Advances in Abdominal Aortic Aneurysm Care - Towards personalized, centralized and endovascular care

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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\textsubscript{RIFLE}) is described. Secondary objectives were to assess the incidence of AKI as defined by the SVS/ISCVS reporting standards (AKI\textsubscript{SVS/ISCVS}) and the association between AKI\textsubscript{RIFLE} and short-term death. In 362 RAAA patients treated by surgery, AKI\textsubscript{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\textsubscript{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\textsubscript{RIFLE} ‘Failure’ was higher than in patients without AKI\textsubscript{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.
Summary and future perspectives

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.