31	22	14
hostile anatomy	208	130	120	105	82	63

Figure 2. Survival analysis of patients with friendly and hostile aortoiliac anatomy for endovascular aneurysm repair.

Logistic regression

After multivariable adjustment for possible confounders, the risk of dying was not higher in patients with hostile anatomy (adjusted odds ratio 0.74, 95% CI 0.39 to 1.40). The risk of dying or developing severe complications was also not higher in patients with hostile anatomy (adjusted odds ratio 1.07, 95% CI 0.59 to 1.93) (Table 4).

Aortoiliac anatomy

The CTA of 215/279 patients could be retrieved from the archives and details of the aortoiliac anatomy are shown in Table 5. In patients with friendly anatomy, the median infrarenal neck length was 23 mm (IQR 17-35 mm) and diameter was 25 mm (IQR 22-27 mm). In patients with hostile anatomy because of the infrarenal neck, the median infrarenal neck length was 10 mm (IQR 5-17 mm) and diameter was 25 mm (IQR 23-32 mm) (P<.01 and P=.01, respectively). In patients with friendly anatomy, the common iliac artery diameters were 16 mm (IQR 12-18 mm) and 14 mm (IQR 12-18 mm). In patients with hostile anatomy because of the iliac arteries, the common iliac artery diameters were 21 mm (IQR 15-31 mm) and 18 mm (IQR 14-25 mm) (P<.01 and P=.02, respectively).

Table 4. Multivariable logistic regression models with the endpoint death (30-day or in-hospital) and the composite endpoint death or severe complication.
CI = confidence interval, SBP = systolic blood pressure

Variable	Odds ratio (95% CI)	
	Endpoint death model	Composite endpoint death or severe complication model
Age <69 (n = 72)	Reference category	Reference category
Age 69-75 (n = 67)	1.52 (0.63 to 3.66)	1.17 (0.56 to 2.44)
Age >75 (n = 141)	2.05 (0.95 to 4.43)	1.44 (0.75 to 2.76)
Men	0.65 (0.33 to 1.27)	0.94 (0.50 to 1.78)
Cardiac co-morbidity	1.26 (0.70 to 2.24)	1.16 (0.68 to 1.98)
Pulmonary co-morbidity	2.33 (1.17 to 4.64)*	1.43 (0.75 to 2.74)
Renal co-morbidity	1.40 (0.60 to 3.25)	0.79 (0.35 to 1.78)
Cerebrovascular co-morbidity	1.29 (0.60 to 2.77)	1.78 (0.85 to 3.73)
Lowest in-hospital SBP (per 10 mmHg)	0.83 (0.76 to 0.90)*	-
Lowest in-hospital SBP >128 (n = 71)	-	Reference category
Lowest in-hospital SBP 100-128 (n = 72)	-	1.77 (0.88 to 3.55)
Lowest in-hospital SBP 76-100 (n = 67)	-	4.50 (2.10 to 9.62)*
Lowest in-hospital SBP <76 (n = 70)	-	2.77 (1.32 to 5.81)*
Cardiopulmonary resuscitation	2.10 (0.70 to 6.33)	2.89 (0.83 to 10.06)
Hostile anatomy	0.74 (0.39 to 1.40)	1.07 (0.59 to 1.93)

The death endpoint model included 279 patients and 90 events: χ^2 statistic 51.9-57.8 (10 df) P<.01, HL test P=.09-.88, AUC 0.75-0.77.
The composite endpoint model included 279 patients and 169 events: χ^2 statistic 28.0-32.7 (12 df) P=<.01-.01, HL test P=.43-.96, AUC 0.69-0.70.
*P<.05

Table 5. Retrospective measurement of aortoiliac anatomy.

Variable	Friendly anatomy n = 58	Hostile anatomy, reason infrarenal neck n = 118	Hostile anatomy, reason iliac arteries n = 28	P[a]
Infrarenal neck length (mm)	23 (17-35)	10 (5-17)	21 (17-35)	<.01
Infrarenal neck diameter (mm)	25 (22-27)	25 (23-32)	23 (19-27)	.01
Infrarenal neck angulation (°)	40 (25-55)	37 (19-50)	36 (18-62)	.47
Aneurysm angulation (°)	51 (30-66)	45 (27-62)	56 (31-74)	.25
Aneurysm diameter (mm)	72 (64-86)	80 (67-91)	70 (61-84)	.03
Common right iliac artery diameter (mm)	16 (12-18)	15 (12-19)	21 (15-31)	<.01
Common left iliac artery diameter (mm)	14 (12-18)	15 (12-18)	18 (14-25)	.02

Data are presented as median (inter-quartile range).
[a] Kruskal-Wallis test

Sensitivity analysis

Most baseline characteristics were comparable between included and not included patients (data not shown). The median preoperative SBP of patients included in the analysis was 100 mmHg (IQR 75-128 mmHg) and 60 mmHg (IQR 18-95 mmHg) of patients not included because no CTA was carried out (P<.01). CPR was needed in 8% (23/279) of patients included in the analysis and in 32% (25/80) of patients not included because no CTA was carried out.

The logistic regression model considering patients in whom no CTA was carried out as hostile anatomy and EVAR treated patients as friendly anatomy included 432 surgically treated patients. Of these patients, 144 had friendly and 288 had hostile anatomy. After multivariable adjustment for age, sex, comorbidity, SBP, CPR, and type of intervention, the risk of dying was not higher in patients with hostile anatomy (adjusted odds ratio 1.09, 95% CI 0.59 to 2.00) (data not shown).

Discussion

In patients with a ruptured abdominal aortic aneurysm treated with open repair, the outcomes are comparable between patients with friendly and hostile aortoiliac anatomy for EVAR. We reject our hypothesis.

For us, the most plausible explanation for this surprising conclusion is optimization of logistics in the Amsterdam ambulance region. In this region care has been centralized in three hospitals with 24-hour full emergency vascular service since 2003. In the Amsterdam Acute Aneurysm Trial, the precursor of the present study, the results after OR were better than anticipated.[6] Further analysis of the referral patterns showed that the lower death rates can be explained by regional cooperation. Thus, we consider logistic aspects of care to be more important contributors to the outcomes after an RAAA than aortoiliac anatomy. Examples of such logistic aspects are permissive hypotension during transport, the availability of a 24-hour full vascular service with specialized staff, a preoperative CTA immediately on arrival at the hospital, specialized anesthetic care, and a level III intensive care unit.

Confounding by aortic anatomy

Some observational studies have reported a higher death rate after OR than after EVAR in patients with an RAAA.[10, 11] However, two randomized trials showed

no significant difference in death rates after OR and EVAR.[6, 12] To date, only patients with friendly anatomy for EVAR have been included in the randomized trials. It has been hypothesized that selection by aortoiliac anatomy explains the inconsistencies between observational and randomized studies.[3] Aortoiliac anatomy might also be an important confounder within observational studies comparing EVAR and OR. The results of the present study contradict these hypotheses. We suspect that other confounding factors explain the conflicting outcomes between observational and randomized studies. Examples of such factors are preoperative blood pressure[13] and resuscitation,[14] intervention at a specialized vascular hospital with a high annual case-load,[15, 16] hypothermia,[17] after-hours surgery,[18] and specialized anesthetic[19] and intensive care.

Friendly anatomy rate

Of patients evaluated with CTA, the friendly anatomy rate for EVAR in the present study was 49% (174/356). The friendly anatomy rate of previous studies ranged between 54% and 99%.[20, 21] Compared with these studies, the friendly anatomy rate in the Amsterdam region was rather low. Caregivers adhered mostly to the IFU because few data or guidelines are available on the use of endografts outside the IFU in patients with an RAAA. One might consider the IFU criteria for friendly and hostile anatomy in our study as conservative. The anatomy of some patients graded as hostile by our observers, might be considered friendly by others. Possibly, this resulted in comparable aortoiliac anatomy between the two groups. However, the retrospective measurements of aortoiliac anatomy showed that in patients with hostile anatomy the infrarenal necks were shorter and wider, indeed, and the common iliac arteries wider.

Previous studies

The present study expands on previous studies that considered the outcomes in patients with friendly or hostile anatomy for EVAR.[3-5, 21] First, aortoiliac anatomy was classified prospectively in the acute setting by the treating vascular surgeon and interventional radiologist. In this way, the classification is applicable to the previously described selection bias by type of intervention in observational studies. Second, the present study was conducted in several hospitals reflecting daily practice and increasing the external validity of our results.

Our results conflict with those of three previous studies.[3-5] The largest and most important study was conducted in 233 patients in Bern, Switzerland.[3] In

the Bern study, the 30-day death rate after OR in patients with suitable aortoiliac anatomy was only 4% (95% CI 1 to 12%), in patients with borderline anatomy 16% (95% CI 9 to 27%), and in patients with unsuitable anatomy 24% (95% CI 17 to 33%). After multivariable adjustment for case-mix and hemodynamic stability, the risk of dying was higher in patients with unsuitable anatomy. It is hard to determine why our results are so conflicting with those of this similar study. Differences between the studies are numerous (Table 6), but their importance is difficult to judge. The most striking difference was the method of anatomical classification (prospectively vs. retrospectively). Moreover, patients hemodynamically unstable to undergo CTA were considered as unsuitable for EVAR in the Bern study. Applying these criteria to our study would not change our conclusions, because the odds ratio for dying in hostile versus friendly anatomy would then be 1.10 (95% CI 0.60 to 2.03) after adjustment for age, sex, comorbidity, SBP, and CPR (data not shown).

In accordance with our results, a retrospective study of 82 patients by Ten Bosch et al. reported a 30-day death rate in patients treated with OR but with anatomy suitable for EVAR of 46% (95% CI 28 to 64%) versus 49% (95% CI 34 to 64%) in patients with anatomy unsuitable for EVAR (P=.75).[21] It is noteworthy that in this study, the assessment of anatomy was retrospective as it was in the Bern study.

No definite conclusions can be drawn from these conflicting results and more studies are needed. A barrier to solving the controversy is that only observational studies can be used and these are always subject to bias. Adjustment to eliminate differences in hemodynamic stability, as was done in the Bern study and in our study, is of major importance in minimizing the risk of confounding within such a study.

Table 6. Comparison between Bern study[3] and the Amsterdam acute aneurysm cohort assessing the influence of aortic anatomy on outcomes after open repair.
SBP = systolic blood pressure, GAS = Glasgow aneurysm score

Variable	Bern n = 233	Amsterdam n = 279
Assessment suitability	Retrospective by a vascular surgeon and an interventional radiologist independently under corelab-conditions	Prospective by a vascular surgeon and an interventional radiologist together in the acute setting
Categorization of patients	Suitable vs. borderline (including debatable patients) vs. unsuitable based on anatomy and hemodynamic stability	Friendly vs. hostile (=suitable vs. unsuitable) based on anatomy (no debatable category included)
Type of study	Single center	Multicenter
Transfer from regional hospital	69% (172/248)	37% (104/279)
Rejection rate	9% (24/274)	12% (66/533)
Age (years)	73-74 (66-80)	76 (69-80)
Male : Female	89% : 11% (207 : 233)	79% : 21% (59 : 279)
Lowest in-hospital SBP (mmHg)	92-95 (70-122) [a]	100 (75-128)
Cardiopulmonary resuscitation	4% (10/248) [a]	8% (23/279)
GAS without cerebrovascular score	79-83 (72-95) [a]	86 (76-96)
Hemoglobin (mmol/L)	5.7-5.9 (4.5-7.0)	6.9 (5.9-8.1)
In-hospital death rate	16% (39/248, 12 to 21%)	32% (90/279, 27 to 38%)

Continuous data are presented as median (inter-quartile range) and categorical data as percentage (number, 95% CI).
[a] Provided by authors of Bern study, included in table with permission

Limitation

An important limitation of the present study was the inclusion of only 279 of all 467 surgically treated patients. We examined the impact of excluding three groups of patients separately. The first and most important group consisted of 80 patients in whom no CTA was carried out and 73 EVAR treated patients. The second group contained 23 patients in whom no prospective evaluation of aortoiliac anatomy was available. The third group harbored 12 patients who were excluded because of their diagnosis. For the first group, the sensitivity analysis was conducted. After multivariable adjustment for possible confounders, the risk of dying was not higher in patients with hostile anatomy Moreover, preoperative SBP per 10 mmHg (adjusted odds ratio 0.86, 95% CI 0.81 to 0.91) and CPR (adjusted odds ratio 2.74, 95% CI 1.23 to 6.11) were significantly associated with dying in this

model. This underlines the importance of hemodynamic stability in patients with an RAAA.

For the second group if we considered these patients as having friendly anatomy, the death rate in patients with friendly anatomy would be 37% (35/94, 95% CI 28 to 47%) and in patients with hostile anatomy 31% (64/209, 95% CI 25 to 37%). If we considered these patients as having hostile anatomy, the death rate in patients with friendly anatomy would be 38% (27/71, 95% CI 28 to 50%) and in patients with hostile anatomy 31% (72/232, 95% CI 25 to 37%). These crude death rates barely differ from the primary outcomes.

The third group of excluded patients was considered as 'extra difficult RAAA patients'. Risk profiles and outcomes of these patients were so unalike, that statistical methods could not eliminate differences in case-mix.

To summarize, the impact of not including 188 of 467 surgically treated patients appears to be little on our conclusions. However, we cannot rule out any residual confounding or selection bias. Moreover, the number of patients in the friendly and hostile anatomy group was disproportional and we might falsely reject our hypothesis.

Another limitation was that in 9% (26/280) of patients some data were missing. Most missing data concerned the variables SBP (5%, 15/280) and CPR (5%, 13/280). In these 26 patients, the death rate was high (58%, 15/26, 95% CI 39 to 75%). We coped with the missing data by multiple imputation and included 'death' as a predictor in the imputation model to adjust for most missing data in the most critically ill patients.

Although statistical methods were used to eliminate differences in observed confounders, another limitation of the present study was that we were unable to adjust for differences in unobserved intraoperative confounders such as blood loss and duration of intervention.

Conclusion

In patients with an RAAA treated with OR in the Amsterdam region, the death rate in patients with friendly and hostile aortoiliac anatomy was comparable. Moreover, severe complication rate, a composite endpoint of in-hospital death or severe complication, long-term survival, length of hospital stay, length of ICU stay, and peroperative blood loss did not differ. Finally, after adjustment for possible confounders the risk of dying or a severe complication was not higher in patients with hostile anatomy than in patients with friendly anatomy. Based

on these results, we conclude that outcomes after open repair for a ruptured abdominal aortoiliac aneurysm are comparable in patients with anatomy friendly and hostile to EVAR.

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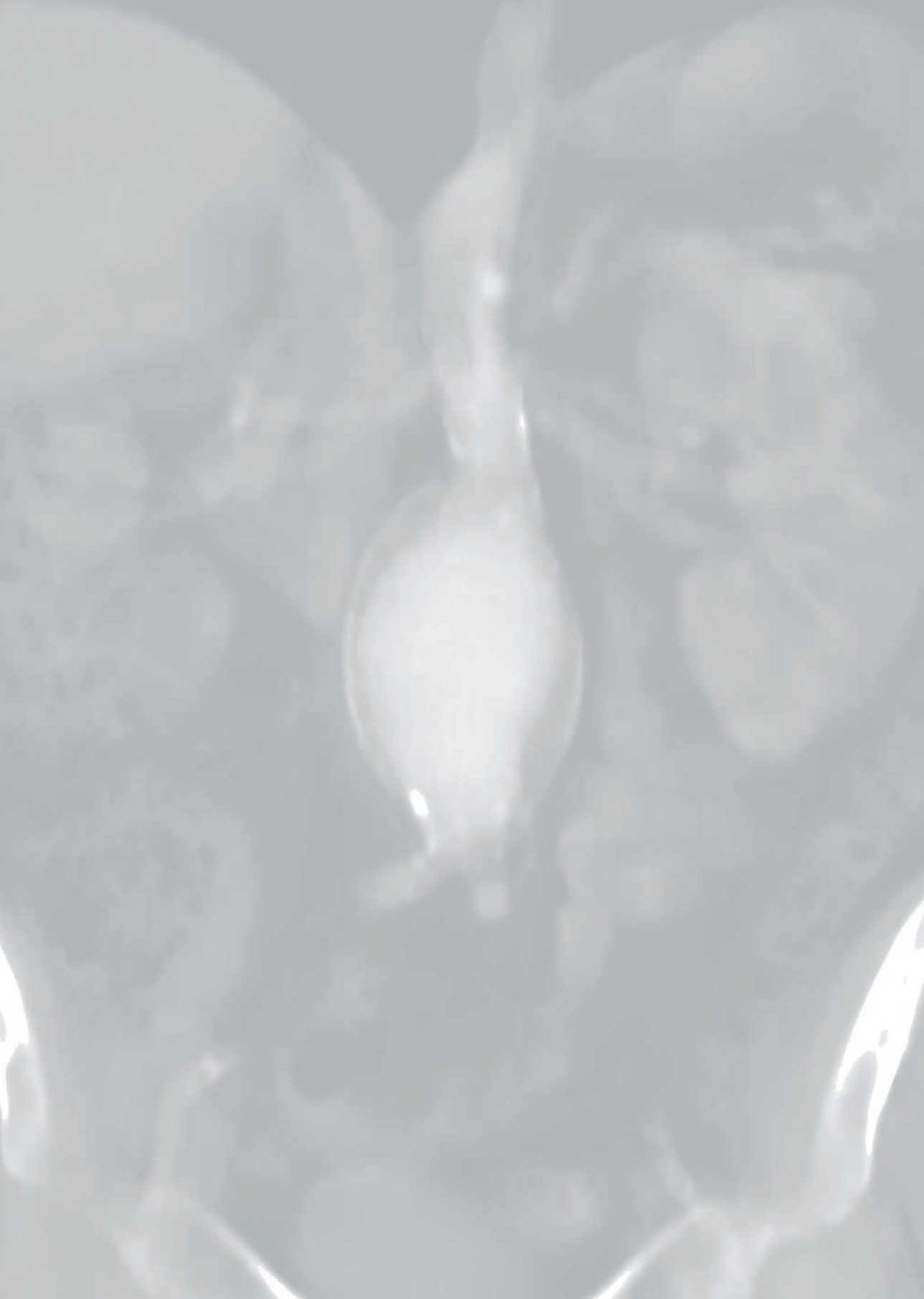


Chapter 11

Summary and future perspectives

This thesis comprises three parts, each concerning advances in care for patients with an abdominal aortic aneurysm (AAA). In the first part 'personalized care' is discussed, in the second part 'centralized care' is discussed and in the third part 'endovascular care' is discussed. Elective aortic surgery is considered in **Chapters 2 and 3** and acute ruptured aneurysm care is considered in **Chapters 4 to 10**. Future perspectives are discussed in each chapter.

Towards personalized care

In **Chapter 2** the external validation of an Australian prediction model known as the 'Endovascular aneurysm repair Risk Assessment (ERA) model' in 433 Dutch patients is described. The ERA model predicts survival (30-day death, 3-year survival, and 5-year survival), reinterventions, and endoleaks after elective endovascular aneurysm repair (EVAR). The area under the receiver operating characteristic curve (AUC) was used as the measure of accuracy (>0.70 was considered as sufficiently accurate). The areas under the curve varied between 0.64 and 0.66 for predictions of survival outcomes and between 0.47 and 0.61 for reinterventions and endoleaks. Hence the predictions by the ERA model are not sufficiently accurate to be used in clinical practice. A multicenter prospective study is underway in Australia that aims to improve the predictive accuracy of the ERA model. Moreover, the data sets of all validation studies to the ERA model done so far could be combined to improve the predictive accuracy by a 'meta-regression'. To increase the reproducibility of the measurements of aortic anatomy, an automatically generated central lumen line might be relevant. Several additional analyses were conducted in the study presented in Chapter 2. First, 'cardiac comorbidity' (adjusted hazard ratio 1.47, 95% confidence interval (CI) 1.01 to 2.15) and 'previous history of malignancy' (adjusted hazard ratio 2.02, 95% CI 1.39 to 2.93) were identified as independent predictors of survival additional to the ERA model. This indicates that these variables might improve the predictions of survival. Second, the 5-year reintervention rate was 29% (95% CI 21 to 37%) in patients treated with an early-generation endograft, and 16% (95% CI 10 to 21%) in patients treated with a late-generation endograft (P<.01). After adjustment for possible confounders such as aortic anatomy, the risk of dying or reintervention was lower in patients treated with a late-generation endograft (adjusted hazard ratio 0.58, 95% CI 0.39 to 0.86). These results suggest that the newer generation of endografts give better outcomes than the older designs.

In **Chapter 3** the external validation of three prediction models is described: the Medicare, the Vascular Governance North West (VGNW), and the British Aneurysm Repair (BAR). These models were validated in 345 patients eligible for both EVAR and open repair (OR) in the Netherlands and Belgium. These models are designed to predict the short-term death rate (combined 30-day or in-hospital) after elective EVAR and OR. Again, the AUC was used as a measure of accuracy (>0.70 was considered sufficiently accurate). The AUC was 0.77 for the Medicare model, 0.88 for the VGNW model, and 0.79 for the BAR model. Thus, these prediction models can be used to support the decision between EVAR and OR in individual patients. To further support decision making, other prediction models are needed to predict reinterventions and endoleaks. An important characteristic of such models would be the accuracy in patients in whom risk assessment is most needed and thereby support decision making. For future research about prediction models in elective aortic surgery, it is important that there is collaboration between hospitals in order to create a large cohort of consecutive patients.

In **Chapter 4** the value of prediction models in patients with a ruptured abdominal aortic aneurysm (RAAA) is discussed. In current clinical practice, the decision to start surgical or conservative treatment is based on a fast evaluation of the patients' clinical condition, the surgeon's experience and the wishes of the patient. It is a subjective interpretation of a harsh reality by the doctor, the patient and their relatives. A prediction model could support this decision. There are four models aiming to predict short-term death after intervention for an RAAA; the updated Glasgow Aneurysm Score (GAS), the Vancouver score, the Edinburgh Ruptured Aneurysm Score (ERAS) and the Hardman index. The AUC was used as a measure of accuracy (>0.70 was considered sufficiently accurate). In prediction models with sufficiently accurate discrimination, correspondence between the predicted and observed outcomes (i.e. calibration) was recalculated. The AUC of the updated GAS was 0.71, of the Vancouver score was 0.72, and of the ERAS was 0.58. After recalibration, predictions made by the updated GAS slightly overestimated the death rate, e.g. predicted death rate 60% versus observed death rate 54% (95% CI 44 to 64%). After recalibration, the predictions of the Vancouver score considerably overestimated the death rate, e.g. predicted death rate 82% versus observed death rate 62% (95% CI 52 to 71%). The performance of the Hardman index on discrimination could not be assessed because 55% of

electrocardiograms were missing. Where the Hardman index could be applied and where a death rate of 100% was predicted, the observed death rate was only 50% (95% CI 27 to 73%). Thus concerning discrimination and calibration, only the updated GAS predicted death after intervention for an RAAA sufficiently accurately. The updated GAS model as reported in **Chapter 4** can be used to predict the risk of dying after intervention. A subgroup analysis in high-risk patients showed that even the updated GAS was not accurate enough to identify patients who would die despite intervention. Therefore, to support the decision to withhold intervention future studies should aim to improve the identification of true high-risk patients.

A serious complication of RAAA is acute kidney injury (AKI).The present Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS) reporting standards classify patients as no dialysis, as temporary dialysis and as permanent dialysis or fatal outcome ('grade I', 'grade II' and 'grade III') and the incidence ranges between 20 and 34%. However, AKI is a broad clinical syndrome including more than the requirement for renal replacement therapy. In 2004 an international working group of nephrologists and intensive care specialists introduced the RIFLE classification for AKI to standardize outcomes. The RIFLE classification comprises three severity categories ('Risk', 'Injury' and 'Failure') based on serum creatinine and urine output. In this way, the RIFLE-criteria can be used to identify high-risk patients. In **Chapter 5** the assessment of the incidence of AKI as defined by the RIFLE criteria (AKI_{RIFLE}) is described. Secondary objectives were to assess the incidence of AKI as defined by the SVS/ISCVS reporting standards ($AKI_{SVS/ISCVS}$) and the association between AKI_{RIFLE} and short-term death. In 362 RAAA patients treated by surgery, AKI_{RIFLE} occurred in 74% (267/362, 95% CI 69 to 78%), with 27% of these patients categorized as 'Risk' (71/267, 95% CI 22 to 32%), 39% categorized as 'Injury' (104/267, 95% CI 33 to 45%) and 34% categorized as 'Failure' (92/267, 95% CI 29 to 40%). $AKI_{SVS/ISCVS}$ occurred in 48% (175/362, 95% CI 43 to 53%), with 53% of these categorized as 'grade I' (92/175, 95% CI 45 to 60%), 19% as 'grade II' (34/175, 95% CI 14 to 26%) and 28% as 'grade III' (49/175, 95% CI 22 to 35%). After multivariable adjustment for shock profiles the risk of dying in patients categorized as AKI_{RIFLE} 'Failure' was higher than in patients without AKI_{RIFLE} (adjusted odds ratio 6.36, 95% CI 2.23 to 18.13). These results indicate that the problem of AKI is much bigger than previously anticipated and that minimizing injury to the kidney could be an important focus of future research on reducing the death rate after RAAA repair. Novel biomarkers

might help to detect AKI earlier and thereby improve AKI diagnostics. Possible future therapies to prevent AKI are goal-directed fluid resuscitation, intravenous mannitol, renal cooling if suprarenal aortic-cross clamping is needed, and the use of carbon dioxide as a contrast agent during EVAR.

Towards centralized care

In the Amsterdam ambulance region, care is concentrated into three vascular centers with a 24-h full emergency vascular service in cooperation with seven referring regional hospitals. All patients suspected of having an RAAA are to be transported to a vascular center, with the exception of those admitted to a referring hospital and deemed unfit for transfer. In the vascular centers, logistics are optimized with a protocol of permissive hypotension during transport, the 24-hr availability of specialized staff, a preoperative CT-angiography, cardiovascular anesthetic care and a level III intensive care unit. In **Chapter 6** the effect of centralization of care on regional outcomes after aneurysm rupture between 2004 and 2011 is discussed. Of 453 patients with an RAAA in the Amsterdam ambulance region, 61 did not undergo intervention (regional rejection rate 13%). The regional 30-day survival rate of 59% (265/453, 95% CI 54 to 63%) was higher than that reported in a previous Dutch population-based study of 46% (95% CI 43 to 49%). It was possible to treat the majority of patients (90%, 352/392) at the vascular centers. After multivariable adjustment for age, sex, comorbidity, type of intervention (EVAR or OR), preoperative systolic blood pressure and cardiopulmonary resuscitation, and year of intervention, patients treated at a vascular center had a higher survival rate than patients treated surgically in a referring hospital (adjusted odds ratio 3.18, 95% CI 1.43 to 7.04). Despite delaying intervention, patient referral was not associated with impaired survival (adjusted odds ratio patient 1.07, 95% CI 0.57 to 2.01). This study concludes that regional cooperation improves the overall survival of patients with an RAAA. Furthermore, most patients received treatment at a vascular center and in these patients survival rates were optimal. It is difficult to provide evidence from randomized controlled trials (RCTs) to support regional cooperation. In Amsterdam, the policy of regional cooperation is still being applied because of our favorable results. Other regions in the Netherlands could easily apply the logistics of centralization to vascular centers. It might be interesting to study to what size regions could be extended and if further centralization in a very limited number of hospitals might be even more advantageous. This applies particularly

to patients in whom complex endovascular techniques requiring a sophisticated infrastructure and a specialised team are necessary.

The safety of delaying surgical intervention in patients with an RAAA is controversial. The intervention could be delayed for a CTA to assess suitability for EVAR and for patient referral from a regional hospital to a specialized vascular center. In **Chapter 7** the duration of in-hospital survival in 40 patients with an RAAA who did not undergo surgical intervention is described. The reasons to refrain from intervention were patient or patient's family decision (15), cardiac arrest or shock (7), unknown (7), severe comorbidity (6), age (3) or aortic anatomic considerations (2). Patients not treated because of the decision of the patient, comorbidity, age and aortic anatomic considerations (26) were put into a subgroup. The median survival was 13 hours (inter-quartile range (IQR) 2 to 45 hours). The majority of patients were still alive after one hour (95%, 95% CI 88 to 100%) and two hours (80%, 95% CI 67 to 92%). The survival rate was even longer in the subgroup (96% after two hours, 95% CI 89 to 100%). We considered the patients in this subgroup to be the most comparable to patients who do receive surgical intervention. Therefore, our results indicate that a reasonable increase of transfer time in order to reach a vascular center is justified on most occasions. However, the extrapolation of these outcomes to patients who are prepared for surgical intervention is hampered by several potential biases and should be interpreted within the context of these limitations.

Towards endovascular care

Chapter 8 is a systematic review and meta-analysis with the purpose of estimating the short-term death rate after EVAR and OR in patients with an RAAA. All RCTs, observational cohort studies and administrative registries comparing EVAR and OR published in Medline, Embase or the World Health Organization International Clinical Trials Registry were included. The methodological quality of all studies was assessed. From a total of 3769 articles, 3 RCTs, 21 observational studies and 8 administrative registries were included. In the RCTs, the risk of bias was lowest and the pooled odds ratio for death after EVAR versus OR was 0.90 (95% CI 0.65 to 1.24). The majority of the observational studies had a high risk of bias and the pooled odds ratio for death was 0.44 (95% CI 0.37 to 0.53). The majority of the administrative registries had a high risk of bias and the pooled odds ratio for death was 0.54 (95% CI 0.47 to 0.62). These results suggest that EVAR is not inferior to OR in patients with an RAAA and support the use of EVAR

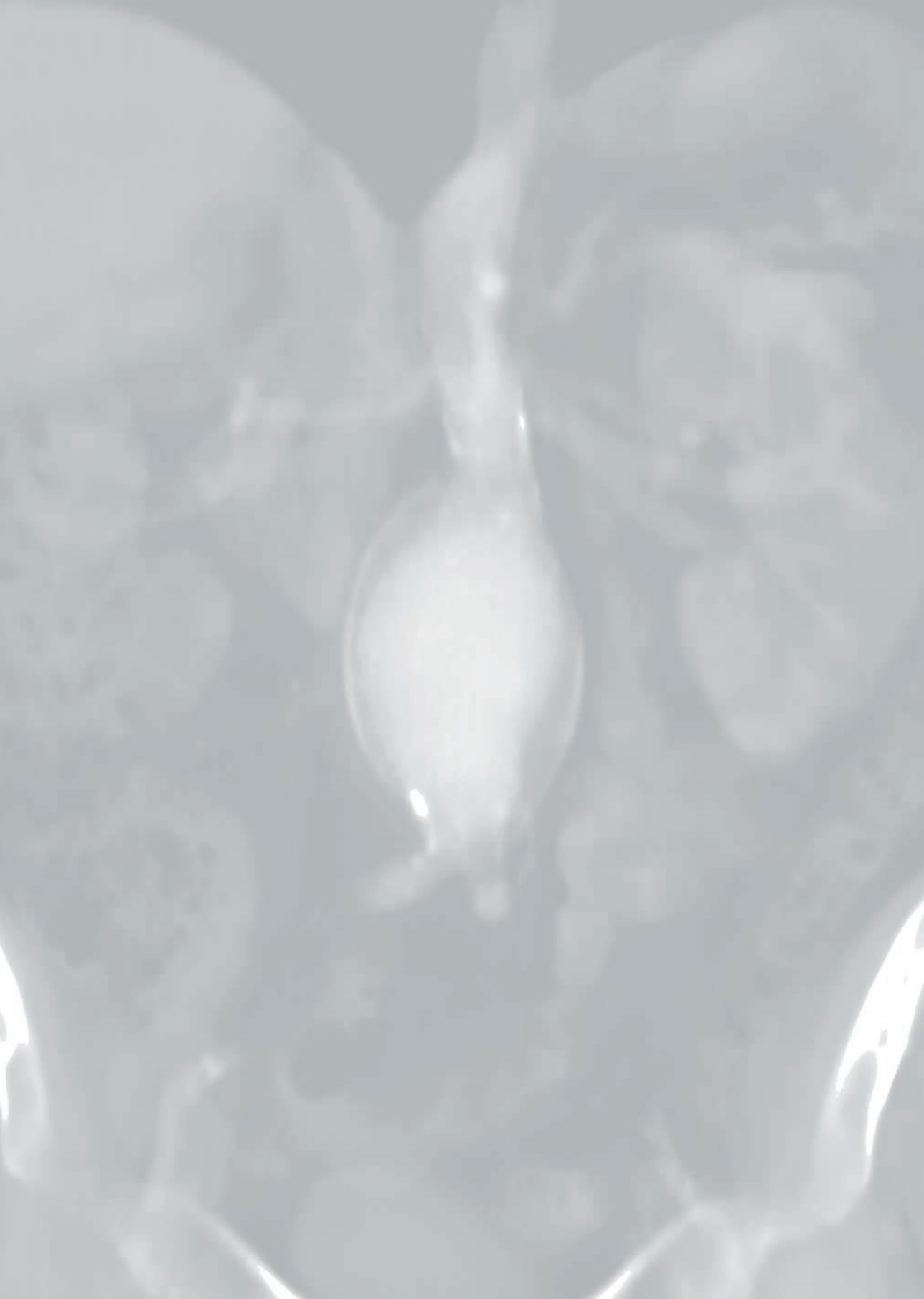
in suitable patients and OR as reasonable alternative. Possible future directions of treatment which were described in the studies included were centralization of care in high-volume hospitals, 'EVAR-first'/hybrid repair, or an 'EVAR-only' approach.

In **Chapter 9** the midterm outcomes after EVAR and OR for an RAAA are discussed. All consecutive surgically treated RAAA patients between 2004 and 2011 in the ten hospitals of the Amsterdam ambulance region were included. The end points were reintervention and death within five years after the primary intervention. Outcomes were estimated in all patients and in patients who survived their hospital stay. Of 467 patients with an RAAA, 73 were treated with EVAR and 394 with OR. Five years after primary intervention, the rates of freedom from reintervention were 49% for EVAR (30/73, 95% CI 36 to 63%) and 60% for OR (128/394, 95% CI 55 to 66%, P=.31). The survival rates were 36% for EVAR (45/73, 95% CI 24 to 47%) and 38% for OR (235/394, 95% CI 33 to 43%, P=.83). In 297 patients who survived their hospital stay, the rates of freedom from reintervention were 66% for EVAR (15/54, 95% CI 52 to 81%) and 90% for OR (20/243, 95% CI 86 to 95%, P<.01). In these patients, the survival rates were 48% (26/54, 95% CI 34 to 62%) for EVAR and 62% for OR (84/243, 95% CI 56 to 69%, P=.04). To conclude, five years after the primary intervention, EVAR and OR for an RAAA resulted in similar reintervention and survival rates. However, in patients who survived their hospital stay the reintervention rate was higher for EVAR than for OR. The RCTs comparing EVAR and OR showed that there was less need for mechanical ventilation and temporary dialysis and a shorter intensive care and hospital stay after EVAR. When deciding between EVAR and OR in the acute setting, caregivers thus have to balance a short-term benefit of secondary outcomes after EVAR with a lower midterm risk of reintervention after discharge for OR. More studies are needed to assess the reintervention rate after EVAR, because the number of patients treated with EVAR in our study was rather low (n = 73) and these patients were treated by using only two types of endografts. Other and newer endografts may have better midterm outcomes.

In **Chapter 10** a study on the influence of aortoiliac anatomy on outcomes after RAAA repair is described. Generally, anatomic suitability for EVAR in these patients depends on aortic neck and iliac artery characteristics. If the aortoiliac anatomy is unsuitable for EVAR ('hostile anatomy'), OR is the next option. Previous studies have reported worse outcomes after OR in patients with hostile anatomy than in patients with friendly anatomy. For this reason,

aortoiliac anatomy might be an important confounder in studies comparing EVAR and OR. We hypothesized that the short-term death rate for OR was higher in patients with hostile anatomy than in patients with friendly anatomy. Aortoiliac anatomy (friendly or hostile) was determined prospectively by the vascular surgeon and the interventional radiologist treating the patient. Of 279 patients who underwent OR for RAAA, aortoiliac anatomy was friendly in 71 patients and hostile in 208 patients. The death rate was 38% (95% CI 28 to 50%) in patients with friendly anatomy and 30% (95% CI 24 to 37%) in patients with hostile anatomy (P=.23). After multivariable adjustment for age, sex, comorbidity, and hemodynamic stability, the risk of dying was found not to be higher in patients with hostile anatomy (adjusted odds ratio hostile versus friendly anatomy 0.74, 95% CI 0.39 to 1.40). Retrospective measurement of aortoiliac anatomy showed in patients with hostile aortoiliac anatomy a short (10 mm, IQR 5 to 17 mm) and wide (25 mm, IQR 23 to 32 mm) infrarenal neck, and a wide left (18 mm, IQR 14 to 25 mm) and right (21 mm, IQR 15 to 31 mm) iliac artery. These results indicate that the death rate after OR for RAAA is comparable in patients with hostile and friendly aortoiliac anatomy. For this reason, aortoiliac anatomy is probably not an important confounder in studies comparing OR and EVAR. From the patient's perspective, the influence of aortoiliac anatomy is less relevant as it cannot be treated or altered. Therefore, future studies should not focus on this subject but on the optimization of treatment for patients with an RAAA.

In conclusion this thesis goes some way towards ending the debate on EVAR *versus* OR for patients with an RAAA. Neither intervention appears to be superior to the other and both have advantages and disadvantages. For the future, the most important question is which patient is best treated with endovascular repair and which patient is best treated with open repair - personalized care.



Hoofdstuk 12

Samenvatting en toekomstperspectieven

Dit proefschrift bestaat uit drie onderdelen over vooruitgang van zorg voor patiënten met een aneurysma van de abdominale aorta (AAA). In het eerste onderdeel wordt 'gepersonaliseerde zorg' besproken, in het tweede onderdeel 'gecentraliseerde zorg' en in het derde onderdeel 'endovasculaire zorg'. Hierbij gaan de **hoofdstukken 2 en 3** over electieve en de **hoofstukken 4 tot 10** over acute aneurysmazorg. De toekomstperspectieven worden per hoofdstuk beschreven.

Naar gepersonaliseerde zorg

Ondanks de beschikbare informatie uit de gerandomiseerde trials kan de keuze voor endovasculaire (EVAR) of open reconstructie (OR) in de individuele patiënt lastig zijn. Met predictiemodellen, waarmee voor iedere individuele patiënt het risico op bepaalde uitkomsten na de operatie kan worden berekend, kan de besluitvorming tussen EVAR, OR of conservatieve therapie worden ondersteund. In **hoofdstuk 2** wordt de externe validatie van een Australisch predictiemodel (het 'Endovascular aneurysm repair Risk Assessment' (ERA) model) in 433 Nederlandse patiënten beschreven. Het ERA model voorspelt de 30-dagen sterfte, de 3-jaars overleving, de 5-jaars overleving, het vóórkomen van re-interventies en het optreden van endoleaks na electieve EVAR. De 'area under the curve' (AUC) werd gebruikt als maat van accuratesse van de predictiemodellen, waarbij een AUC >0,70 werd beschouwd als voldoende accuraat. De AUC varieerde tussen 0,64 en 0,66 voor de voorspellingen op overleving en tussen 0,47 en 0,61 voor de voorspellingen op re-interventies en endoleaks. De voorspellingen van het ERA model waren dus onvoldoende accuraat om de besluitvorming in de praktijk te ondersteunen. In Australië wordt op dit moment een prospectieve multicenter studie uitgevoerd om de accuratesse van het ERA model te verbeteren. Daarnaast zou de data van alle tot op heden uitgevoerde validatie studies kunnen worden gecombineerd om de accuratesse te verbeteren met een 'meta-regressie'. Om de reproduceerbaarheid van de metingen aan de aorta te verbeteren kan een automatisch gecreëerde 'central lumen line' relevant zijn. In de studie beschreven in dit hoofdstuk werden twee extra analyses gedaan. Ten eerste werden 'cardiale comorbiditeit' (gecorrigeerde hazard ratio 1,47, 95% betrouwbaarheidsinterval (BI) 1,01-2,15) en 'voorgeschiedenis van maligniteit' (gecorrigeerde hazard ratio 2,02, 95% BI 1,39-2,93) naast de variabelen van het ERA model geïdentificeerd als onafhankelijke voorspellers van overleving. Dit suggereert dat deze variabelen de voorspellingen van het ERA model kunnen verbeteren. Ten tweede was het percentage 5-jaars re-interventies 29% (95% BI 21-37%) in patiënten met een ouder

type endoprothese en 16% (95% BI 10-21%) in patiënten met een nieuwer type endoprothese (P<,01). Na correctie voor mogelijke confounders, zoals anatomie van de aorta, was het gecombineerde risico op overlijden of re-interventie lager in patiënten met een nieuwer type endoprothese dan in patiënten met een ouder type endoprothese (gecorrigeerde hazard ratio 0,58, 95% BI 0,39-0,86). Deze resultaten suggereren dat uitkomsten beter zijn bij patiënten die behandeld zijn met een nieuw type endoprothese dan bij patiënten die behandeld zijn met een ouder type endoprothese.

In **hoofdstuk 3** wordt de externe validatie beschreven van drie predictiemodellen in 345 Nederlandse en Belgische patiënten die geschikt waren voor zowel EVAR als voor OR; het Medicare, het Vascular Governance North West (VGNW) en het British Aneurysm Repair (BAR) predictiemodel. Deze predictiemodellen voorspellen sterfte op korte termijn (gecombineerde 30-dagen of ziekenhuissterfte) na electieve EVAR en OR. De AUC werd wederom gebruikt als maat van accuratesse. De AUC was 0,77 voor het Medicare model, 0,88 voor het VGNW model en 0,79 voor het BAR model. Deze resultaten tonen dat de drie predictiemodellen kunnen worden gebruikt voor de ondersteuning van de besluitvorming tussen EVAR of OR. Echter, om de besluitvorming verder te ondersteunen zijn er ook predictiemodellen nodig die het vóórkomen van re-interventies en endoleaks voorspellen. Een belangrijke eigenschap van deze modellen moet zijn dat de accuratesse het beste is in patiënten bij wie een voorspelling het meest nodig is; patiënten met een klinisch dilemma. In deze patiënten heeft ondersteuning van besluitvorming de meeste toegevoegde waarde. Voor toekomstig onderzoek over predictiemodellen in de electieve aneurysmachirurgie is samenwerking tussen ziekenhuizen belangrijk om grote cohorten van opeenvolgende patiënten te creëren.

In **hoofdstuk 4** wordt de waarde van predictiemodellen voor patiënten met een geruptureerd aneurysma van de abdominale aorta (RAAA) bediscussieerd. In de huidige klinische praktijk is de beslissing om te opereren of om af te zien van operatie gebaseerd op een snelle evaluatie van de conditie van de patiënt, op voorgaande ervaringen van de chirurg en op de wensen van de patiënt. Het is een subjectieve inschatting van de harde realiteit door de dokter, de patiënt en de familie. Een predictiemodel kan een objectieve inschatting van kansen op overleving na operatie geven en zou daarmee de besluitvorming kunnen ondersteunen. Er bestaan vier modellen die als doel hebben de sterfte op korte termijn na operatie voor een RAAA te voorspellen; de updated Glasgow Aneurysm

Score (GAS), de Vancouver score, de Edinburgh Ruptured Aneurysm Score (ERAS) en de Hardman index. De AUC werd wederom gebruikt als maat van accuratesse. Daarnaast werd in predictiemodellen met voldoende accurate voorspellingen de overeenkomst tussen voorspelde en geobserveerde uitkomsten (calibratie) her berekend. De AUC van de updated GAS was 0,71, van de Vancouver score was 0,72, en van de ERAS was 0,58. De AUC van de Hardman index kon niet worden bepaald. In de subgroep patiënten bij wie de Hardman index wel kon worden bepaald en waarbij de voorspelde sterfte 100% was, was de geobserveerde sterfte slechts 50% (95% BI 27-73%). De voorspellingen van de updated GAS overschatten na recalibratie de sterfte in een lichte mate; bijvoorbeeld bij een voorspelde sterfte van 60% was de geobserveerde sterfte 54% (95% BI 44-64%). De voorspellingen van de Vancouver score overschatten de geobserveerde sterfte aanzienlijk, bijvoorbeeld bij een voorspelde sterfte van 82% was de geobserveerde sterfte 62% (95% BI 52-71%). Concluderend voorspelde alleen de updated GAS de sterfte voldoende accuraat. Het model zoals getoond in **hoofdstuk 4** kan worden gebruikt voor de voorspelling van de kansen op overleving na een operatie voor een RAAA. Een subgroep analyse in hoog-risico patiënten toonde dat zelfs de voorspellingen van de updated GAS onvoldoende accuraat waren om patiënten te identificeren die overleden ondanks interventie. Om deze reden moeten toekomstige studies zich richten op een betere identificatie van deze echte hoog-risico patiënten, zodat de besluitvorming tot onthouding van interventie kan worden ondersteund.

Acute nierschade is een veel voorkomende en ernstige complicatie na een operatie voor een RAAA. In de huidige rapportage standaard van de Society for Vascular Surgery/International Society for CardioVascular Surgery (SVS/ISCVS) worden patiënten geclassificeerd als 'geen dialyse', als 'tijdelijke dialyse' en als 'permanente dialyse of fatale uitkomst' (respectievelijk 'graad I', 'graad II' en 'graad III'). Met deze classificatie werd in voorgaande studies de incidentie van acute nierschade na een RAAA geschat tussen de 20 en 34%. Echter, acute nierschade is een klinisch syndroom dat meer inhoudt dan de noodzaak tot (tijdelijke) dialyse. In 2004 is door een internationale werkgroep van intensivisten en nefrologen de RIFLE-classificatie geïntroduceerd ter standaardisatie van de definitie. De RIFLE-classificatie bestaat uit drie categorieën van ernst van nierfalen ('risk', 'injury' en 'failure') en is gebaseerd op het serum creatinine en de urineproductie. In **hoofdstuk 5** is de bepaling van de incidentie van acute nierschade volgens de RIFLE-classificatie beschreven. Secundaire doelen waren het bepalen van de

incidentie van acute nierschade volgens de 'SVS/ISCVS reporting standards' en het bepalen van de associatie tussen sterfte en acute nierschade volgens de RIFLE-classificatie. Van de 362 geopereerde patiënten ontwikkelde 74% (267/362, 95% BI 69-78%) acute nierschade volgens de RIFLE-classificatie. Van deze patiënten werd 27% geclassificeerd als 'risk' (71/267, 95% BI 22-32%), 39% als 'injury' (104/267, 95% BI 33-45%) en 34% als 'failure' (92/267, 95% BI 29-40%). Achtenveertig procent van de patiënten ontwikkelde acute nierschade volgens de SVS/ISCVS standaard (95% BI 43-53%), waarvan 53% geclassificeerd als 'graad I' (92/175, 95% BI 45-60%), 19% als 'graad II' (34/175, 95% BI 14-26%) en 28% als 'graad III' (49/175, 95% BI 22-35%). Patiënten die waren geclassificeerd als 'failure' hadden, na correctie voor pre- en postoperatieve shock, een hoger risico op overlijden dan patiënten zonder acute nierschade (gecorrigeerde odds ratio 6,36, 95% BI 2,23-18,13). Deze resultaten tonen dat het probleem van acute nierschade na een RAAA groter is dan verwacht. Mogelijk kan de sterfte na een RAAA worden verlaagd door behandeling en onderzoek te richten op acute nierschade. Nieuwe biomarkers zouden de diagnostiek van acute nierschade kunnen verbeteren door een vroegere diagnose. Mogelijke toekomstige behandelingen ter preventie van acute nierschade zijn 'early-goal directed fluid resuscitation', intraveneuze mannitol, nierkoeling tijdens plaatsing van de klem boven de nierarteriën, en het gebruik van koolstofdioxide als contrastmiddel tijdens EVAR.

Naar gecentraliseerde zorg

In de Amsterdamse ambulance regio is vanaf 2003 de zorg voor patiënten met een RAAA gecentraliseerd in drie ziekenhuizen waarbij wordt samengewerkt met de zeven omliggende regionale ziekenhuizen. Alle patiënten die door de huisarts of door het ambulance personeel worden verdacht van een RAAA worden direct getransporteerd naar één van de drie gespecialiseerde ziekenhuizen. Alleen patiënten die zijn opgenomen in een regionaal ziekenhuis en niet geschikt geacht worden voor transport, worden niet verwezen en ter plaatse behandeld. In de gespecialiseerde ziekenhuizen is de logistiek geoptimaliseerd door een vaatchirurgische 24-uurs dienst met continue beschikbaarheid van gespecialiseerd personeel, een protocol van 'permissive hypotension' tijdens transport en bij opvang op de spoedeisende hulp, een preoperatieve CT-angiografie en beschikbaarheid van een cardiovasculaire anesthesist en een level III intensive care unit. In **hoofdstuk 6** is het effect van deze centralisatie van zorg op de regionale overleving in de periode tussen 2004 en 2011 bediscussieerd.

Van de 453 patiënten met een RAAA in de Amsterdamse ambulance regio zijn uiteindelijk 61 patiënten niet geopereerd (regionaal afwijzingspercentage 13%). De regionale 30-dagen overleving van 59% (95% BI 54-63%) was hoger dan in een eerdere Nederlandse nationale studie van 46% (95% BI 43-49%). Het was mogelijk om de meerderheid van de patiënten in de gespecialiseerde ziekenhuizen te behandelen (90%, 352/392). Na multivariabele correctie voor leeftijd, geslacht, comorbiditeit, operatie (EVAR of OR), preoperatieve systolische bloeddruk en reanimatie, en jaar van operatie en de overleving was in deze patiënten de overleving nog beter (gecorrigeerde odds ratio 3,18, 95% BI 1,43-7,04). Daarnaast was de verwijzing van patiënten van een regionaal ziekenhuis naar een gespecialiseerd ziekenhuis, ondanks uitstel van operatie door transport, niet geassocieerd met een slechtere overleving (gecorrigeerde odds ratio 1,07, 95% BI 0,57-2,01). Al deze resultaten suggereren dat regionale samenwerking resulteert in een verbeterde overleving van patiënten met een RAAA. Het is moeilijk om bewijs uit gerandomiseerde gecontroleerde trials (RCTs) voor regionale samenwerking te verkrijgen. In Amsterdam is het beleid van regionale samenwerking nog steeds van kracht vanwege onze gunstige resultaten. Andere Nederlandse ambulance regio's kunnen de logistiek van centralisatie in gespecialiseerde ziekenhuizen gemakkelijk overnemen. Het zou interessant zijn om te onderzoeken tot hoe ver deze regio's kunnen worden uitgebreid en of verdere centralisatie in een beperkter aantal ziekenhuizen tot nog gunstigere resultaten leidt. Dit geldt met name voor patiënten waarbij complexe endovasculaire technieken nodig zijn die om een gestroomlijnde infrastructuur en een gespecialiseerd team vragen.

Uitstel van acute aneurysmachirurgie bij patiënten met een RAAA is controversieel. Een preoperatieve CT-angiografie om de geschiktheid voor EVAR te bepalen, transport en verwijzing van een regionaal ziekenhuis naar een gespecialiseerd ziekenhuis leveren vertraging op. In **hoofdstuk 7** is de duur van overleving in het ziekenhuis beschreven in 40 patiënten met een RAAA zonder operatie. De redenen om af te zien van operatie waren de wens van de patiënt en/of de familie (15), hartstilstand of diepe shock (7), onbekend (7), ernstige comorbiditeit (6), leeftijd (3) of anatomische karakteristieken van de aorta (2). De patiënten waarbij is afgezien van operatie vanwege de wens van de patiënt, comorbiditeit, leeftijd en anatomie (26) werden in een subgroep bestudeerd. De mediane overleving was 13 uur (inter-kwartiel range (IKR) 2-45 uur). De meerderheid van de patiënten was nog in leven na respectievelijk één (95%, 95% BI 88-100%) en twee uur (80%, 95% BI 67-92%). De overleving was nog langer in

de subgroep (96% na twee uur, 95% BI 89-100%). Wij beschouwen de patiënten in deze subgroep het meest vergelijkbaar met patiënten die wel worden geopereerd. Om deze reden rechtvaardigen de resultaten een kort uitstel van operatie voor verwijzing naar een gespecialiseerd ziekenhuis in de meeste patiënten met een RAAA. Echter, de extrapolatie van resultaten naar patiënten die wél voor operatie gaan wordt beperkt door bias en dus moeten onze resultaten worden geïnterpreteerd in de context van deze beperking.

Naar endovasculaire zorg

In **hoofdstuk 8** wordt een systematische review en meta-analyse ter inschatting van de sterfte op korte termijn na EVAR en OR voor een RAAA beschreven. Na een systematische search door Medline, Embase en the World Health Organisation International Clinical Trials Registry werden alle RCTs, observationele studies en administratieve registraties met een vergelijking tussen EVAR en OR geïncludeerd. De methodologische kwaliteit van de geïncludeerde studies werd beoordeeld door twee onderzoekers onafhankelijk van elkaar. Van een totaal van 3769 artikelen werden 3 RCTs, 21 observationele studies en 8 administratieve registraties geïncludeerd. Het risico op bias was het laagste in de RCTs en de gepoolde odds ratio op sterfte na EVAR versus (versus) OR was 0,90 (95% BI 0,65-1,24). De meerderheid van de observationele studies had een hoog risico op bias en de gepoolde odds ratio EVAR versus OR was 0,44 (95% BI 0,37-0,53). Ook de meerderheid van de administratieve registraties had een hoog risico op bias en de gepoolde odds ratio EVAR versus OR was 0,54 (95% BI 0,47-0,62). Deze resultaten tonen dat EVAR niet inferieur is aan OR in patiënten met een RAAA en ondersteunen het gebruik van EVAR in geschikte patiënten en ondersteunen OR als redelijk alternatief. Mogelijke toekomstige behandelingen die werden beschreven in de geïncludeerde studies waren centralisatie van zorg in gespecialiseerde ziekenhuizen, 'EVAR-eerst'/hybride operatie of een 'EVAR-voor allen' beleid.

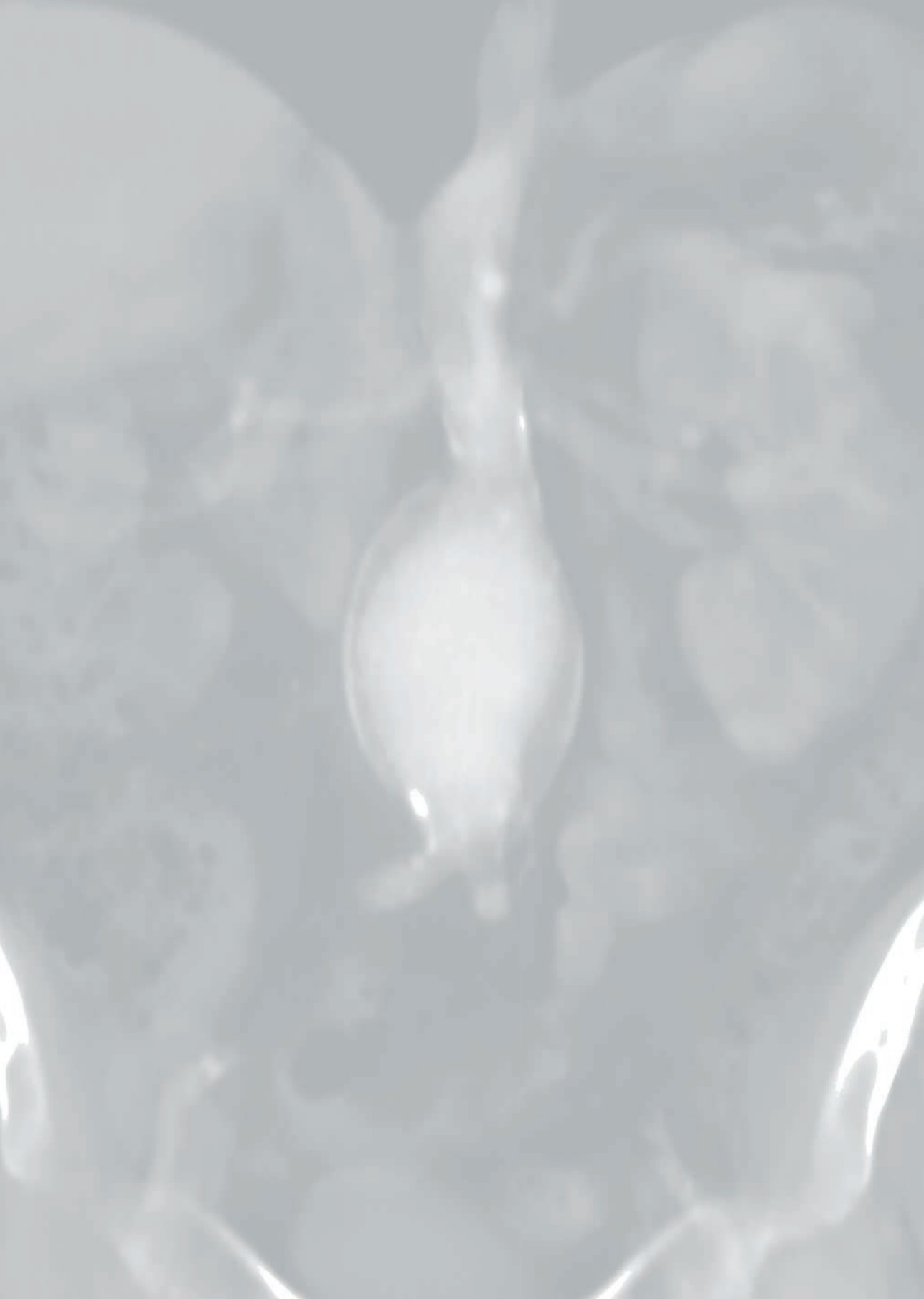
Op de middellange termijn is het risico op re-interventies in de electieve aneurysmachirurgie hoger na EVAR dan na OR. In **hoofdstuk 9** zijn de uitkomsten op de middellange termijn na EVAR en OR voor een RAAA beschreven. Alle opeenvolgende chirurgisch behandelde patiënten met een RAAA tussen 2004 en 2011 in de tien ziekenhuizen van de Amsterdamse ambulance regio werden geïncludeerd. De onderzochte uitkomsten waren re-interventies en overlijden binnen vijf jaar na de primaire interventie. De uitkomsten werden onderzocht

in alle patiënten en in patiënten die hun primaire opname hadden overleefd. Vijf jaar na de primaire interventie was de re-interventie vrije overleving na EVAR 49% (30/73, 95% BI 36-63%) en na OR 60% (128/394, 95% BI 55-66%, P=,31). Vijf jaar na de primaire interventie was de overleving na EVAR 36% (45/73, 95% BI 24-47%) en na OR 38% (235/394, 95% BI 33-43%, P=,83). In 297 patiënten die hun primaire opname hadden overleefd was de re-interventie vrije overleving na EVAR 66% (15/54, 95% BI 52-81%) en na OR 90% (20/243, 95% BI 54-67%, P<,01). In deze patiënten was de 5-jaars overleving na EVAR 48% (26/54, 95% BI 34-62%) en na OR 62% (84/243, 56-69%, P=,04). Concluderend, vijf jaar na de primaire interventie zijn de re-interventie vrije overleving vergelijkbaar na EVAR en na OR voor een RAAA. Echter, als specifiek gekeken wordt naar de patiënten die de primaire opname overleven, zijn er meer re-interventies na EVAR dan na OR. Uit de RCTs die EVAR en OR met elkaar vergeleken bleek dat er na EVAR sprake is van minder mechanische beademing, minder tijdelijke dialyse en een korter verblijf op de intensive care unit en in het ziekenhuis. Voor de besluitvorming tussen EVAR en OR in de acute setting moeten behandelaars dus op de korte termijn een voordeel op secundaire uitkomsten na EVAR wegen met op de middellange termijn na ontslag een voordeel qua re-interventies na OR. Meer studies zijn nodig om de re-interventie vrije overleving na EVAR te bepalen, omdat het aantal patiënten na EVAR in onze studie relatief laag was (n = 73) en deze patiënten werden behandeld met slechts twee verschillende types endoprotheses. Andere en nieuwere endoprotheses kunnen betere resultaten hebben op de middellange termijn.

In **hoofdstuk 10** wordt een studie naar het belang van aorto-iliacale anatomie bij patiënten met een RAAA beschreven. Bij patiënten met een RAAA is geschiktheid voor EVAR afhankelijk van de anatomie van de infrarenale hals en de iliacale arteriën. Bij patiënten met ongeschikte aorto-iliacale anatomie voor EVAR is OR het alternatief. Voorgaande studies hebben in patiënten met ongeschikte anatomie slechtere uitkomsten gerapporteerd dan in patiënten met geschikte anatomie. Om deze reden zou aorto-iliacale anatomie een belangrijke confounder kunnen zijn in vergelijkende studies tussen EVAR en OR. De hypothese in deze studie was dat na OR de sterfte hoger zou zijn in patiënten met ongeschikte anatomie dan in patiënten met geschikte anatomie. De aorto-iliacale anatomie (geschikt versus ongeschikt) werd prospectief bepaald door de behandelende vaatchirurg en interventieradioloog. Van de 279 patiënten met een OR voor een RAAA was de aorto-iliacale anatomie geschikt in 71 patiënten en

ongeschikt in 208 patiënten. De sterfte was 38% (95% BI 28-50%) in patiënten met geschikte anatomie en 30% (95% BI 24-37%) in patiënten met ongeschikte anatomie (P=,23). Na multivariabele correctie voor leeftijd, geslacht, comorbiditeit en preoperatieve systolische bloeddruk en reanimatie was het risico op overlijden niet hoger in patiënten met ongeschikte anatomie (gecorrigeerde odds ratio geschikte versus ongeschikte anatomie 0,74, 95% BI 0,39-1,40). Retrospectieve meting van de aorto-iliacale anatomie toonde in patiënten met ongeschikte anatomie een kortere (10 mm, IKR 5-17 mm) en bredere (25 mm, IKR 23-32 mm) infrarenale hals, en een bredere linker (18 mm, IKR 14-25 mm) en rechter (21 mm, IKR 15-31 mm) iliacale arterie. Op basis van deze resultaten lijkt na OR voor een RAAA de sterfte vergelijkbaar tussen patiënten met geschikte en patiënten met ongeschikte aorto-iliacale anatomie voor EVAR. Om deze reden is aorto-iliacale anatomie waarschijnlijk geen belangrijke confounder in vergelijkende studies tussen EVAR en OR. Vanuit het perspectief van de patiënt is het belang van aorto-iliacale anatomie minder relevant aangezien het niet kan worden behandeld of veranderd. Om deze reden zouden toekomstige studies zich niet moeten richten op dit onderwerp, maar op de beste behandeling voor patiënten met een RAAA.

Concluderend lijkt dit proefschrift het debat endovasculaire *versus* open reconstructie voor patiënten met een geruptureerd aneurysma van de abdominale aorta grotendeels te beëindigen. Geen van beide interventies is superieur aan de ander en beide interventies hebben voordelen en nadelen. Voor de toekomst is de belangrijkste vraag welke patiënt het beste kan worden behandeld met endovasculaire reconstructie en welke patiënt het beste kan worden behandeld met open reconstructie; gepersonaliseerde zorg.



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Academic Medical Center, Amsterdam (32): R. Balm, J.A. Reekers
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University Hospital, Groningen (27): E.L.G. Verhoeven, T. Prins
St. Franciscus Gasthuis, Rotterdam (27): A.C. van der Ham, J.J.I.M. van der Velden
Rijnstate Hospital, Arnhem (14): S.M.M. van Sterkenburg, G.B. ten Haken
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Atrium Medical Center, Heerlen (8): J.A.W. Teijink, H.F. Odink
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Jeroen Bosch Hospital, Den Bosch (7): R.M.M. van Loenhout, M.J. Rutten
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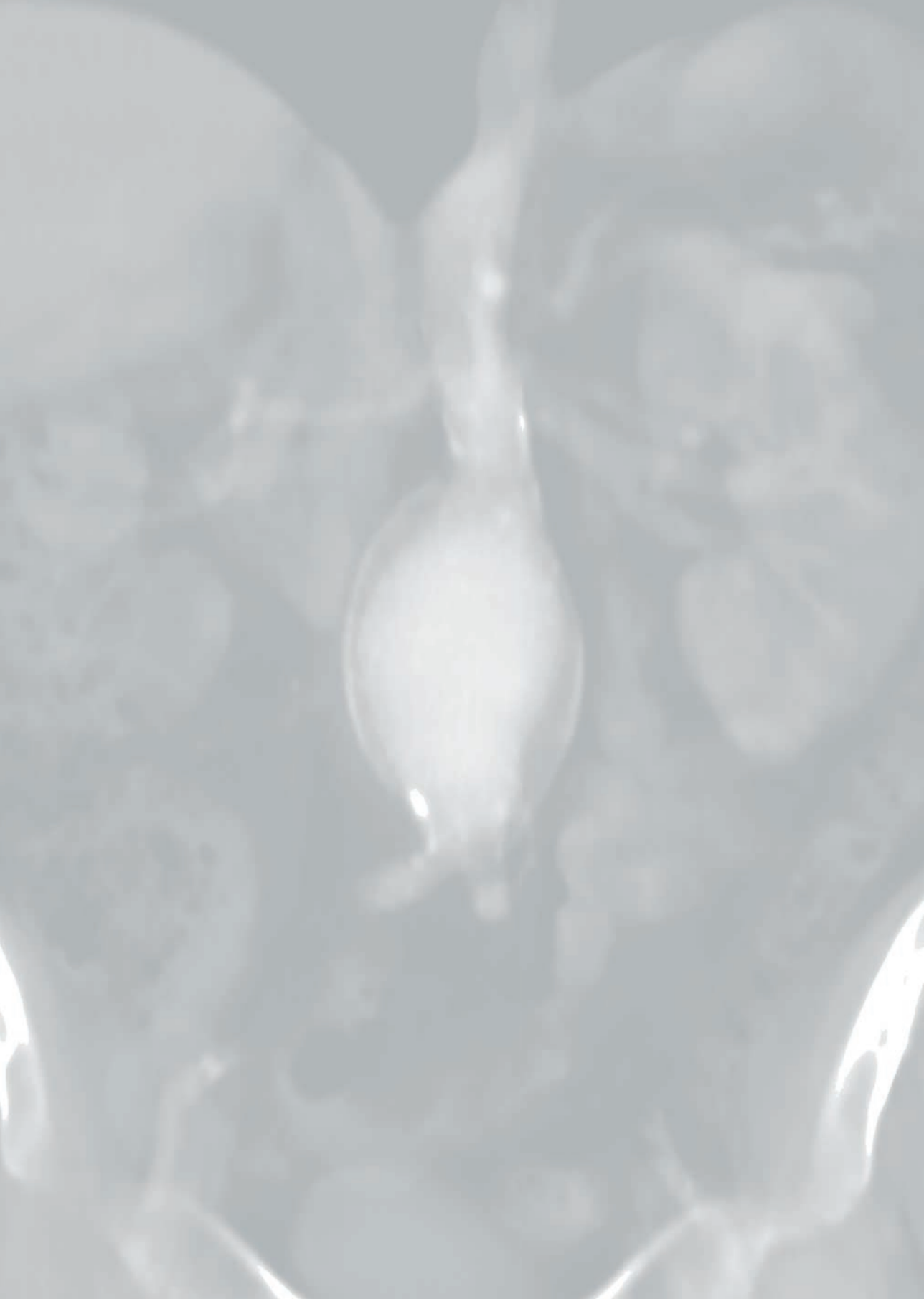
Maxima Medical Center, Veldhoven (5): M.H.M. Bender, H. Pasmans
Onze Lieve Vrouwe Gasthuis, Amsterdam (5): A.C. Vahl, C. de Vries
Meander Medical Center, Amersfoort (4): A.J.C. Mackaay

Vlietland Hospital, Schiedam (4): L.M.C. van Dortmont
University Medical Center, Nijmegen (4): A.J. van der Vliet, L.J. Schultze Kool
Martini Hospital, Groningen (3): J.H.B. Boomsma, H.R. van Dop
Medical Center Haaglanden, 's-Gravenhage (3): J.C.A. de Mol van Otterloo, T.P.W. de Rooij
Hospital Bernhoven, Oss (3): T.M. Smits
Oosterschelde Hospital, Goes (3): E.N. Yilmaz
Vrije Universiteit Medical Center, Amsterdam (2): W. Wisselink, F.G. van den Berg
Leiden University Medical Center, Leiden (1): M.J.T. Visser, E. van der Linden
University Medical Center, Maastricht (1): G.W.H. Schurink, M. de Haan
Bronovo Hospital, 's-Gravenhage (1): H.J. Smeets

Clinical centers Belgium

St. Jozef Hospital, Turnhout (4): P. Stabel
St. Trudo Hospital, St. Truiden (3): F. van Elst
University Hospital, Antwerp (1): J. Poniewierski
University Medical Center, Gent (1): F.E.G. Vermassen



PhD Portfolio

Name PhD student:	Sytse C. van Beek
PhD period:	September 2011 - October 2014
Name supervisor:	D.A. Legemate MD PhD, J.A. Reekers MD PhD
Name co-supervisors:	R. Balm MD PhD, A.C. Vahl MD PhD, W. Wisselink MD PhD

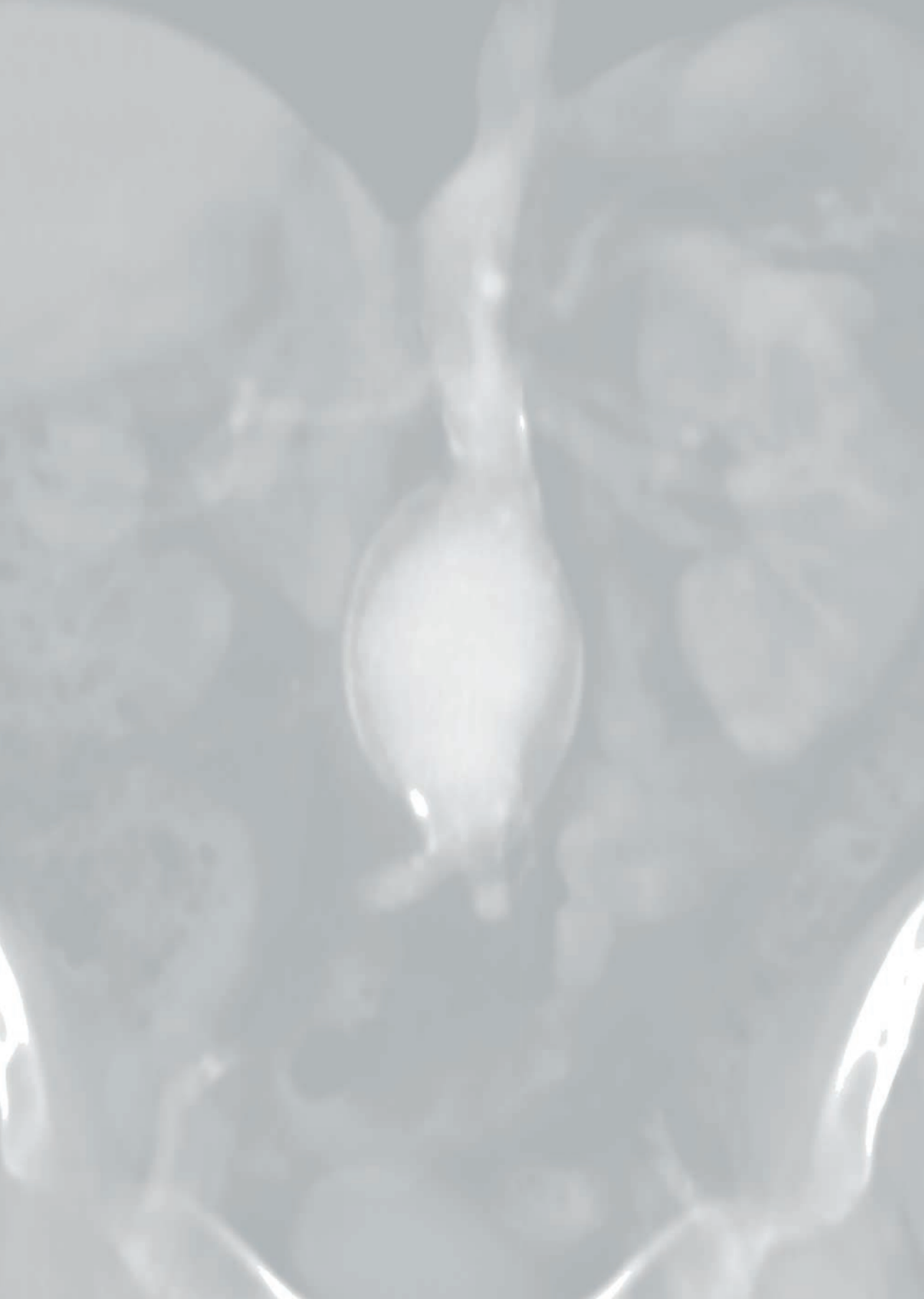
PhD training	Year	Workload (ECTS)
Courses Graduate School AMC Amsterdam		
The AMC World of Science	2011	0.7
Expert management of medical literature	2011-2012	0.4
Oral Presentation	2012	0.8
Project management	2012	0.6
Clinical Data Management	2013	0.3
Clinical Epidemiology	2011	0.6
Advanced Topics in Clinical Epidemiology	2013	1.1
Practical biostatistics	2012	1.1
Advanced Topics in Biostatistics	2013	2.1
Genetic epidemiology	2012	1.1
Systematic reviews	2011	0.3
Basic Course in Legislation and Organization for Clinical Researchers	2012	0.9
Computing in R	2013	0.4
Infectious diseases	2011	1.3
Courses NIHES Erasmus MC Rotterdam		
Clinical Trials	2012	0.7
Introduction to Global Public Health	2012	0.7
Advances in Epidemiologic Analysis	2012	0.4
Logistic Regression	2012	1.4
Advanced Analysis of Prognosis Studies	2013	0.4
Topics in Meta-analysis	2013	0.7
Clinical Decision Analysis	2013	0.7
Causal Inference	2013	0.7

PhD training continued	Year	Workload (ECTS)
Other courses		
Cardiovascular epidemiology, Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht	2014	1.5
Oral presentations		
Voorspellen van overleving en endoprothese gerelateerde complicaties met het ERA-predictiemodel na electieve EVAR - Najaarsvergadering NVvV, Ede	2012	0.5
The external validation of predictions of survival and endograft related complications by the ERA model - Vascular Conference, Melbourne (Australia)	2012	0.5
Regionale zorg voor patiënten met een geruptureerd aneurysma van de abdominale aorta - Vaatdagen, Noordwijkerhout	2013	0.5
Het voorspellen van overlijden na elective interventie voor een aneurysma van de abdominale aorta - Chirurgendagen, Veldhoven	2013	0.5
De voorspelling van sterfte in patiënten met een geruptureerd aneurysma van de abdominale aorta - Chirurgendagen, Veldhoven	2013	0.5
The prediction of death after intervention in patients with a ruptured abdominal aortic aneurysm - CIRSE, Barcelona (Spain)	2013	0.5
Outcomes after open repair for a ruptured abdominal aortoiliac aneurysm in patients with hostile and friendly anatomy - ESVS, Budapest (Hungary)	2013	0.5
Uitkomsten na open reconstructie van een geruptureerd aneurysma van de abdominale aorta in patiënten met aorto-iliacale anatomie geschikt of ongeschikt voor endovasculaire behandeling - Vaatdagen, Noordwijkerhout	2014	0.5
The RIFLE criteria for acute kidney injury in ruptured abdominal aortic aneurysms - Charing Cross Symposium, London (United Kingdom)	2014	0.5
Regional cooperation improves survival in ruptured abdominal aortic aneurysms - Charing Cross Symposium, London (United Kingdom)	2014	0.5
Het geruptureerde aneurysma van de abdominale aorta: de overlevingsduur zonder operatie - Chirurgendagen, Veldhoven	2014	0.5
Acute nierschade bij patiënten met een geruptureerd aneurysma van de abdominale aorta: een onderschat probleem - Chirurgendagen, Veldhoven	2014	0.5
Acute kidney injury in ruptured abdominal aortic aneurysms: an underestimated problem - CIRSE, Glasgow (United Kingdom)	2014	0.5

PhD training continued	Year	Workload (ECTS)
Endovascular aneurysm repair versus open repair for patients with a ruptured abdominal aortic aneurysm: a systematic review and meta-analysis - CIRSE, Glasgow (United Kingdom)	2014	0.5
Mid-term Survival and Reinterventions after Endovascular Versus Open Repair in Ruptured Abdominal Aortic Aneurysms - ESVS, Stockholm (Sweden)	2014	0.5
Poster presentations		
The prediction of in-hospital death after endovascular and open repair in patients with an asymptomatic abdominal aortic aneurysm - CIRSE, Barcelona (Spain)	2013	0.5
The RIFLE criteria as reporting standards for acute kidney injury in ruptured abdominal aortic aneurysms - ESVS, Budapest (Hungary)	2013	0.5
Regional cooperation improves survival in ruptured abdominal aortic aneurysms - CIRSE, Glasgow (United Kingdom)	2014	0.5
(Inter)national conferences		
Vaatdagen, Noordwijkerhout	2012-2014	1.5
Chirurgendagen, Veldhoven	2012-2014	1.5
Vascular Conference, Melbourne	2012	1
ESVS, Budapest and Stockholm	2013	1.5
CIRSE, Barcelona and Glasgow	2013	2

Teaching	Year	Workload (ECTS)
Supervising 2 students	2011-2013	2

Parameters of esteem (grants, awards and prizes)	Year
Invited speaker Vascular Conference, Melbourne	2012
Travel Grant ESVS, Budapest and Stockholm	2013-2014
Best poster presentation ESVS, Budapest	2013
Best abstract session Chirurgendagen, Veldhoven	2014



Acknowledgements - Dankwoord

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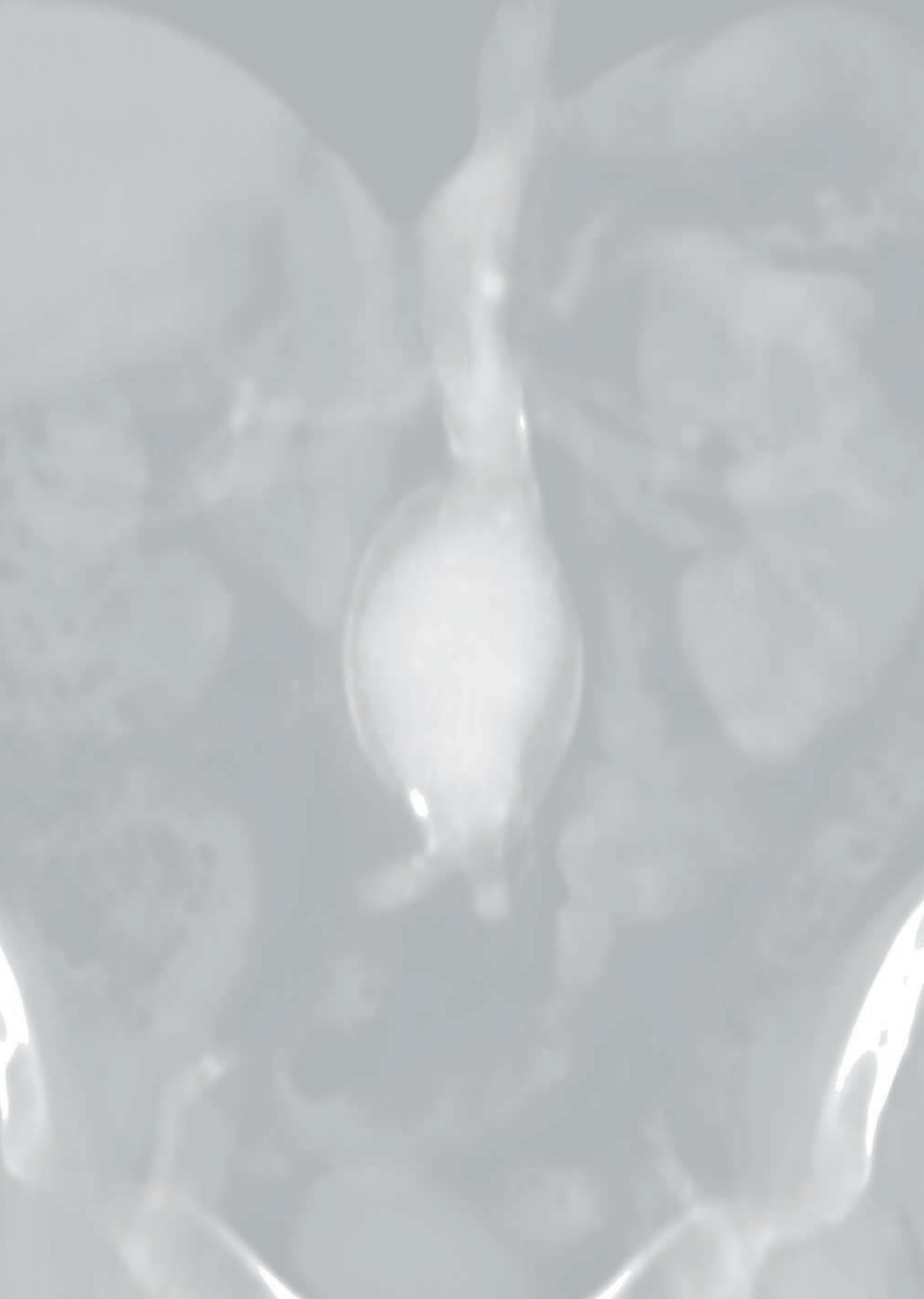
Lieve Debbie…blijf lachen, het verwar(m)t mij!



Curriculum Vitae

Sytse van Beek was born on 16 October 1985 in Alphen aan den Rijn in the Netherlands. In 2003 he graduated from the Groene Hart Lyceum (pre-university secondary education), after which he enrolled in medical school at Leiden University Medical Centre (LUMC). He graduated cum laude as a Medical Doctor (MD) in 2010. During his medical training, he did scientific and surgical internships at the University Hospital Malmö in Sweden, at the National Hospital for Tuberculosis and Respiratory Diseases in Hanoi Vietnam and at the Academic Hospital Paramaribo in Surinam. The report of his scientific internship 'Measurement of exhaled nitric oxide as a potential screening tool for pulmonary tuberculosis' was published in the International Journal of Tuberculosis and Lung Diseases in 2011. Sytse has also worked as an assistant at the Department of Anatomy supervising anatomy classes, as an electrocardiogram assistant and as a tutor for the course 'cardiac and pulmonary function'. Apart from studying and working, Sytse was a member of the executive board of the Leiden Medical Student Association, participated in the Bright Students Conference 'The ageing Europe' in Stockholm, Sweden and attended the LUMC Honours Class 'Global Health and Humanitarian assistance'.

After his MD degree in 2011, he started working as a 'resident not in training' at the Department of Surgery of the Groene Hart Ziekenhuis in Gouda. Eight months later he took the opportunity to work as a PhD student at the Department of Surgery at the Academic Medical Center in Amsterdam. His research was focused on care for patients with an abdominal aortic aneurysm. During his PhD project, he further developed his research skills by certifying as a clinical epidemiologist.

2004	amc	155	vrouw	.	.	
2004	[illegible]	85	man	.	.	
2004	amc	150	man	hostile	.	
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2004	olvg	120	man	.	endo	
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