RUPTURED ABDOMINAL AORTIC ANEURYSMS: ENDOVASCULAR REPAIR VERSUS OPEN SURGERY

A DECISION-ANALYTIC APPROACH

JACOB JOHANNES VISSER

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A DECISION-ANALYTIC APPROACH

Geruptureerde aneurysmata van de abdominale aorta: endovasculaire behandeling versus open chirurgie

Een medisch besliskundige benadering

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Chapter 6

Visser JJ, Bosch JL, Hunink MGM, van Dijk LC, Bosch JL. Endovascular repair versus open surgery in patients with ruptured abdominal aortic aneurysms: cost-effectiveness and value of information analysis. Submitted.

CONTENTS

1
GENERAL INTRODUCTION

GENERAL INTRODUCTION

In the western world, the population is aging. People over 65 years are the fastest growing age group in the coming decades. Therefore, it is not surprising that several studies have indicated an increase in abdominal aortic aneurysms (AAAs) and consequently, ruptured AAAs (1-4).

An AAA is a weak area of the abdominal aorta that expands or bulges. This aneurysm is most likely caused by inflammation of the abdominal aorta that may lead to suspension of its wall. The AAA will enlarge by the pressure generated by each heartbeat, much like a balloon. Mostly, the AAA is not symptomatic until its rupture. Ruptured AAA is a life threatening condition that requires immediate intervention in order to avoid death.

In the Netherlands, the prevalence of AAAs among people over 55 years is 2.1%. The male:female ratio is 6:1 (5). Each year, about 800 people suffer from ruptured AAA (6).

The traditional approach to treat a ruptured AAA is open surgery. During open surgery, an incision is made in the abdomen to replace the ruptured part of the aorta with a tube-like aortic graft. Since 1994, endovascular repair in patients with a ruptured AAA has proven to be feasible (7). During endovascular repair, incisions are made in the groin through which catheters are threaded to place an endovascular stent graft to treat the ruptured AAA.

Mortality in patients with a ruptured AAA treated with open surgery remains high. Among patients who arrive in the hospital alive and undergo open surgery, the reported mortality rates varied between 32% and 70% and the morbidity rates between 30% and 50% (8, 9). Initial results of endovascular repair compared with open surgery were promising (10-22).

Important advantages of endovascular repair are potential avoidance of general anesthesia and minimization of invasiveness, and blood loss is considerably less than with open surgery. Patients treated with endovascular repair, however, are expected to have complications in the long run due to graft failure, such as endoleak and graft migration (23-27). Patients treated with open surgery may have more severe complications during and immediately following the procedure, such as bleeding, cardiac and pulmonary complications, and ischemia of the sigmoid, whereas during follow-up complications are rare after open surgery.

Until now, no systematic evaluation of endovascular repair versus open surgery in patients with a ruptured AAA has been performed. In addition, it is not clear whether one treatment is superior in all patients. Endovascular repair may be a good option for some patients, whereas in other cases, open surgery may still be the best way to repair the ruptured AAA.

APPROACH

Decisions in health care should be based on available evidence, the so-called evidence-based medicine approach. In a time when evidence from all over the world is available and accessible for physicians anywhere in the world, a systematic evaluation of the available evidence is needed. Furthermore, effects as well as costs should be taken into account when evaluating the best treatment option for patients. In addition, different people may require different treatment options and therefore, a prediction tool may be helpful in identifying those patients who would benefit from endovascular repair as opposed to open surgery. Since all available evidence needs to be used in a structured way, decision-analytic modeling should be incorporated in every decision-making process in health care.

AIM AND OUTLINE OF THIS THESIS

In this thesis, the approach described above was applied to patients with ruptured AAA. Our aim was to investigate whether endovascular repair or open surgery would be the preferred treatment in this group of patients from a decision analytic approach, taking clinical effectiveness as well as costs into account.

In **chapter 2**, we systematically evaluated published studies comparing endovascular repair with open surgery in patients with ruptured AAA and adjusted for differences in inclusion criteria among the studies.

In **chapter 3**, we compared the clinical outcomes of treatment after endovascular repair and open surgery in patients with ruptured infrarenal AAAs including one-year follow-up.

The Glasgow Aneurysm Score (GAS) is a prediction rule recommended to predict in-hospital mortality after open surgery for patients with ruptured and unruptured AAA (28). In **chapter 4**, we validated the GAS in patients with ruptured AAA treated with endovascular repair or open surgery. In addition, we modified the GAS into an updated prediction rule that predicts 30-day mortality, taking into account the treatment modality, endovascular repair versus open surgery.

In **chapter 5**, we retrospectively assessed in-hospital costs and costs of 1-year follow-up of endovascular aneurysm repair and conventional open surgery in patients with an acute infrarenal AAA, using the resource utilization approach.

In **chapter 6**, we evaluated the cost-effectiveness of endovascular repair compared with open surgery in patients with ruptured AAA and investigated whether it is worth to perform future

research to obtain additional information using value of information analysis techniques.

Finally, **chapter 7** summarizes the main findings of the preceding chapters and discusses endovascular repair versus open surgery in patients with ruptured AAA. In addition, methodological considerations and future research are discussed.

REFERENCES

1. Filipovic M, Goldacre MJ, Roberts SE, Yeates D, Duncan ME, Cook-Mozaffari P. Trends in mortality and hospital admission rates for abdominal aortic aneurysm in England and Wales, 1979-1999. Br J Surg 2005; 92:968-975.
2. Best VA, Price JF, Fowkes FG. Persistent increase in the incidence of abdominal aortic aneurysm in Scotland, 1981-2000. Br J Surg 2003; 90:1510-1515.
3. Gillum RF. Epidemiology of aortic aneurysm in the United States. J Clin Epidemiol 1995; 48:1289-1298.
4. Reitsma JB, Pleumeekers HJ, Hoes AW, et al. Increasing incidence of aneurysms of the abdominal aorta in The Netherlands. Eur J Vasc Endovasc Surg 1996; 12:446-451.
5. Pleumeekers HJ, Hoes AW, van der Does E, et al. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. Am J Epidemiol 1995; 142:1291-1299.
6. Centraal Bureau voor de Statistiek. Available at: http://statline.cbs.nl/StatWeb/start.asp?lp=search. Date accessed: April 18, 2007.
7. Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. Lancet 1994; 344:1645.
8. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. Br J Surg 2002; 89:714-730.
9. Bown MJ, Cooper NJ, Sutton AJ, et al. The postoperative mortality of ruptured abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2004; 27:65-74.
10. Greco G, Egorova N, Anderson PL, et al. Outcomes of endovascular treatment of ruptured abdominal aortic aneurysms. J Vasc Surg 2006; 43:453-459.
11. Franks S, Lloyd G, Fishwick G, Bown M, Sayers R. Endovascular treatment of ruptured and symptomatic abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31:345-350.
12. Vaddineni SK, Russo GC, Patterson MA, Taylor SM, Jordan WD, Jr. Ruptured abdominal aortic aneurysm: a retrospective assessment of open versus endovascular repair. Ann Vasc Surg 2005; 19:782-786.
13. Larzon T, Lindgren R, Norgren L. Endovascular treatment of ruptured abdominal aortic aneurysms: a shift of the paradigm? J Endovasc Ther 2005; 12:548-555.
14. Kapma MR, Verhoeven EL, Tielliu IF, et al. Endovascular treatment of acute abdominal aortic aneurysm with a bifurcated stentgraft. Eur J Vasc Endovasc Surg 2005; 29:510-515.

15. Hechelhammer L, Lachat ML, Wildermuth S, Bettex D, Mayer D, Pfammatter T. Midterm outcome of endovascular repair of ruptured abdominal aortic aneurysms. J Vasc Surg 2005; 41:752-757.
16. Alsac JM, Desgranges P, Kobeiter H, Becquemin JP. Emergency endovascular repair for ruptured abdominal aortic aneurysms: feasibility and comparison of early results with conventional open repair. Eur J Vasc Endovasc Surg 2005; 30:632-639.
17. Lee WA, Hirneise CM, Tayyarah M, Huber TS, Seeger JM. Impact of endovascular repair on early outcomes of ruptured abdominal aortic aneurysms. J Vasc Surg 2004; 40:211-215.
18. Resch T, Malina M, Lindblad B, Dias NV, Sonesson B, Ivancev K. Endovascular repair of ruptured abdominal aortic aneurysms: logistics and short-term results. J Endovasc Ther 2003; 10:440-446.
19. Reichart M, Geelkerken RH, Huisman AB, van Det RJ, de Smit P, Volker EP. Ruptured abdominal aortic aneurysm: endovascular repair is feasible in 40% of patients. Eur J Vasc Endovasc Surg 2003; 26:479-486.
20. Peppelenbosch N, Yilmaz N, van Marrewijk C, et al. Emergency treatment of acute symptomatic or ruptured abdominal aortic aneurysm. Outcome of a prospective intent-to-treat by EVAR protocol. Eur J Vasc Endovasc Surg 2003; 26:303-310.
21. Castelli P, Caronno R, Piffaretti G, et al. Ruptured abdominal aortic aneurysm: endovascular treatment. Abdom Imaging 2005; 30:263-269.
22. Brandt M, Walluscheck KP, Jahnke T, Graw K, Cremer J, Muller-Hulsbeck S. Endovascular repair of ruptured abdominal aortic aneurysm: feasibility and impact on early outcome. J Vasc Interv Radiol 2005; 16:1309-1312.
23. Tolia AJ, Landis R, Lamparello P, Rosen R, Macari M. Type II endoleaks after endovascular repair of abdominal aortic aneurysms: natural history. Radiology 2005; 235:683-686.
24. Prinssen M, Wixon CL, Buskens E, Blankensteijn JD. Surveillance after endovascular aneurysm repair: diagnostics, complications, and associated costs. Ann Vasc Surg 2004; 18:421-427.
25. Verhagen HJ, Prinssen M, Milner R, Blankensteijn JD. Endoleak after endovascular repair of ruptured abdominal aortic aneurysm: is it a problem? J Endovasc Ther 2003; 10:766-771.
26. van Marrewijk C, Buth J, Harris PL, Norgren L, Nevelsteen A, Wyatt MG. Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: The EUROSTAR experience. J Vasc Surg 2002; 35:461-473.
27. Laheij RJ, Buth J, Harris PL, Moll FL, Stelter WJ, Verhoeven EL. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR). Br J Surg 2000; 87:1666-1673.
28. Samy AK, Murray G, MacBain G. Glasgow aneurysm score. Cardiovasc Surg 1994; 2:41-44.

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SYSTEMATIC REVIEW

ABSTRACT

Purpose: To perform a systematic review of studies that compared endovascular repair with open surgery in the treatment of patients with a ruptured abdominal aortic aneurysm (AAA).

Materials and methods: A search of the English-language literature from January 1994 until March 2006 was performed. Inclusion criteria for articles were: patients who underwent endovascular repair were compared to patients who underwent open surgery, each treatment group included at least 5 patients, information about patients' hemodynamic condition upon presentation was reported, and (30-day) mortality was reported for each treatment group. Two reviewers independently extracted the data, and discrepancies were resolved by an arbiter. Random effects models and meta-regression analysis were used to calculate crude and adjusted odds ratios (endovascular versus open repair).

Results: Ten studies met the inclusion criteria in which the results of 478 procedures were reported (n = 148 for endovascular repair, n = 330 for open surgery). All studies were observational; no randomized controlled trials were found. The pooled 30-day mortality was 22% (95%-confidence interval (CI) 16–29%) for endovascular repair and 38% (95%-CI 32–45%) for open surgery. The pooled total systemic complications were 28% (95%-CI 17–48%) for endovascular repair and 56% (95%-CI 37–85%) for open surgery. The crude odds ratio for the 30-day mortality for endovascular repair compared to open surgery was 0.45 (95%-CI 0.28–0.72). After adjustment for patients' hemodynamic condition, the odds ratio was 0.67 (95%-CI 0.31–1.44).

Conclusion: In our systematic review, after adjustment for patients' hemodynamic condition upon presentation, a benefit in 30-day mortality for endovascular repair compared to open surgery for patients with a ruptured AAA was observed but was not statistically significant.

INTRODUCTION

Open surgery has traditionally been the approach to treat abdominal aortic aneurysm (AAA) ruptures. Since 1994, endovascular repair has become available (1). Since then, this new technique has increasingly been used to treat ruptured AAAs (2). The initial results are very promising (3-5) and many hospitals have implemented the policy to treat patients with a ruptured AAA with endovascular repair provided the anatomy is suitable. Recently, however, published randomized trials comparing endovascular repair with open surgery in patients with an elective asymptomatic AAA concluded that there is only a short-term advantage of endovascular repair in these patients; (6, 7) in the long term (i.e., 4 years), they found that endovascular repair offers no survival advantage compared with open surgery (7). No randomized controlled trials comparing endovascular repair and open surgery in patients with a ruptured AAA have been published, to our knowledge.

In several non-randomized studies mortality and morbidity data of endovascular repair were compared with conventional open surgery in patients with a ruptured AAA (8-17). The matching criteria for endovascular repair and open surgery varied across the studies. As a result, these studies reported a wide range of estimates for short-term mortality and morbidity; for example, in patients with a ruptured AAA short-term mortality estimates for endovascular repair varied between 10% and 29% (10, 17), and for open surgery between 15% and 54% (12, 17). These studies were rather heterogeneous with respect to the inclusion of hemodynamically unstable patients in the open surgery group. To enable comparison of the results of endovascular repair with open surgery in patients with a ruptured AAA, it is important to systemically evaluate these published studies and to adjust for differences in inclusion criteria among the studies. Thus, the purpose of our study was to perform a systematic review of studies that compared endovascular repair with open surgery in the treatment of patients with a ruptured AAA.

MATERIALS AND METHODS

To find the best available evidence, we formulated a PICO question ("the patient, population, or problem (P); the intervention or independent variable (I); the comparison (C); and the dependent variables or outcome(s) of interest (O)") (18). The question was: "In patients with a ruptured AAA, would endovascular repair compared with open surgery lead to lower mortality and morbidity?"

The literature was searched using the MEDLINE database and the Cochrane Library on literature reporting on endovascular repair and open surgery in patients with a ruptured AAA. The search was carried out on March 2, 2006 by one of the authors. We used keywords describing ruptured

abdominal aortic aneurysm, endovascular repair, open surgery, and outcome. Our search was limited to the English language and started from 1994 onward, when Yusuf published a case report on endovascular treatment of ruptured AAA in 1994 (1). To obtain additional references, articles that met our inclusion criteria were checked by one author by reviewing the reference list of each article. Furthermore, these articles were entered into the Web of Science database (19) in order to find where the articles that met our inclusion criteria were cited, so that related articles could be found. In addition, the computerized search strategy was validated by one author performing a manual search of the journals that reported most frequently about the topic of interest. These journals were searched from 1994 and included Radiology, Journal of Vascular and Interventional Radiology, Journal of Vascular Surgery, Journal of Endovascular Therapy, and European Journal of Vascular and Endovascular Surgery. Meeting abstracts, unpublished data, and theses were not included in our search.

Prospective as well as retrospective studies were included if: (a) Patients who underwent endovascular repair were compared to patients who underwent open surgery, (b) each treatment group included at least 5 patients, (c) information about patients' hemodynamic condition upon presentation to the hospital was reported, (d) and (30-day) mortality was reported for each treatment group. If studies reported results of current and historic controls separately, we included only the results of current controls. When multiple reports from one single institution were retrieved, the most recent report was included to avoid double counting.

Two authors independently extracted data from each article using a standard form. Each of these two authors independently reviewed all articles. The arbiter considered discrepancies. The following data were recorded: (a) number of patients in each treatment group, (b) reasons to treat patients with open surgery, (c) patient characteristics, (d) AAA morphology, (e) whether a computed tomography (CT)-scan was performed prior to the procedure, (f) procedure characteristics such as type of anesthesia, type of graft, blood loss, procedure time, (g) mortality and morbidity rates during hospital stay, and (h) aneurysm-related complications during follow-up.

Data and Statistical Analysis

We assumed that the articles included in our systematic review were a random, unselective sample of a hypothetical population of studies comparing endovascular repair with open surgery in patients with a ruptured AAA. Therefore, to pool data, we used the random-effects model described by DerSimonian and Laird (20). This model took into account the between-study variability as well as the within-study variability. The pooled 30-day mortality with the 95%-confidence interval was calculated for both treatment groups. The total systemic complications were calculated as the sum of cardiac, pulmonary, cerebrovascular, and renal complications, multiorgan failure, and sepsis and were based on the studies that reported systemic complications for each treatment group (8, 11, 13, 15, 17). The pooled proportion of total systemic complica-

tions with the 95%-confidence interval was calculated for each treatment group. Furthermore, we calculated the weighted means with the 95%-confidence interval for the mean age, mean AAA diameter, mean neck diameter, mean neck length, mean days in hospital, mean days in the intensive care unit (ICU), mean blood loss, mean blood transfusions, and mean time of the procedure. The crude odds ratio for 30-day mortality with the 95%-confidence interval was calculated for endovascular repair versus open surgery (i.e., an odds ratio < 1.0 favored endovascular repair). Furthermore, an odds ratio for 30-day mortality adjusted for patients' hemodynamic condition upon presentation in the hospital was calculated by performing a meta-regression analysis. In the regression model, we included the proportion of patients with low systolic blood pressures of each treatment group as covariate in the model.

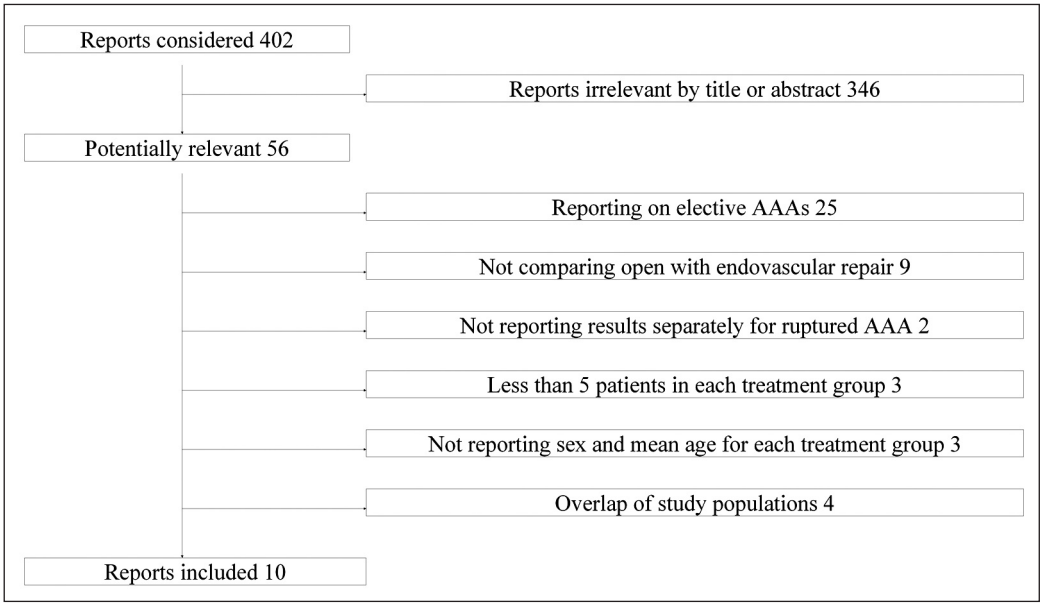
Publication bias (i.e., bias resulting from the greater likelihood of publishing favorable results) was detected by a funnel plot (21). In the current study, we plotted the reciprocal of the standard error of the 30-day mortality odds ratio of each study as a function of the natural logarithm of the 30-day mortality odds ratio. If no publication bias is present, the data points will be distributed in a symmetric fashion and shaped like an inverted V. Furthermore, to test for heterogeneity in patients' hemodynamic condition upon presentation to the hospital across the studies, we used the $\chi 2$-test; $p < 0.05$ was considered statistically significant. Analyses were performed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA) and SAS Version 8.2 (Statistical Analysis System, Cary, NC).

RESULTS

Literature search

A total of 402 articles were identified from the MEDLINE database and Web of Science (Figure 1).

Figure 1: Flowchart of the study selection procedure.



No additional articles were retrieved from the Cochrane Library, the review of the reference list of each article, and the manual search. Of these 402 articles, 56 papers were retrieved in full, of which 10 met our inclusion criteria (8-17). The total number of procedures was 478, 148 patients underwent endovascular repair and 330 patients underwent open surgery. Nine studies were performed in Europe and one in the United States (Table 1).

Table 1: Characteristics of studies comparing endovascular repair and open surgery in patients with a ruptured Abdominal Aortic Aneurysm (AAA)

Study	Year of publication	Study location	No. of institutions	Study period	Type of study
Peppelenbosch et al (8)	2003	Netherlands	1	2001-2002	Observational, prospective
Reichart et al (9)	2003	Netherlands	1	2000-2002	Observational
Resch et al (10)*	2003	Sweden	1	2001-2002	Observational, both prospective and retrospective
Alsac et al (11)	2005	France	1	2001-2004	Observational
Brandt et al (12)	2005	Germany	1	2003-2004	Observational, retrospective
Castelli et al (13)†	2005	Italy	1	2001-2004	Observational
Kapma et al (14)	2005	Netherlands	1	1998-2004	Observational
Larzon et al (15)	2005	Sweden	1	2001-2004	Observational, retrospective
Vaddineni et al (16)	2005	USA	1	1999-2004	Observational, retrospective
Franks et al (17)‡	2006	UK	1	1996-2003	Observational, both prospective and retrospective

* From 2001-July 2002, patients who underwent endovascular repair were followed prospectively; from January 2001-June 2002, patients who underwent open surgery were analyzed retrospectively. Confirmation of ruptured AAA by a computed tomography (CT)-scan or free blood during laparotomy was not reported.
† Confirmation of ruptured AAA only reported if patients underwent endovascular repair, 23 with CT-scan and two with abdominal ultrasound.
‡ From July 1996-April 2003, patients who underwent endovascular repair were analyzed retrospectively; from December 2000-July 2001, patients who underwent open surgery were included prospectively.

The articles were published between June 2003 and January 2006; patients were enrolled from 1996 to 2004. All studies were observational and single-center; no randomized controlled trials were found. The size of the treatment groups varied between 6 and 25 for endovascular repair and between 10 and 172 for open surgery. Two studies did not report results for current and historic controls separately for patients treated with open surgery, therefore we used the combined results (8, 14).

Patient selection

Across the studies, the treatment choice for endovascular repair or open surgery in patients with a ruptured AAA varied (Table 2).

Table 2: Reasons to treat patients with a ruptured Abdominal Aortic Aneurysm (AAA) with open surgery instead of endovascular repair

Study	Number of patients treated with open surgery	Hemodynamic instability (%)*	Anatomic considerations (%)†	Logistic reasons (%)‡
Peppelenbosch et al (8)§	14	3/14 (21)	5/14 (36)	6/14 (43)
Reichart et al (9)	17	3/17 (18)	12/17 (71)	2/17 (12)
Resch et al (10)	23	2/23 (9)	3/23 (13)	18/23 (78)
Alsac et al (11)	20	8/20 (40)	7/20 (35)	5/20 (25)
Brandt et al (12)	13	0/13 (0)	11/13 (85)	2/13 (15)
Castelli et al (13)	21	0/21 (0)	18/21 (86)	3/21 (14)
Kapma et al (14)‖	172	8/41 (20)	29/41 (71)	4/41 (10)
Larzon et al (15)	26	5/26 (19)	4/26 (15)	17/26 (65)#
Vaddineni et al (16)	15	6/15 (40)	9/15 (60)**	0/15 (0)
Franks et al (17)	13	6/13 (46)††	NR	NR
Pooled outcome (95%-CI)	-	0.24 (0.17-0.34)	0.52 (0.32-0.71)	0.28 (0.14-0.49)

CI = confidence interval, NR = not reported
* The definition for hemodynamic instability differed across the selected studies.
† Anatomic considerations were: inaccessible iliac arteries, too short infrarenal neck, sharply angled infrarenal neck, diameter infrarenal neck too large, calcified neck, or mycotic aneurysm.
‡ Unavailability of endovascular equipment or trained staff.
§ Not reported separately for patients with a ruptured AAA (n = 10) and patients with a symptomatic AAA (n = 4).
|| Not reported separately for patients with a ruptured AAA and patients with a symptomatic AAA and only reported for patients treated between January 2003 and August 2004 (15 patients underwent endovascular repair and 41 underwent open surgery).
In 6/17 patients endovascular repair was not considered at all by the surgeon.
** Six of these 9 patients underwent open surgery at discretion of the attending surgeon.
†† We assumed that all patients who were too unstable to tolerate a CT-scan prior to the procedure and transported immediately to the operating theatre for open surgery, were patients with a ruptured AAA.

In general, the policy of the hospitals in the selected studies was to preferentially treat patients with endovascular repair. Patients who were stable enough (i.e., no hypovolemic shock or cardiac arrest) underwent CT-scan prior to the procedure. If the AAA was anatomically suitable and the required endovascular equipment and trained staff were available, the patient was treated with endovascular repair. In some studies the majority of patients were treated with open surgery instead of endovascular repair because of anatomic considerations (12, 13), whereas in other studies open surgery instead of endovascular repair was performed because of logistic reasons such as unavailability of endovascular equipment or trained staff (Table 2) (10, 15). Across the studies, the majority of the patients were male and this proportion was similar between the endovascular repair and the open surgery group ($p = 0.74$). Mean age was similar for the endovascular repair and the open surgery group. The hemodynamic condition of patients upon presentation to the hospital varied between the studies for both endovascular repair and open surgery (Table 3).

Procedure characteristics

In 7 of 10 studies, all patients treated with endovascular repair had a CT-scan prior to the procedure, whereas the proportion of patients treated with open surgery that underwent a CT-scan prior to the procedure varied between 43% and 74% across the studies (Table 4).

In some studies, the use of regional and/or epidural anesthesia was preferred for patients treated with endovascular repair (8, 9, 14), whereas in the other studies general anesthesia was preferred for those patients. In studies that reported on the type of anesthesia in patients treated with open surgery, general anesthesia was mostly used in those patients. In some studies, the majority of patients treated with endovascular repair received an aorto-uni-iliac graft (8-10, 12), whereas in other studies the majority of patients treated with endovascular repair received a bifurcated graft (13-17). In studies that reported on the type of grafts used in patients treated with open surgery, most patients received a tubular graft.

Outcomes

In studies that reported intraoperative mortality for the endovascular repair and the open surgery group, the intraoperative mortality was lower for patients treated with endovascular repair (Table 5).

In addition, all studies showed lower 30-day mortality rates for patients treated with endovascular repair compared to those patients who underwent open surgery. The pooled 30-day mortality was 22% (95%-confidence interval 16–29%) for endovascular repair and 38% (95%-confidence interval 32–45%) for open surgery. The crude odds ratio for 30-day mortality of endovascular repair versus open surgery was 0.45 (95%-confidence interval 0.28–0.72). Heterogeneity was demonstrated for the patients' hemodynamic condition upon presentation to the hospital across the studies for both treatment groups ($p < 0.01$). After adjustment for patients' hemodynamic

Table 3: Patient characteristics and Abdominal Aortic Aneurysm (AAA) morphology of patients with a ruptured AAA treated with endovascular repair or open surgery

Study	Number of patients	Ruptured - Symptomatic	Male (%)	Mean age (yr)	Circulatory shock (%)*	Mean AAA diameter (mm)	Mean neck diameter (mm)	Mean neck length (mm)
Endovascular repair								
Peppelenbosch et al (8)	16	16-10	23/26 (88)†	74.1†	8/16 (50)‡	67†	23.8†	18.0†
Reichart et al (9)	6	-	23/26 (88) §, ||	71§, ||	0/6 (0)	64	NR	23
Resch et al (10)	14	-	11/14 (79)	79	5/14 (36)	60	NR	NR
Alsac et al (11)	17	-	16/17 (94)	72.9	0/17 (0)	85	22.1	27.4
Brandt et al (12)	11	-	19/24 (79) §	75§	0/11 (0) #	71	NR	NR
Castelli et al (13)†	25	-	21/25 (84)	76	7/25 (28)	73	NR	NR
Kapma et al (14)	25	25-15	37/40 (93)†	75†, **	7/25 (28)	NR	NR	NR
Larzon et al (15)	15	-	14/15 (93)	73**	11/15 (73)	NR	NR	NR
Vaddineni et al (16)	9	-	7/9 (78)	70.8	0/9 (0)	67	NR	NR
Franks et al (17)	10	10-11	19/21 (90)†	73.7†	3/10 (30)	NR	NR	NR
Pooled outcome (95%-CI)	-	-	0.85 (0.80-0.89)	74.2 (70.3-78.1)	0.29 (0.17-0.46)	71 (56-85)	23 (21-25)	22 (13-31)
Open surgery								
Peppelenbosch et al (8)	10	10-4	11/14 (79)†	71.0†	8/10 (80)‡	77	27.8	7.5
Reichart et al (9)	17	17-1	23/26 (88) §, ||	71§, ||	3/17 (18)	88††	NR	NR
Resch et al (10)	23	-	20/23 (87)	73	17/23 (74)	70	NR	NR
Alsac et al (11)	20	-	20/20 (100)	72.8	8/20 (40)	78.8	21.2	13.5
Brandt et al (12)	13	-	19/24 (79) §	75§	4/13 (31) #	77	NR	NR
Castelli et al (13)	21	-	17/21 (81)	NR	8/21 (38)	NR	NR	NR
Kapma et al (14)	172	172-41	185/213 (87)†	71†, **	8/41 (20) ‡‡	NR	NR	NR
Larzon et al (15)	26	-	23/26 (88)	75**	10/26 (38)	NR	NR	NR
Vaddineni et al (16)	15	-	12/15 (80)	72.2	6/15 (40)	64	NR	NR
Franks et al (17)	13	13-9	20/22 (91)†	71.8†	6/13 (46) §§	NR	NR	NR
Pooled outcome (95%-CI)	-	-	0.85 (0.81-0.88)	71.8 (69.1-74.5)	0.41 (0.30-0.54)	75 (61-89)	24 (18-31)	11 (5.2-17)

mm = millimeter, NR = not reported, CI = confidence interval

* Circulatory shock was defined by Peppelenbosch et al and by Franks et al for endovascular patients as systolic blood pressure < 100 millimeter Mercury (mm Hg), by Reichart et al, Castelli et al, Larzon et al, and Vaddineni et al as systolic blood pressure < 80 mm Hg, by Resch et al as syncope before procedure, by Alsac et al as systolic blood pressure < 60 mm Hg, by Brandt et al as preoperative hypotension, by Kapma et al as systolic blood pressure < 70 mm Hg for patients undergoing endovascular repair and as too shocked to undergo a CT-scan prior to the procedure for patients undergoing open surgery, and by Franks et al as patients transported directly to the operating theatre for patients under-going open surgery.

† Patient characteristics were not reported separately for patients with a ruptured AAA and patients with a symptomatic AAA; Peppelenbosch: total number of patients treated with endovascular repair = 26, total number of patients treated with open surgery = 14; Kapma: total number of patients treated with endovascular repair = 40, total number of patients treated with open surgery = 213; Franks: total number of patients treated with endovascular repair = 21, total number of patients treated with open surgery = 22.

‡ We assumed that all patients with systolic blood pressure < 100 mm Hg were patients with a ruptured AAA.

§ Patient characteristics were not reported separately for endovascular and open treated patients; Reichart: total number of patients treated with endovascular repair = 6, total number of patients treated with open surgery = 18; Brandt: total number of patients treated with endovascular repair = 11, total number of patients treated with open surgery = 13.

|| One patient with a symptomatic AAA was included who underwent open surgery.

We assumed that all patients with preoperative hypotension were treated with open surgery since Brandt et al stated that patients who were in hemodynamically unstable condition went directly to the operating room and underwent open surgery.

** Median.

†† Only reported for patients who underwent a CT-scan prior to the procedure; one patient was treated for a symptomatic AAA.

‡‡ Only reported for 41 patients treated with open surgery between January 2003 and August 2004.

§§ We assumed that all patients who were transported immediately to the operating theatre were patients with a ruptured AAA.

Table 4: Procedure characteristics of patients with a ruptured Abdominal Aortic Aneurysm treated with endovascular repair or open surgery

Study	CT-scan prior to procedure (%)	Local anesthesia (%)	General anesthesia (%)	AUI-graft (%)	Bifurcated graft (%)	Tubular graft (%)
Endovascular repair						
Peppelenbosch et al (8)	23/26 (88)*,†	15/16 (94)‡	1/16 (6)	19/26 (73)†	3/16 (19)†	2/26 (8)†
Reichart et al (9)	6/6 (100)	4/6 (67)	2/6 (33)	6/6 (100)	0/6 (0)	0/6 (0)
Resch et al (10)	12/14 (86)*	6/21 (29)§	15/21 (79)§	12/21 (57)§	9/21 (43)§	0/21 (0)
Alsac et al (11)	17/17 (100)	1/17 (6)	16/17 (94)	8/17 (47)	8/17 (47)	1/17 (6)‖
Brandt et al (12)	11/11 (100)	0/11 (0)	11/11 (100)	8/11 (73)	3/11 (27)	0/11 (0)
Castelli et al (13)†	23/25 (92)	0/25 (0)	25/25 (100)	4/25 (16)	21/25 (84)	0/25 (0)
Kapma et al (14)	15/15 (100)#	33/40 (83)†	7/40 (17)†,††	1/40 (3)†	39/40 (97)†	0/40 (0)†
Larzon et al (15)	15/15 (100)	2/15 (13)	13/15 (87)	NR	13/15 (87)**	NR
Vaddineni et al (16)	9/9 (100)	0/9 (0)	9/9 (100)	0/9 (0)	9/9 (100)	0/9 (0)
Franks et al (17)	10/10 (100)	7/21 (33)†,**	14/21 (67)†	4/21 (19)†	17/21 (81)†	0/21 (0)†
Pooled outcome (95%-CI)	0.91 (0.85-0.95)	0.29 (0.11-0.58)	0.71 (0.42-0.89)	0.38 (0.17-0.64)	0.64 (0.38-0.83)	0.05 (0.03-0.10)
Open surgery						
Peppelenbosch et al (8)	10/14 (71)‡‡	0/10 (0)	10/10 (100)	0/14 (0)‡‡	5/14 (29)‡‡	9/14 (64)‡‡
Reichart et al (9)	12/17 (71)	NR	NR	0/17 (0)	5/17 (29)	12/17 (71)
Resch et al (10)	17/23 (74)	0/23 (0)	23/23 (100)	0/23 (0)	7/23 (30)	16/23 (70)
Alsac et al (11)	12/20 (60)	0/20 (0)	20/20 (100)	0/20 (0)	10/20 (50)	10/20 (50)
Brandt et al (12)	NR	NR	NR	0/13 (0)	NR	NR
Castelli et al (13)	9/21 (43)	0/21 (0)	21/21 (100)	NR	NR	NR
Kapma et al (14)	26/41 (63)‡‡	NR	NR	NR	NR	NR
Larzon et al (15)	15/26 (58)	1/26 (4)	25/26 (96)	0/26 (0)	4/26 (15)	22/26 (85)
Vaddineni et al (16)	9/15 (60)	0/15 (0)	15/15 (100)	NR	NR	NR
Franks et al (17)	7/13 (54)	NR	NR	NR	NR	NR
Pooled outcome (95%-CI)	0.61 (0.54-0.67)	0.04 (0.01-0.09)	0.96 (0.91-0.99)	0.03 (0.01-0.08)	0.33 (0.22-0.45)	0.67 (0.55-0.78)

AAA = Abdominal Aortic Aneurysm, CT = computed tomography, AUI = aorto-uni-iliac, NR = not reported

* Peppelenbosch: Three patients underwent fluoroscopic assessment in the operating room to establish neck diameter and neck length. Resch: One patient with a known AAA had a rupture in-hospital; one patient had intraoperative CO2 angiography to verify the AAA rupture.

† Procedure characteristics were not reported separately for patients treated with endovascular repair with a ruptured AAA and with a symptomatic AAA; Peppelenbosch: 16 patients with a ruptured AAA, 10 patients with a symptomatic AAA; Kapma: 25 patients with a ruptured AAA, 15 patients with a symptomatic AAA; Franks: 10 patients with a ruptured AAA, 11 patients with a symptomatic AAA.

‡ Regional or local anesthesia.

§ Only reported for 21 patients with a ruptured AAA who underwent endovascular repair between 1997 and July 2002.

|| Iliac extension.

Only reported for 15 patients with a ruptured AAA treated with endovascular repair between January 2003 and August 2004.

** Among patients treated with endovascular repair, 2/15 received combinations of different stent-grafts.

†† Four patients received general anesthesia only, 3 patients received local anesthesia with sedation.

‡‡ Procedure characteristics were not reported separately for patients treated with open surgery with a ruptured AAA and with a symptomatic AAA; Peppelenbosch: 10 patients with a ruptured AAA, 4 patients with a symptomatic AAA; Kapma: only reported for patients treated between January 2003 and August 2004, not reported how many patients had ruptured AAA or symptomatic AAA in this period.

Table 5: Outcomes in patients with a ruptured Abdominal Aortic Aneurysm treated with endovascular repair or open surgery

Study	Intraoperative mortality (%)	30-day mortality (%)	Mean days in hospital	Mean days in the ICU	Mean blood loss in ml	Mean blood transfusions	Mean procedure time (minutes)
Endovascular repair							
Peppelenbosch et al (8)	NR	4/16 (25)	7.2*,†	1.9*,†	1100*	4700 ml*	154*
Reichart et al (9)	0/6 (0)	1/6 (17)	8	2.25	300	0 ml	163
Resch et al (10)	NR	4/14 (29)	NR	1‡	800†	2 units†	NR
Alsac et al (11)	NR	4/17 (24)	11.5‡	3‡	NR	1520 ml	156
Brandt et al (12)	NR	0/11 (0)§	13.9	4.8	NR	964 ml	178
Castelli et al (13)†	NR	5/25 (20)||	7	4.7	243	NR	115
Kapma et al (14)	1/25 (4)	5/25 (20)	5*,‡	0*,‡	200*,‡	0 p.c.*,‡	110*,‡
Larzon et al (15)	0/15 (0)	2/15 (13)	NR	NR	NR	NR	NR
Vaddineni et al (16)	0/9 (0)	2/9 (22)	19.5	13	475	3.78 units	143
Franks et al (17)	0/10 (0)	1/10 (10)	8.5*	1.5*	NR	0.86 units*	156*
Pooled outcome (95%-CI)	0.05 (0.02-0.14)	0.22 (0.16–0.29)	8.5# (1.2-16)	2.6# (0-8.5)	500# (0-1218	1255# (0-4571)	138# (92-184)
Open surgery							
Peppelenbosch et al (8)	NR	4/10 (40)	22.1†,**	6.4†,**	2600**	10400 ml**	155**
Reichart et al (9)	NR	7/17 (41)††	29‡‡	13‡‡	4500‡‡	1600 ml‡‡	132‡‡
Resch et al (10)	NR	8/23 (35)	NR	3‡	4000†	9 units†	NR
Alsac et al (11)	NR	10/20 (50)	20‡	13‡	NR	3075 ml	222
Brandt et al (12)	NR	2/13 (15)§	19.1	8.5	NR	1968 ml	207
Castelli et al (13)	NR	10/21 (48)||	NR	NR	NR	NR	NR
Kapma et al (14)	NR	57/172 (33)§	12‡,**	2‡,**	3500‡,**	6 p.c.‡,**	180‡,**
Larzon et al (15)	6/26 (23)	12/26 (46)	NR	NR	NR	NR	NR
Vaddineni et al (16)	3/15 (20)	4/15 (27)	27	19.5	2880	6.93 units	181
Franks et al (17)	NR	7/13 (54)	17.5**	6.1**	NR	10.7 units**	186**
Pooled outcome (95%-CI)	0.23 (0.13-0.38)	0.38 (0.32–0.45)	15# (5.0-25)	4.7# (0-14)	3509# (2806-4213)	2268# (0-5732)	181# (149-213)

AAA = Abdominal Aortic Aneurysm, ICU = intensive care unit, ml = milliliter, NR = not reported, p.c. = units of packed cells, CI = confidence interval

* Outcomes were not reported separately for patients treated with endovascular repair with a ruptured AAA and with a symptomatic AAA; Peppelenbosch: 16 patients with a ruptured AAA, 10 patients with a symptomatic AAA; Kapma: 25 patients with a ruptured AAA, 15 patients with a symptomatic AAA; Franks: 10 patients with a ruptured AAA, 11 patients with a symptomatic AAA.

† Not stated if mean or median was reported.

‡ Median.

§ In-hospital mortality.

|| Not stated whether 30-day or in-hospital mortality was reported.

Weighted mean.

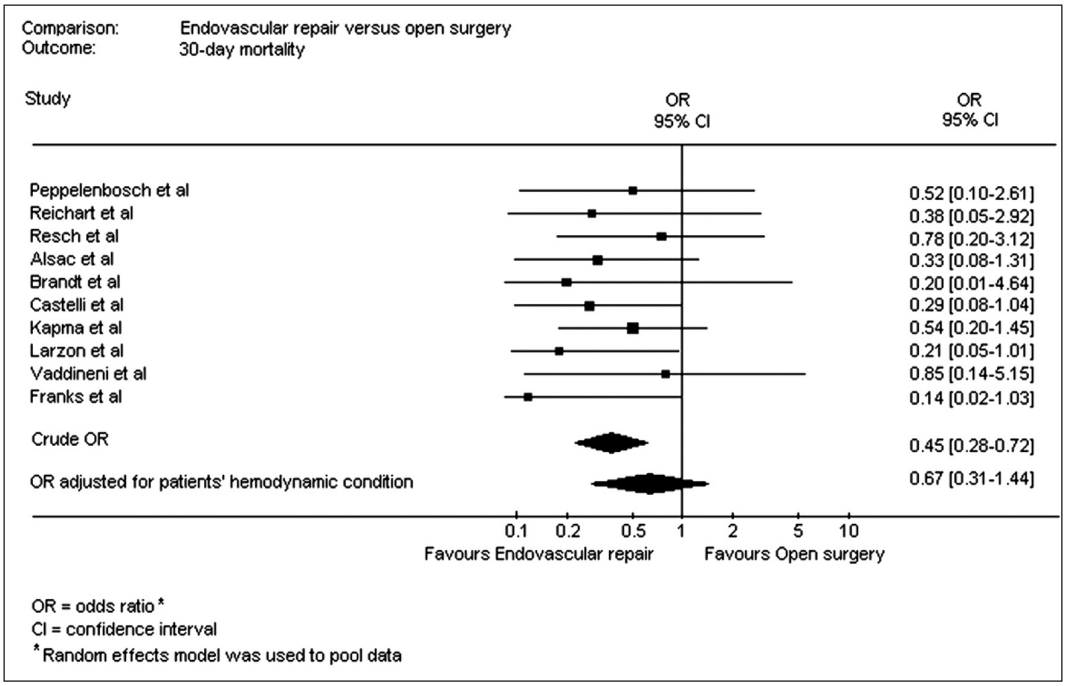
** Outcomes were not reported separately for open treated patients with a ruptured AAA and with a symptomatic AAA; Peppelenbosch: 10 patients with a ruptured AAA, 4 patients with a symptomatic AAA; Kapma: 172 patients with a ruptured AAA, 41 patients with a symptomatic AAA; Franks: 13 patients with a ruptured AAA, 9 patients with a symptomatic AAA.

†† Total in-hospital mortality was 7/17, 4/12 patients who underwent a computed tomography (CT)-scan died in-hospital, 3/5 patients who did not undergo a CT-scan died in-hospital.

‡‡ Only reported for 13 patients who underwent a CT-scan prior to procedure. One patient underwent open surgery for symptomatic AAA.

condition upon presentation to the hospital, the odds ratio was 0.67 (95%-confidence interval 0.31–1.44; p = 0.37) indicating that the difference in 30-day mortality was, in part, explained by this variable (Figure 2).

Figure 2: Forest plot representation on 30-day mortality as reported in included studies.



The mean number of days spent in hospital (8.5 versus 15 days for endovascular repair and open surgery, respectively) and in the ICU (2.6 versus 4.7 days for endovascular repair and open surgery, respectively) was less after endovascular repair than after open surgery (Table 5). In addition, studies that reported blood loss and blood transfusions during the procedure showed less blood loss and less blood transfusions following endovascular repair than following open surgery. The duration of an endovascular procedure was shorter in most studies compared to an open surgical procedure (138 versus 181 minutes for endovascular repair and open surgery, respectively).

Five studies reported complications for both endovascular repair and open surgery (Table 6) (8, 11, 13, 15, 17).

Table 6: In-hospital complications in patients with a ruptured Abdominal Aortic Aneurysm treated with endovascular repair or open surgery

Study	Cardiac* (%)	Pulmonary† (%)	Cerebrovascular‡ (%)	Renal§ (%)	Multiorgan failure or sepsis (%)	Endoleak (%)	Graft infection (%)	Wound infection‖ (%)	Abdominal compartment syndrome (%)
Endovascular repair									
Peppelenbosch et al (8)	2/26 (8)#	1/26 (4)#	1/26 (4)#	NR	0/16 (0)	NR	NR	4/26 (15)#	NR
Alsac et al (11)**	0/17 (0)	1/17 (6)	2/17 (12)	2/17 (12)	1/17 (6)	NR	0/17 (0)	NR	1/17 (6)
Castelli et al (13)††	0/25 (0)	0/25 (0)	NR	2/25 (8)	NR	3/25 (12)‡‡	NR	2/25 (8)	1/25 (4)
Larzon et al (15)§§	2/15 (13)	0/15 (0)	2/15 (13)	2/15 (13)	2/15 (13)	NR	NR	0/15 (0)	1/15 (7)
Franks et al (17)‖‖‖	2/21 (10)	2/21 (10)	NR	2/21 (10)	NR	4/21 (19)##	NR	1/21 (5)	NR
Pooled outcome (95%-CI)	0.10 (0.05-0.18)	0.07 (0.03-0.14)	0.12 (0.05-0.23)	0.12 (0.07-0.22)	0.10 (0.04-0.24)	0.17 (0.09-0.30)	-	0.11 (0.06-0.20)	0.08 (0.03-0.18)
Open surgery									
Peppelenbosch et al (8)	0/10 (0)	2/14 (14)***	0/10 (0)	NR	1/14 (7)***	-	NR	0/10 (0)	NR
Alsac et al (11)†††	2/20 (10)	5/20 (25)	2/20 (10)	4/20 (20)	2/20 (10)	-	1/20 (5)	NR	0/20 (0)
Castelli et al (13)‡‡‡	1/21 (5)	1/21 (5)	NR	4/21 (19)	NR	-	NR	2/21 (10)	NR
Larzon et al (15)§§§	4/26 (15)	6/26 (23)	0/26 (0)	4/26 (15)	4/26 (15)	-	NR	1/26 (4)	NR
Franks et al (17)‖‖‖‖	6/22 (27)	7/22 (32)	NR	3/22 (14)	2/22 (9)	-	NR	1/22 (5)	1/22 (5)
Pooled outcome (95%-CI)	0.16 (0.09-0.26)	0.24 (0.16-0.33)	0.07 (0.02-0.21)	0.18 (0.12-0.28)	0.13 (0.07-0.22)	-	-	0.08 (0.03-0.16)	0.05 (0.01-0.18)

AAA = Abdominal Aortic Aneurysm, NR = not reported, CI = confidence interval

* Reported in studies as cardiac complications, myocardial infarction, (cardiac) arrhythmia, angina, and congestive cardiac failure.

† Reported in studies as pulmonary complications, pneumopathy, pulmonary embolism, respiratory complications, respiratory tract infection, and respiratory failure.

‡ Reported in studies as cerebrovascular accident, stroke, and cerebrovascular complications.

§ Reported in studies as (acute) renal failure, renal complications, and renal impairment.

|| Reported in studies as wound infection, hematoma, and deep infection.

Complications were not reported separately for patients with a ruptured AAA (n = 16) and patients with a symptomatic AAA (n = 10).

** In addition, Alsac et al reported that among patients treated with endovascular repair, 1/17 patients had visceral ischemia and 1/17 patients had limb ischemia.

†† In addition, Castelli et al reported that among patients treated with endovascular repair, 3/25 patients had post-implant syndrome.

‡‡ Two of 25 patients had type 1 endoleaks, 1/25 patients had type 3 endoleak.

§§ In addition, Larzon et al reported that among patients treated with endovascular repair, 4/15 patients had thrombo-embolic complications.

|||| In addition, Franks et al reported that among patients treated with endovascular repair, 1/21 patients had colon ischemia and 2/21 patients had groin seromas. Complications were not reported separately for patients with a ruptured AAA (n = 10) and patients with a symptomatic AAA (n = 11).

Type 1 endoleak.

*** Complications were not reported separately for patients with a ruptured AAA (n = 10) and patients with a symptomatic AAA (n = 4).

††† In addition, Alsac et al reported that among patients treated with open surgery, 3/20 patients had visceral ischemia and 1/20 patients had limb ischemia.

‡‡‡ In addition, Castelli et al reported that among patients treated with open surgery, 3/21 patients had disseminated intravascular coagulopathy, 1/21 patients had colon ischemia, 1/21 patients had aortic thrombosis, and 1/21 patients had gangrene.

§§§ In addition, Larzon et al reported that among patients treated with open surgery, 5/26 patients had thrombo-embolic complications.

|||||| In addition, Franks et al reported that among patients treated with open surgery, 4/22 patients had colon ischemia, 1/22 patients had gastro-intestinal bleeding, and 1/22 patients had common femoral artery embolus. Complications were not reported separately for patients with a ruptured AAA (n = 13) and patients with a symptomatic AAA (n = 9).

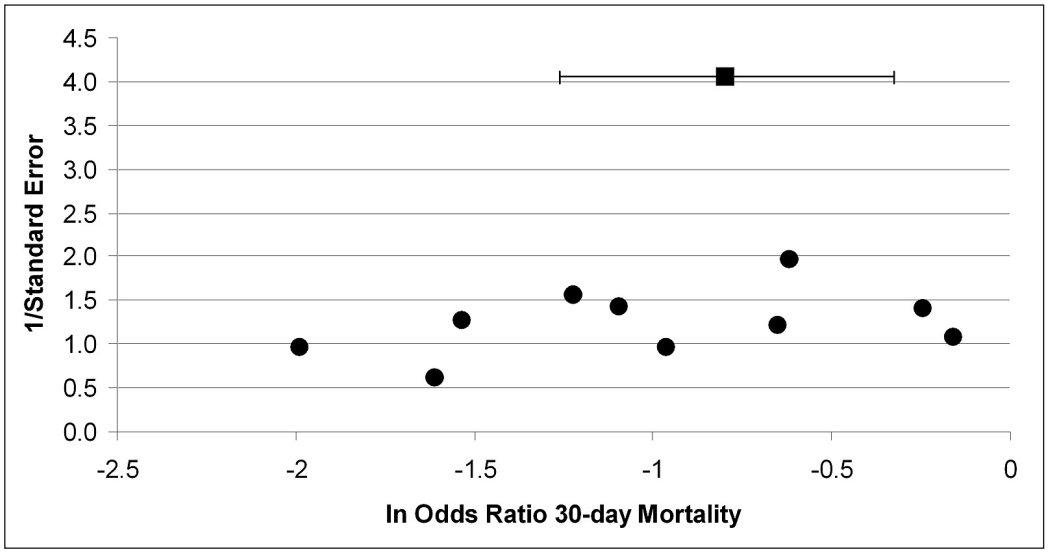
The pooled proportion of total systemic complications (i.e., the sum of cardiac, pulmonary, cerebrovascular, and renal complications, multiorgan failure, and sepsis) was 28% (95%-confidence interval 17–48%) for endovascular repair and 56% (95%-confidence interval 37–85%) for open surgery.

Follow-up data were reported in 5 studies and only in patients treated with endovascular repair (8, 9, 11, 13, 17). Peppelenbosch et al reported type 1 endoleaks in two patients and a type 2 endoleak in one patient during follow-up from 30 days to 14 months. Reichart et al reported an additional endovascular procedure to exclude an iliac aneurysm in one patient during follow-up from 6 to 24 months. Alsac et al reported a conversion to open surgery for endografts sepsis in one patient, type 1 endoleaks in three patients, and a second rupture in one patient during follow-up from 30 days to 250 days. Castelli et al reported an occlusion of an iliac limb in one patient and type 2 endoleaks in two patients during follow-up from 4 to 24 months. Franks et al reported type 2 endoleaks in 4 patients during follow-up from 7 to 106 months. It should be noted that Peppelenbosch et al and Franks et al did not report data on follow-up separately for patients with a symptomatic AAA and patients with a ruptured AAA.

Funnel plot

Publication bias was evaluated with a funnel plot (Figure 3).

Figure 3: Funnel plot.



Funnel plot shows the reciprocal of the standard error of the 30-day mortality odds ratio, endovascular repair versus open surgery, as a function of the natural logarithm of the 30-day mortality odds ratio. The square with the horizontal bars indicates the natural logarithm of the pooled 30-day mortality odds ratio with the 95%-confidence interval. The funnel plot shows an asymmetrical distribution of the data points, indicating that publication bias may be present. In the lower right-hand corner, studies appear to be missing. This suggests that small studies with higher mortality rates for endovascular repair than for open surgery are underrepresented. ● = studies.

DISCUSSION

In this systematic review, we reviewed and compared 10 articles that reported results of both endovascular repair and open surgery in patients treated for ruptured AAA. The results of our review demonstrated lower 30-day mortality and less postoperative systemic complications after endovascular repair than after open surgery. Among patients included in the studies, however, heterogeneity was found in patients' hemodynamic condition upon their presentation to the hospital. Because a hemodynamic unstable condition may result in poorer clinical outcome (22-24), we calculated a 30-day mortality odds ratio adjusted for patients' hemodynamic condition. After adjustment, a benefit in 30-day mortality for endovascular repair compared to open surgery, was still demonstrated, however, the benefit was reduced and was not statistically significant anymore.

Caution must be exercised when interpreting the results of this review. The principal limitation of our study was that no randomized controlled clinical trials were included and that only observational studies were available. Systematic reviews of observational studies may be a better representation of daily clinical practice than randomized controlled trials . In the comparison of therapies, however, it means that the studies included may have suffered from selection bias. The decision to treat patients with a ruptured AAA with endovascular repair or open surgery was based on patients' hemodynamic condition upon presentation to the hospital, anatomical considerations, and/or logistic reasons, such as availability of adequate endovascular equipment and sufficiently trained staff. A selection based on patients' hemodynamic condition may result in poorer clinical outcomes for open surgery, which was confirmed by our analysis in which we adjusted 30-day mortality for this condition. The effect of potential bias due to other selection criteria remains unknown, but is likely to be in favor of endovascular repair.

Other major limitations of our review, as with many reviews, are variation in definitions and protocols across the studies and the quality of reported data. Across the studies in our review, procedure protocols varied, type of grafts used varied, definitions of characteristics and clinical outcomes varied, and sometimes definitions or data were not reported. This lack of standardization in treatment protocol and reporting data complicated the comparison of endovascular repair and open surgery. In addition, over two times as many patients were treated with open surgery as with endovascular repair and complications. Furthermore, data on in-hospital complications for both treatment groups were reported in only 5 of 10 included studies and data on follow-up were only available for patients treated with endovascular repair in 5 of 10 included studies. Nevertheless, showing the data of the studies in a systematic way and performing analyses with adjustment for a major confounder demonstrated current status of treatment management for patients with a ruptured AAA.

Our study may have been affected by publication bias (i.e. the greater likelihood of publication of positive results or results based on large sample sizes). To investigate this bias we constructed a funnel plot. Our funnel plot was not symmetrically shaped, small studies with higher mortality rates for endovascular repair than for open surgery seemed to be underrepresented, which may have favored endovascular repair. It should be noted that our literature search was thorough; therefore it is unlikely that we missed relevant articles. We did, however, limit our search to the English language literature, based on a report that demonstrated that literature searches limited to the English literature often produce results that are close to results produced by comprehensive searches with no language restriction (28, 29).

Unfortunately, only small numbers are available for follow-up and the studies in our review did not report long-term follow-up. Thus, uncertainty remains concerning the long-term effectiveness of endovascular repair for patients with a ruptured AAA. In the long-run, threats to the effectiveness of endovascular repair are endoleaks, thrombosis, stenosis, and graft migration (30, 31). Therefore, a clinical benefit due to the favorable short-term results of endovascular repair compared to open surgery may be negated when long-term follow-up is taken into account. Recently this was demonstrated in randomized controlled trials comparing clinical effectiveness of elective endovascular repair compared to open surgery in patients with asymptomatic AAAs. The results of these trials suggested that the short-term reduction in mortality for patients treated with endovascular repair was not sustained after two years of follow-up (6, 7). In addition, in a time of budget constraints, costs or cost-effectiveness of a new therapy compared to the traditional therapy may influence treatment policy. Of note, a recently performed study on the costs of endovascular repair versus open surgery in patients with acute AAAs showed that endovascular repair was cost saving compared to open surgery, even after one-year follow-up (32).

Furthermore, to avoid selection bias and enhance the comparability between the two treatments, hemodynamically unstable patients should be excluded from the analysis. This will increase the homogeneity between patients treated with endovascular repair and patients treated with open surgery. Ideally, logistic reasons to treat patients with open surgery instead of endovascular repair should be avoided by having trained staff 24 hours a day, 7 days per week on call and adequate endovascular equipment on stock. To enable combining results of different studies reporting on endovascular repair and open surgery in patients with a ruptured AAA in a meta-analysis, we would recommend that researchers describe patient and procedure characteristics, and selection criteria for endovascular repair in accurate detail (33-35).

In conclusion, after adjustment for patients' hemodynamic condition upon presentation, a benefit in 30-day mortality for endovascular repair compared to open surgery for patients with a ruptured AAA was observed but was not statistically significant. For the decision whether patients

with ruptured AAA should be treated with endovascular repair or open surgery, more research is needed, especially larger series and longer follow-up with adequate reporting of data.

REFERENCES:

1. Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. Lancet 1994; 344:1645.
2. Leon LR, Jr., Labropoulos N, Laredo J, Rodriguez HE, Kalman PG. To what extent has endovascular aneurysm repair influenced abdominal aortic aneurysm management in the state of Illinois? J Vasc Surg 2005; 41:568-574.
3. Hinchliffe RJ, Yusuf SW, Macierewicz JA, MacSweeney ST, Wenham PW, Hopkinson BR. Endovascular repair of ruptured abdominal aortic aneurysm--a challenge to open repair? Results of a single centre experience in 20 patients. Eur J Vasc Endovasc Surg 2001; 22:528-534.
4. van Sambeek MR, van Dijk LC, Hendriks JM, et al. Endovascular versus conventional open repair of acute abdominal aortic aneurysm: feasibility and preliminary results. J Endovasc Ther 2002; 9:443-448.
5. Veith FJ, Ohki T. Endovascular approaches to ruptured infrarenal aorto-iliac aneurysms. J Cardiovasc Surg (Torino) 2002; 43:369-378.
6. Blankensteijn JD, de Jong SE, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005; 352:2398-2405.
7. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005; 365:2179-2186.
8. Peppelenbosch N, Yilmaz N, van Marrewijk C, et al. Emergency treatment of acute symptomatic or ruptured abdominal aortic aneurysm. Outcome of a prospective intent-to-treat by EVAR protocol. Eur J Vasc Endovasc Surg 2003; 26:303-310.
9. Reichart M, Geelkerken RH, Huisman AB, van Det RJ, de Smit P, Volker EP. Ruptured abdominal aortic aneurysm: endovascular repair is feasible in 40% of patients. Eur J Vasc Endovasc Surg 2003; 26:479-486.
10. Resch T, Malina M, Lindblad B, Dias NV, Sonesson B, Ivancev K. Endovascular repair of ruptured abdominal aortic aneurysms: logistics and short-term results. J Endovasc Ther 2003; 10:440-446.
11. Alsac JM, Desgranges P, Kobeiter H, Becquemin JP. Emergency endovascular repair for ruptured abdominal aortic aneurysms: feasibility and comparison of early results with conventional open repair. Eur J Vasc Endovasc Surg 2005; 30:632-639.
12. Brandt M, Walluscheck KP, Jahnke T, Graw K, Cremer J, Muller-Hulsbeck S. Endovascular repair of ruptured abdominal aortic aneurysm: feasibility and impact on early outcome. J Vasc Interv Radiol 2005; 16:1309-1312.
13. Castelli P, Caronno R, Piffaretti G, et al. Ruptured abdominal aortic aneurysm: endovascular

treatment. Abdom Imaging 2005; 30:263-269.
14. Kapma MR, Verhoeven EL, Tielliu IF, et al. Endovascular treatment of acute abdominal aortic aneurysm with a bifurcated stentgraft. Eur J Vasc Endovasc Surg 2005; 29:510-515.
15. Larzon T, Lindgren R, Norgren L. Endovascular treatment of ruptured abdominal aortic aneurysms: a shift of the paradigm? J Endovasc Ther 2005; 12:548-555.
16. Vaddineni SK, Russo GC, Patterson MA, Taylor SM, Jordan WD, Jr. Ruptured abdominal aortic aneurysm: a retrospective assessment of open versus endovascular repair. Ann Vasc Surg 2005; 19:782-786.
17. Franks S, Lloyd G, Fishwick G, Bown M, Sayers R. Endovascular treatment of ruptured and symptomatic abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31:345-350.
18. Stone PW. Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res 2002; 15:197-198.
19. ISI Web of Knowledge: Web of Science. Available at: http://portal.isiknowledge.com/. Date accessed January 2006.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188.
21. Begg CB, JA. B. Publication bias: a problem in interpreting medical data. J R Statist Soc. 1988; 151:419-463.
22. Johansen K, Kohler TR, Nicholls SC, Zierler RE, Clowes AW, Kazmers A. Ruptured abdominal aortic aneurysm: the Harborview experience. J Vasc Surg 1991; 13:240-245.
23. Halpern VJ, Kline RG, D'Angelo AJ, Cohen JR. Factors that affect the survival rate of patients with ruptured abdominal aortic aneurysms. J Vasc Surg 1997; 26:939-945.
24. Turton EP, Scott DJ, Delbridge M, Snowden S, Kester RC. Ruptured abdominal aortic aneurysm: a novel method of outcome prediction using neural network technology. Eur J Vasc Endovasc Surg 2000; 19:184-189.
25. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. Cardiovasc Drugs Ther 2002; 16:75-77.
26. Lloyd-Williams F, Mair F, Shiels C, et al. Why are patients in clinical trials of heart failure not like those we see in everyday practice? J Clin Epidemiol 2003; 56:1157-1162.
27. Hordijk-Trion M, Lenzen M, Wijns W, et al. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. Eur Heart J 2006; 27:671-678.
28. Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technol Assess 2003; 7:1-76.
29. Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. Health Technol Assess 2003; 7:1-90.
30. Sampram ES, Karafa MT, Mascha EJ, et al. Nature, frequency, and predictors of secondary procedures after endovascular repair of abdominal aortic aneurysm. J Vasc Surg 2003; 37:930-937.

31. Hobo R, Buth J. Secondary interventions following endovascular abdominal aortic aneurysm repair using current endografts. A EUROSTAR report. J Vasc Surg 2006; 43:896-902.
32. Visser JJ, van Sambeek MR, Hunink MG, et al. Acute abdominal aortic aneurysms: cost analysis of endovascular repair and open surgery in hemodynamically stable patients with 1-year follow-up. Radiology 2006; 240:681-689.
33. A proposal for structured reporting of randomized controlled trials. The Standards of Reporting Trials Group. Jama 1994; 272:1926-1931.
34. Checklist of information for inclusion in reports of clinical trials. The Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature. Ann Intern Med 1996; 124:741-743.
35. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. Jama 1996; 276:637-639.

3
CLINICAL OUTCOMES WITH 1-YEAR FOLLOW-UP

ABSTRACT

Objective: To compare the clinical outcomes of treatment after endovascular repair and open surgery in patients with ruptured infrarenal abdominal aortic aneurysms (AAAs) including one-year follow-up.

Materials and methods: All consecutive conscious patients with ruptured infrarenal AAAs who presented to our tertiary-care teaching hospital between January 1, 2001 and December 31, 2005 were included in this study (n = 55). Twenty-six patients underwent endovascular repair and 29 patients underwent open surgery. Patients who were hemodynamically too unstable to undergo a computed tomography scan were excluded. Outcomes evaluated were intra-operative mortality, 30-day mortality, systemic complications, complications requiring surgical intervention, and mortality and complications during one-year follow-up. The statistical tests we used were student t-test, $\chi 2$-test, Fisher's Exact-Test, and Mann Whitney U-test (two-sided, $\alpha = 0.05$).

Results: Thirty-day mortality was 8/26 (31%) for patients who underwent endovascular repair and 9/29 (31%) for patients who underwent open surgery ($p = 0.98$). Systemic complications and complications requiring surgical intervention during the initial hospital stay were similar in both treatment groups (8/26 (31%) and 5/26 (19%) for endovascular repair, respectively, and 9/29 (31%) and 8/29 (28%) for open surgery, respectively, $p > 0.40$). During one-year follow-up, two patients initially treated with endovascular repair died due to non-aneurysm related causes; no deaths occurred in the open surgery group. Complications during one-year follow-up were 1/20 (5%) for endovascular repair and 4/25 (16%) for open surgery ($p = 0.36$).

Conclusion: Based on our study with a highly selective population, the mortality and complication rates after endovascular repair may be similar compared to after open surgery in patients treated for ruptured infrarenal AAAs.

INTRODUCTION

Mortality in patients with a ruptured abdominal aortic aneurysm (AAA) treated with open surgery remains high. Among patients who arrive in the hospital alive and undergo open surgery, the reported mortality rates vary between 32% and 70%, and the morbidity rates vary between 30% and 50% (1, 2). Since 1994, endovascular aneurysm repair in patients with a ruptured AAA has been proven to be feasible (3). Recently, this technique has become routine practice in Europe, and it is increasingly performed in the United States. Several studies have demonstrated a reduction in mortality and morbidity rates of endovascular repair compared with conventional open surgery in patients with ruptured AAAs (4-16). Most of these studies, however, included hemodynamically unstable patients in the open surgery group, whereas in the endovascular group mostly hemodynamically stable patients were included. To assess the clinical effectiveness of endovascular repair and open surgery in patients with a ruptured AAA, it is essential to compare both treatments in a homogeneous group of patients. Therefore, in the absence of a randomized controlled clinical trial, we compared endovascular repair and open surgery in patients who were hemodynamically stable enough to undergo a computed tomography (CT)-scan before the procedure.

Several advantages and disadvantages of endovascular repair over open surgery exist. Important advantages of endovascular repair are potential avoidance of general anesthesia and minimization of invasiveness. During endovascular repair, the aorta is not clamped, and blood loss is considerably less than with open surgery. Patients treated with endovascular repair, however, are expected to have complications in the long run as a result of graft failure, such as endoleak and graft migration (17-21). Therefore, follow-up after endovascular repair is essential. Patients treated with open surgery may have more severe complications during and immediately after the procedure, such as bleeding, cardiac and pulmonary complications, and ischemia of the sigmoid, whereas during follow-up complications are rare after open surgery. Thus, to evaluate the clinical effectiveness of both procedures, it is important to determine these complications both during the hospital stay and during follow-up.

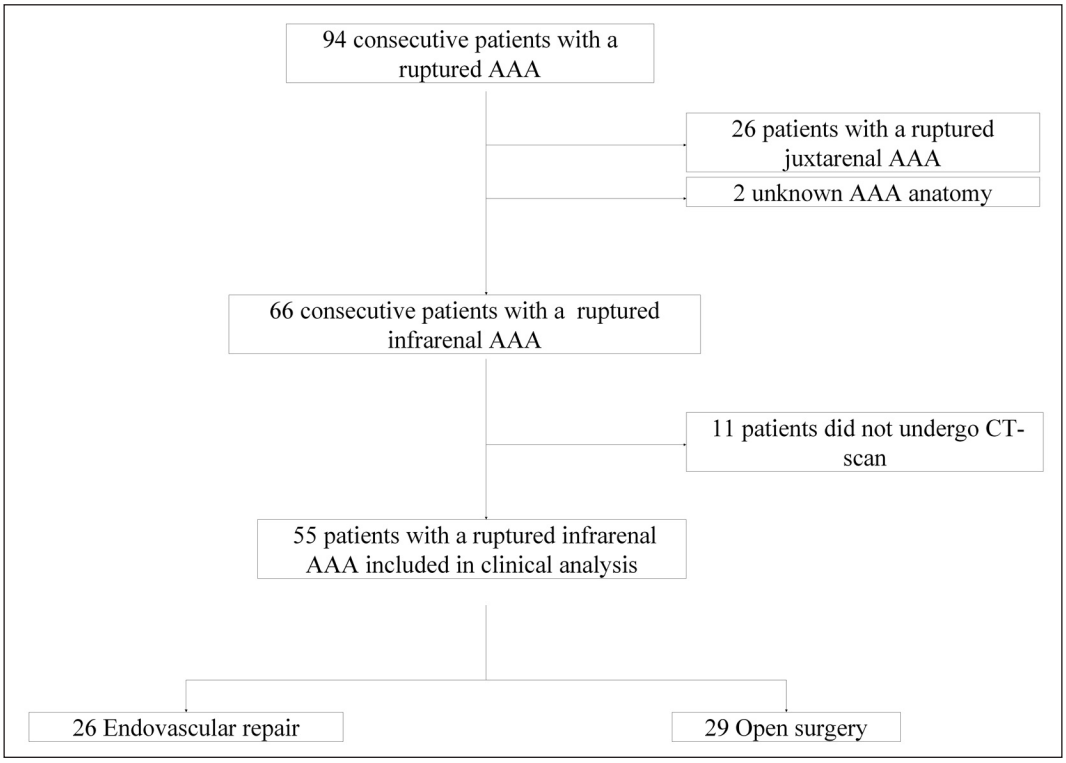
The objective of our study was to compare the clinical outcomes of treatment after endovascular repair and open surgery in patients with ruptured infrarenal AAAs, including 1-year follow-up.

MATERIALS AND METHODS

Patients and protocol

All consecutive patients treated for a ruptured AAA in our university-based tertiary care center between January 1, 2001 and December 31, 2005 were evaluated (n = 94). The study period started from 2001, because January 2001 marked the initiation of endovascular repair of ruptured AAAs in our hospital. To make comparable groups of patients treated with endovascular repair and patients treated with open surgery, we excluded patients with a juxtarenal or suprarenal AAA (necessitating suprarenal clamping; n = 26), those with an AAA unknown AAA anatomy (n = 2), and those who were hemodynamically too unstable (i.e., systolic blood pressure < 70 millimeter Mercury and no adequate verbal reply) and therefore were unable to undergo a CT-scan before the procedure (n = 11; Figure 1).

Figure 1: Flowchart of patients with a ruptured Abdominal Aortic Aneurysm (AAA) included in analysis.



CT = computed tomography

Hemodynamically too unstable patients (n = 11) were immediately transported to the operating room, where they all underwent open surgery. In this study, 55 patients with ruptured infrarenal AAAs were included in the analysis.

The records of all patients with a ruptured AAA were identified from the medical registry by using operation codes. These codes are valid for our institution specifically. Patient data were obtained partly retrospectively and partly prospectively. Retrospectively data were retrieved from a computerized hospital database and, subsequently, from medical records. To obtain information about patients' readmissions, we verified patients' medical records and the computerized database of our hospital or of the hospital to which they were readmitted. From December 2004 onward, patients (n = 16) were prospectively enrolled in our study. Institutional Review Board approval was obtained, and informed consent to verify patient data was waived because we analyzed only patient data documented as part of routine clinical care and collected from the medical records. Note that in The Netherlands, patients' formal written informed consent is not obtained for good clinical practice. Use of new or emerging therapies can be applied after Institutional Review Board approval of the hospital.

Once the emergency department was informed that a patient with a ruptured AAA was in transport to the hospital, a team consisting of a vascular surgeon, an interventional radiologist, and an anesthesiologist was waiting for the patient in the emergency room. This team was available 24 hours a day, 7 days a week. Upon the patient's arrival in the emergency room, an abdominal ultrasound scan was performed to confirm the diagnosis of an AAA. Furthermore, an electrocardiogram was performed, and laboratory findings were assessed to determine the patient's clinical condition. Hemodynamically stable patients were transported to the CT-suite to perform an abdominal CT-scan to assess whether the AAA was ruptured or not and to decide whether the AAA was suitable for endovascular repair. An infrarenal AAA was considered ruptured in the presence of leakage on the preoperative CT-scan. The anatomic inclusion criteria for endovascular repair were a proximal neck >15 millimeter, neck diameter < 28 millimeter, angulation < 90°, and accessibility of the iliac arteries. After the CT-scan confirmed rupture of the AAA, the patient was immediately transported to the operating room, where endovascular repair was performed if the AAA was suitable; otherwise, open surgery was performed. In our protocol, the decision to treat patients with endovascular repair or open surgery was not based on intraoperative aortography only. Hemodynamically too unstable patients (n = 11) were immediately transported to the operating room for open surgery and were excluded from this analysis. The median time interval between arrival in the emergency room and arrival in the operating room was 43 minutes (range, 15 minutes to 59 hours) for patients with a ruptured AAA. In total, in our analysis we included 55 patients with a ruptured infrarenal AAA. One-year follow-up was completed for 45 patients who underwent operation between January 1, 2001, and December 31, 2005.

In patients treated with endovascular repair, 1 Cook (Zenith, Bloomington, Ind) and 24 Excluder (Gore, Flagstaff, Ariz) endografts were used. In patients treated with open surgery, Sulzer/Terumo (Vascutek, Renfrewshire, Scotland) vascular prostheses were used. In our local setting, a large variety of endografts and vascular prostheses is on stock. Endovascular repair of a ruptured AAA was performed in the operating room by a vascular surgeon (four involved; on average, 4 years of experience in endovascular AAA repair and 20 years of experience in open AAA repair, as of 2001) and an interventional radiologist (two involved; on average, 4 years of experience in endovascular AAA repair, as of 2001). Patients with ruptured AAAs who underwent endovascular repair preferentially received local or regional anesthesia. According to our protocol, we accepted hypotension (i.e., systolic blood pressure < 90 millimeter Mercury) without massive fluid resuscitation (permissive hypotension) in order to prevent further bleeding. Patients treated with open surgery received general anesthesia. In patients treated with endovascular repair, a groin cut down was performed to obtain access to the common femoral artery. A bifurcated endograft was preferentially used. If iliac occlusions were present on one side, an aorto-mono-iliac endograft was used. The first intraoperative angiography was performed only after the main body of the endograft was introduced. After completion of the endovascular procedure, control angiography was performed to exclude a type I or type III endoleak. A CT-scan was performed before discharge to assess complete exclusion of the AAA. If an endoleak was seen on the predischarge CT-scan, a reintervention was scheduled, and the patient was treated within 1 month. The management of early endoleaks was similar after ruptured AAA repair and after intact AAA repair.

During follow-up, for patients who underwent endovascular repair, physician visits, and CT-scans were scheduled 3, 6, and 12 months after the initial procedure. For patients who underwent open surgery, physician visits were scheduled at 3 and 6 months, and at 6 months an ultrasound scan was performed.

Clinical outcomes

The outcomes evaluated were intraoperative mortality, 30-day mortality, systemic complications, complications necessitating surgical intervention, and mortality and complications during 1-year follow-up. Surgical interventions included tracheostomy, bowel resection, and surgical evacuation of an access site hematoma or infection.

We defined relevant comorbidity factors for patients with a ruptured infrarenal AAA based on published covariates in the literature (22-25). Comorbidity was assessed by one author by using the patients' medical history. Patients were stratified using the Lee risk index (26). This index was used to identify patients at higher risk for cardiac complications after the procedure. Patients were assigned to risk class II, III, or IV, depending on the presence of a set of risk factors. Patients in a higher risk class had a greater risk of cardiac complications after the procedure than those in a lower risk class. Diabetes mellitus was defined as receiving either oral medication and/or

insulin therapy for diabetes mellitus. Ischemic heart disease included angina pectoris and myocardial infarction in the medical history. Congestive heart failure included symptoms of congestive heart failure and receipt of medication for this diagnosis. History of a cerebrovascular event included stroke or transient ischemic attack. Hypertension included a systolic blood pressure ≥ 140 millimeter Mercury and/or a diastolic blood pressure ≥ 90 millimeter Mercury and receipt of at least one antihypertensive drug. Renal dysfunction included a creatine level > 2.0 milligram per deciliter. Chronic pulmonary disease included a forced expiratory volume in 1 second < 70%. Complications were identified by using the "Reporting Standards for Endovascular Aortic Aneurysm Repair" of Chaikof et al (27).

Data analysis

Patient and lesion characteristics, procedure data, and clinical outcomes during hospital stay and 1-year follow-up of patients with ruptured AAAs who underwent endovascular repair and open surgery were compared by using the Student t-test, $\chi 2$-test, Fisher's Exact-Test, and Mann Whitney U-test (two-sided; $\alpha = 0.05$). For data with a skewed distribution, we reported the median. Clinical results were calculated by taking all patients with a ruptured AAA (n = 55) into account, including patients who died. Data on mortality and morbidity were complete for all included patients. A few items related to the patient and procedure characteristics, however, were missing. In the tables, we identified the missing data; in total, < 1% of the data were missed. Analyses were performed by using Microsoft Excel 2000 (Microsoft Corporation, Redmond, Wash), and SPSS for Windows Version 11.0.1 (SPSS Inc., Chicago, Ill).

RESULTS

Patient characteristics

Patient and lesion characteristics are listed in Table 1.

The mean AAA diameter was similar for patients who underwent endovascular repair and for those who received open surgery (74 millimeter versus 76 millimeter ($p = 0.64$) for endovascular repair and open surgery, respectively). Reasons to treat patients with open surgery were neck too short (n = 10), too much mural thrombus neck (n = 1), neck angulation > 90° (n = 5), conical neck (n = 4), inaccessible iliac tract (n = 4), aneurysm iliac tract (n = 2), and logistic reasons (n = 3). Upon arrival in the emergency room, four patients had systolic blood pressures < 90 millimeter Mercury (although they were not hemodynamically unstable), of whom two were treated with open surgery and two with endovascular repair.

Table 1: Patient and lesion characteristics in patients with a ruptured Abdominal Aortic Aneurysm (n = 55)

	Endovascular repair n = 26	Open surgery n = 29	P - value
Mean age in years (SD)	72.5 (8.4)	73.9 (7.9)	0.53
Male	25 (96%)	28 (97%)	0.51
Mean AAA diameter in mm (SD)	74 (13)	76 (16)	0.61
Diabetes mellitus	1 (4%)	0 (0%)	0.47
Ischemic heart disease*	7 (27%)	6 (21%)	0.64
Congestive heart failure*	2 (8%)	1 (4%)	0.37
History of CVA*	4 (15%)	2 (7%)	0.22
Hypertension*	13 (50%)	12 (43%)	0.60
Renal dysfunction*	5 (19%)	2 (7%)	0.14
Chronic pulmonary disease*	7 (27%)	5 (18%)	0.42
Systolic blood pressure < 90 mmHg†	2 (8%)	2 (7%)	0.39
Medication			
Beta-blockers‡	6 (25%)	8 (29%)	0.77
Statins§	4 (16%)	0 (0%)	0.04
Antiplatelet agents§	4 (16%)	9 (32%)	0.17
ACE inhibitors§	5 (20%)	4 (14%)	0.25
Calcium-channel blockers§	0 (0%)	2 (7%)	0.27
Anticoagulants§	5 (20%)	3 (11%)	0.20

SD = standard deviation, mm = millimeter, CVA = cerebrovascular accident, mmHg = millimeter Mercury, ACE = angiotensin converting enzyme
* These data were missing for one patient who underwent open surgery.
† Upon arrival in the emergency room.
‡ No information on the use of beta-blockers was available for two patients who underwent endovascular repair and for one who underwent open surgery.
§ These data were missing for one patient who underwent endovascular repair and for one who underwent open surgery.

Procedure

Table 2 shows procedure characteristics.

Of all patients treated with endovascular repair, two patients were converted to open surgery during the procedure because of persistent blood loss, and one patient underwent a decompression laparotomy for an abdominal compartment syndrome. All three of these patients died. Of the patients with persistent blood loss, the patient with persistent blood loss due to profuse bleeding of the lumbar arteries died during the procedure (i.e., intraoperative mortality rate was 1 of 26 (4%) patients), and the patient with persistent blood loss due to a tear in the aortic wall near the proximal attachment died within 4 hours after the procedure. The patient with abdomi-

Table 2: Procedure data in patients with a ruptured Abdominal Aortic Aneurysm

	Endovascular repair n = 26	Open surgery n = 29	P - value
General anesthesia	12 (46%)	29 (100%)	<0.001
Tubular graft	1 (4%)*	19 (66%)*	<0.001
Bifurcated graft	24 (92%)*	9 (31%)*	<0.001
Conversion to open surgery during initial procedure	3 (12%)	-	-
Technical failure during initial procedure	4 (15%)	-	-
Additional procedures during initial procedure	0 (0%)	5 (17%)	0.04
Intraoperative mortality	1 (4%)	4 (14%)	0.18
Median blood loss in ml (range)	<100 (<100-30000)	6750 (<100-31000)	<0.001
Median transfusions units e.c. (range)	1.5 (0-27)	10 (0-31)	<0.001
Median transfusions units FFP (range)	0 (0-20)	10 (0-45)	<0.001
Median transfusions units platelet (range)	0 (0-15)	5 (0-20)	<0.001
Median procedure time (range)	149 (79-400)	232 (40-434)	<0.001

ml = milliliter, e.c. = erytrocytes concentrate, FFP = fresh frozen plasma
* In one patient who underwent endovascular repair no access was obtained because of calcified iliac arteries. This patient refused conversion to open surgery and subsequently died; one patient who underwent open surgery died before graft placement.

nal compartment syndrome died 13 days after the initial procedure as a result of sepsis. In addition to these three conversions, one failure occurred because no access was obtained as a result of calcified iliac arteries. Conversion to open surgery was offered to this patient, but she refused open surgery and subsequently died. One patient initially treated with endovascular repair underwent a decompression laparotomy 7 hours after the initial procedure because of a suspected abdominal compartment syndrome. This patient died 4 days after the initial procedure as a result of respiratory insufficiency. No additional procedures were performed during endovascular repair.

During open surgery, four of 29 (14%) patients died as a result of persisting blood loss (coagulopathy leading to continued bleeding (n = 1), nonidentifiable venous bleeding (n = 1), diffuse bleeding after admitting heparine and local thrombolysis with medicinase (n = 1), and bleeding leading to no cardiac output (n = 1)). Additional procedures were performed in five patients during open surgery: resection of the sigmoid (n = 2), thrombectomy of the superficial femoral artery (n = 1), local endarterectomy of the common femoral artery (n = 1), and treatment of a scrotal hernia (n = 1). The median blood loss was lower with endovascular repair compared with that with open surgery (< 100 milliliter versus 6750 milliliter; $p < 0.001$).

Outcomes

In total, 8 of 26 (31%) patients and 9 of 29 (31%) patients treated with endovascular repair and open surgery, respectively, died within 30 days after the initial procedure (p = 0.98; Table 3).

Table 3: Mortality, complications, and admissions in patients with a ruptured Abdominal Aortic Aneurysm

	Endovascular repair n = 26	Open surgery n = 29	P - value
Intraoperative mortality	1 (4%)	4 (14%)	0.18
30-day mortality	8 (31%)	9 (31%)	0.98
Complications requiring surgical intervention*	5 (19%)	8 (28%)	0.47
Systemic complications†	8 (31%)	9 (31%)	0.98
Access site hematoma‡	2 (8%)	3 (10%)	0.34
Access site infection§	0 (0%)	3 (10%)	0.14
Cardiac complications¶	3 (12%)	1 (3%)	0.22
Pulmonary complications‖	2 (8%)	2 (7%)	0.39
Pulmonary embolism**	2 (8%)	1 (3%)	0.36
Renal complications††	0 (0%)	1 (3%)	0.53
Sepsis	3 (12%)	3 (10%)	0.33
Deep venous thrombosis**	0 (0%)	2 (7%)	0.27
Bowel ischemia‡‡	1 (4%)	2 (7%)	0.40
Endoleak	5 (19%)§§	-	-
Mean (SD), median			
Postoperative days in the ICU	4.3 (8.6), 0.9	11.7 (15.0), 5.5	0.01
Postoperative days in hospital	10.9 (17.4), 4.0	26.7 (28.3), 15.3	0.003

SD = standard deviation, ICU = intensive care unit
* Complications requiring surgical intervention included surgical evacuation of an access site hematoma or infection, tracheostomy, and bowel resection.
† Systemic complications included cardiac arrest, progressive heart failure with fatal outcome, pulmonary complications requiring tracheostomy or with fatal outcome, pulmonary embolism requiring anticoagulation therapy or with fatal outcome, renalcomplications requiring temporary dialysis, sepsis, and deep venous thrombosis.
‡ requiring surgical evacuation.
§ requiring operative drainage.
¶ cardiac arrest and progressive heart failure with fatal outcome.
‖requiring tracheostomy or pulmonary complications with fatal outcome.
** requiring anticoagulation therapy or with fatal outcome.
†† requiring temporary dialysis.
‡‡ requiring bowel resection.
§§ One patient had a type 1 endoleak and was treated within one month after the initial procedure One patient had a type 3 endoleak and was treated two months after the initial procedure. Three patients had type 2 endoleaks. They were treated conservatively and their endoleaks disappeared spontaneously. None of these 3 patients were treated for endoleaks during one-year follow-up.

In addition to the patient who died intraoperatively during endovascular repair, 7 patients died within 30 days. The causes of postoperative death were persistent blood loss (i.e., due to a tear

in the aortic wall near the proximal attachment; n = 1), sepsis (n = 1), respiratory insufficiency (n = 1), pulmonary embolism (n = 1), ventricular fibrillation (n = 1), progressive heart failure (n = 1), and technical failure of the endovascular procedure with refusal of conversion to open surgery, leading to death (n = 1). During the hospital stay, one patient who underwent endovascular repair died 35 days after the initial procedure as a result of sepsis. In addition to the 4 patients who died intraoperatively during open surgery, 5 patients died within 30 days. The causes of postoperative death were septic shock (n = 2), renal insufficiency (n = 1), respiratory insufficiency (n = 1), and progressive heart failure (n = 1). During the hospital stay, one patient who underwent open surgery died 109 days after the initial procedure as a result of the inability to wean the patient from mechanical ventilation.

Systemic complications and complications necessatating surgical intervention were not different between treatment groups. In patients treated with endovascular repair, 1 patient required tracheotomy for respiratory failure. In patients treated with open surgery, 2 patients required tracheotomy for respiratory failure. Table 3 shows postoperative complications in more detail. The mean postoperative days in the intensive care unit (ICU) was 4.3 and 11.7 for endovascular repair and open surgery, respectively (p = 0.01). In total, the mean number of postoperative days in the hospital was 10.9 for endovascular repair and 26.7 for open surgery (p = 0.003; Table 3). In the endovascular repair group, one patient was discharged to a nursing hospital. In the open surgery group, three patients were discharged to a nursing hospital.

In table 4 we stratified 30-day mortality and systemic complications by the Lee risk index.

Table 4: In-hospital systemic complications and 30-day mortality in patients with a ruptured Abdominal Aortic Aneurysm stratified by the Lee risk index

Endovascular repair			Open surgery		
Lee risk index	**30-day mortality**	**Systemic complications***	**Lee risk index**	**30-day mortality**	**Systemic complications***
Class II (n=13)	4 (31%)	5 (38%)	**Class II (n=19)**	4 (21%)	4 (21%)
Class III (n=8)	3 (38%)	2 (25%)	**Class III (n=7)**	3 (43%)	3 (43%)
Class IV (n=5)	1 (20%)	1 (20%)	**Class IV (n=2)**	1 (50%)	1 (50%)
Missing (n=0)	0	0	**Missing (n=1)**	1	1

* Systemic complications included cardiac arrest, progressive heart failure with fatal outcome, pulmonary complications requiring tracheostomy, pulmonary embolism requiring anticoagulation therapy, renal complications requiring temporary dialysis, sepsis, and deep venous thrombosis.

For patients in Lee risk class II (i.e., those at a lower risk for cardiac complications), 30-day mortality and systemic complication rates were higher for endovascular repair compared with open surgery, although not statistically significant. For patients in Lee risk class III and IV (i.e., those at

a higher risk for cardiac complications), 30-day mortality and systemic complication rates were lower for endovascular repair compared with open surgery (Table 4).

One-year follow-up

One-year follow-up was completed for 45 (82%) of 55 patients (Table 5).

Table 5: One-year follow-up of patients with a ruptured Abdominal Aortic Aneurysm

	Endovascular repair n = 20	Open surgery n = 25	P - value
Patients at risk	14	16	-
Median number of visits (range)	2.0 (0-6)	2.0 (0-6)	0.66
Median number of CTA's (range)	1.5 (0-3)	0.0 (0-1)	< 0.001
New diagnosed endoleaks*	2 (10%)	-	-
Complications†	1 (5%)	4 (16%)	0.21
Readmissions	1 (5%)‡	2 (8%)	0.42
Died during follow-up	2 (10%)§	0 (0%)	0.19
Total deaths at one year follow-up	8 (40%)	9 (36%)	0.78

* Type 2 endoleaks diagnosed at 4 months; they were treated conservatively.
† After endovascular repair: a false aneurysm at 3 months, treated conservatively, n=1. After open surgery: aneurysm of the femoral artery at 4 months, readmitted for aneurysm repair, n=1; scar hernia at 6 months, treated conservatively, n=1; abdominal hernia at 7 months, treated conservatively, n=1; back pain suspected for aneurysm related problems at 8 months, readmitted, treated conservatively, n=1.
‡ This patient was readmitted for repair of a type 1 endoleak that was detected during the initial hospital stay.
§ Non-aneurysm related death.

During follow-up, two patients who were initially treated with endovascular repair died as a result of non-aneurysm related causes (i.e., pulmonary infection and cancer). One patient initially treated with endovascular repair and two patients initially treated with open surgery were readmitted to the hospital because of aneurysm-related complications. The patient treated with endovascular repair was readmitted for endovascular repair of a type 1 endoleak that was detected during the initial hospital stay. The patients treated with open surgery had aneurysm repair of the femoral artery and back pain suggestive of aneurysm-related problems.

Juxtarenal AAA and hemodynamically unstable patients

For patients with juxtarenal AAAs, the intraoperative mortality was 4/26 (15%) and the 30-day mortality was 9/26 (35%). One-year follow-up was completed for 25 patients, of whom 11 (44%) died within 1 year. For patients who were hemodynamically too unstable to undergo a CT-scan before the procedure, the intraoperative mortality was 1/11 (9%), and the 30-day mortality was 4/11 (36%). One-year follow-up was completed for 10 patients, of whom 5 (50%) died within 1 year.

DISCUSSION

Endovascular repair has become an increasingly performed alternative to open surgery in patients with ruptured infrarenal AAAs. In our study, we compared clinical outcomes of patients treated with endovascular versus patients treated with open surgery. In the absence of randomization, we focused our comparison on hemodynamically stable patients to make the treatment groups more homogeneous and the comparison more adequate. In our treatment groups, the selection between endovascular repair and open surgery was based on anatomic criteria. Patients who were eligible (i.e., had suitable anatomy) for endovascular repair received this treatment; patients whose aneurysm anatomy was not suitable for endovascular repair received open surgery. Note that, in our hospital, vascular surgeons and interventional radiologists are available 24 hours a day, 7 days a week, and that endografts are always on stock. The principal finding of our study was that 30-day mortality and morbidity were similar for endovascular repair and open surgery in patients with a ruptured AAA; this similarity was sustained after 1-year follow-up.

Results from the stratification suggested that patients with a lower risk for cardiac complications (i.e., Class II) had a better chance to survive and less morbidity after open surgery than after endovascular repair. In addition, patients with a higher risk for cardiac complications (i.e., Class III and IV) were better off with endovascular repair than with open surgery. It should be acknowledged that 50% of the patients treated with endovascular repair and 32% of the patients treated with open surgery were considered at high risk for cardiac complications (Class III and IV). Therefore, it seems that selection criteria other than aneurysms anatomy may have played a role in the treatment choice. It should be noted, however, that these thoughts are highly speculative because of the low number of patients and the highly selected population.

So far, to our knowledge, no randomized controlled trial comparing endovascular repair and open surgery in patients with ruptured AAAs has been published. In other studies comparing the outcomes of endovascular repair and open surgery in patients with a ruptured AAA, results showed lower mortality for endovascular repair than was found in our study (5-16). Most of these studies, however, did not report on patients' comorbidity. Therefore, it remains unclear whether this difference in mortality was due to differences in case mix. Furthermore, most other studies reported higher mortality rates for patients treated with open surgery compared with what we found. These studies included hemodynamically unstable patients who received open surgery and were not eligible for endovascular repair, whereas we excluded those patients. A recently published study in which the proportion of hemodynamically unstable patients was equal in both treatment groups showed similar results with our study (28). In addition, follow-up results reported in most other studies demonstrated more complications after endovascular repair than after open surgery because of graft related problems such as graft migration and endoleak,

whereas in our study, the complication rates in follow-up were similar for endovascular repair and open surgery (17-21).

The results of our study should be interpreted with caution because of several limitations. The patients in our study were not randomly assigned to endovascular repair and open surgery, the sample sizes of both treatment groups were small, and follow-up was limited to 1 year. Despite these limitations, however, our study was a first attempt for a fair comparison in a time when endovascular repair is increasingly performed and data on effectiveness are needed. It is clear that more research comparing endovascular repair with open surgery in patients with ruptured AAAs in larger series with longer follow-up is needed, as suggested in the long-term effectiveness of the trials in elective AAAs (29, 30). As far as we know, one randomized controlled trial is ongoing (31), but it may take years before results are available. Because endovascular repair is increasingly performed, data from solid research are needed at this time.

In addition, more research focusing on selection criteria and survival chances needs to be performed. As in our study, among patients initially treated with endovascular repair, two were converted to open surgery, and two underwent a decompression laparotomy. All of these patients died. Whether the patients' comorbidities, AAA anatomy, or the delay caused by first performing endovascular repair instead of open surgery played a role in their survival chances remains unknown. These findings, however, do emphasize the need for a predictive tool that can identify patients who may benefit from endovascular repair and those who are unlikely to benefit from this procedure.

In conclusion, on the basis of our study with a highly selected population, mortality and morbidity may be similar for patients with ruptured infrarenal AAAs treated with endovascular repair compared with open surgery, even after 1-year follow-up. In addition to the aneurysm anatomy, other criteria may be needed for endovascular repair to improve clinical outcomes. To obtain more evidence regarding whether endovascular repair or open surgery is better in selected patients with a ruptured infrarenal AAA, more research is needed.

REFERENCES

1. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. Br J Surg 2002; 89:714-730.
2. Bown MJ, Cooper NJ, Sutton AJ, et al. The postoperative mortality of ruptured abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2004; 27:65-74.
3. Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. Lancet 1994; 344:1645.

4. Greco G, Egorova N, Anderson PL, et al. Outcomes of endovascular treatment of ruptured abdominal aortic aneurysms. J Vasc Surg 2006; 43:453-459.
5. Franks S, Lloyd G, Fishwick G, Bown M, Sayers R. Endovascular treatment of ruptured and symptomatic abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31:345-350.
6. Vaddineni SK, Russo GC, Patterson MA, Taylor SM, Jordan WD, Jr. Ruptured abdominal aortic aneurysm: a retrospective assessment of open versus endovascular repair. Ann Vasc Surg 2005; 19:782-786.
7. Larzon T, Lindgren R, Norgren L. Endovascular treatment of ruptured abdominal aortic aneurysms: a shift of the paradigm? J Endovasc Ther 2005; 12:548-555.
8. Kapma MR, Verhoeven EL, Tielliu IF, et al. Endovascular treatment of acute abdominal aortic aneurysm with a bifurcated stentgraft. Eur J Vasc Endovasc Surg 2005; 29:510-515.
9. Hechelhammer L, Lachat ML, Wildermuth S, Bettex D, Mayer D, Pfammatter T. Midterm outcome of endovascular repair of ruptured abdominal aortic aneurysms. J Vasc Surg 2005; 41:752-757.
10. Alsac JM, Desgranges P, Kobeiter H, Becquemin JP. Emergency endovascular repair for ruptured abdominal aortic aneurysms: feasibility and comparison of early results with conventional open repair. Eur J Vasc Endovasc Surg 2005; 30:632-639.
11. Lee WA, Hirneise CM, Tayyarah M, Huber TS, Seeger JM. Impact of endovascular repair on early outcomes of ruptured abdominal aortic aneurysms. J Vasc Surg 2004; 40:211-215.
12. Resch T, Malina M, Lindblad B, Dias NV, Sonesson B, Ivancev K. Endovascular repair of ruptured abdominal aortic aneurysms: logistics and short-term results. J Endovasc Ther 2003; 10:440-446.
13. Reichart M, Geelkerken RH, Huisman AB, van Det RJ, de Smit P, Volker EP. Ruptured abdominal aortic aneurysm: endovascular repair is feasible in 40% of patients. Eur J Vasc Endovasc Surg 2003; 26:479-486.
14. Peppelenbosch N, Yilmaz N, van Marrewijk C, et al. Emergency treatment of acute symptomatic or ruptured abdominal aortic aneurysm. Outcome of a prospective intent-to-treat by EVAR protocol. Eur J Vasc Endovasc Surg 2003; 26:303-310.
15. Castelli P, Caronno R, Piffaretti G, et al. Ruptured abdominal aortic aneurysm: endovascular treatment. Abdom Imaging 2005; 30:263-269.
16. Brandt M, Walluscheck KP, Jahnke T, Graw K, Cremer J, Muller-Hulsbeck S. Endovascular repair of ruptured abdominal aortic aneurysm: feasibility and impact on early outcome. J Vasc Interv Radiol 2005; 16:1309-1312.
17. Tolia AJ, Landis R, Lamparello P, Rosen R, Macari M. Type II endoleaks after endovascular repair of abdominal aortic aneurysms: natural history. Radiology 2005; 235:683-686.
18. Prinssen M, Wixon CL, Buskens E, Blankensteijn JD. Surveillance after endovascular aneurysm repair: diagnostics, complications, and associated costs. Ann Vasc Surg 2004; 18:421-427.
19. Verhagen HJ, Prinssen M, Milner R, Blankensteijn JD. Endoleak after endovascular repair of ruptured abdominal aortic aneurysm: is it a problem? J Endovasc Ther 2003; 10:766-771.

20. van Marrewijk C, Buth J, Harris PL, Norgren L, Nevelsteen A, Wyatt MG. Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: The EUROSTAR experience. J Vasc Surg 2002; 35:461-473.
21. Laheij RJ, Buth J, Harris PL, Moll FL, Stelter WJ, Verhoeven EL. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR). Br J Surg 2000; 87:1666-1673.
22. Kertai MD, Boersma E, Klein J, van Urk H, Poldermans D. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. Arch Intern Med 2005; 165:898-904.
23. Kertai MD, Steyerberg EW, Boersma E, et al. Validation of two risk models for perioperative mortality in patients undergoing elective abdominal aortic aneurysm surgery. Vasc Endovascular Surg 2003; 37:13-21.
24. Shuhaiber JH, Hankins M, Robless P, Whitehead SM. Comparison of POSSUM with P-POSSUM for prediction of mortality in infrarenal abdominal aortic aneurysm repair. Ann Vasc Surg 2002; 16:736-741.
25. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, van Bockel JH, Eijkemans MJ, Habbema JD. Perioperative mortality of elective abdominal aortic aneurysm surgery. A clinical prediction rule based on literature and individual patient data. Arch Intern Med 1995; 155:1998-2004.
26. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043-1049.
27. Chaikof EL, Blankensteijn JD, Harris PL, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002; 35:1048-1060.
28. Peppelenbosch N, Geelkerken RH, Soong C, et al. Endograft treatment of ruptured abdominal aortic aneurysms using the Talent aortouniiliac system: an international multicenter study. J Vasc Surg 2006; 43:1111-1123.
29. Blankensteijn JD, de Jong SE, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005; 352:2398-2405.
30. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005; 365:2179-2186.
31. Acute endovascular treatment to improve outcome of ruptured aortoiliac aneurysms. In: ISRCTN66212637 Available at: http://www.trialregister.nl. Date accessed: October 25, 2006.

4
PREDICTION OF 30-DAY MORTALITY

ABSTRACT

Purpose: To validate the Glasgow Aneurysm Score (GAS) in patients with ruptured abdominal aortic aneurysms (AAAs) treated with endovascular repair or open surgery and to update the GAS into the Dutch Aneurysm Score (DAS) that predicts 30-day mortality for patients with ruptured abdominal aortic aneurysm (AAA) treated with endovascular repair or open surgery.

Materials and methods: In a multicenter prospective observational study, 233 consecutive patients with ruptured AAA were evaluated. All patients who were treated with endovascular repair (n = 58) or open surgery (n = 143) were included. The GAS was calculated for each patient. The area under the receiver operating characteristics curve (AUC) was used to indicate discriminative ability. We tested for interactions between risk factors and the procedure performed. The GAS was updated to predict 30-day mortality after endovascular repair or open surgery in patients with ruptured AAA using logistic regression analysis and resulted in the DAS.

Results: Thirty-day mortality was 15/58 (26%) for patients treated with endovascular repair and 57/143 (40%) for patients treated with open surgery (p = 0.06). The AUC for GAS was 0.686. No relevant interactions were found. The DAS (AUC = 0.683) can be calculated with the following formula: + 3 if hemodynamically unstable prior to the procedure - 9 for endovascular repair + age in years + 17 for shock + 7 for myocardial disease + 10 for cerebrovascular disease + 14 for renal disease.

Conclusion: We showed limited discriminative ability of the GAS and therefore updated the GAS by adding patients' hemodynamic stability prior to the procedure and the type of procedure performed. This DAS predicts 30-day mortality for patients with ruptured AAAs treated with endovascular repair or open surgery.

INTRODUCTION

The traditional approach to treat ruptured abdominal aortic aneurysms (AAA) is open surgery. The Glasgow Aneurysm Score (GAS) is used to predict in-hospital mortality after open surgery for patients with ruptured or unruptured AAA (1). Several studies have validated this prediction rule in patients with ruptured AAA treated with open surgery. Two validations reported good validity (2, 3) and one reported poor validity (4).

Since 1994, endovascular repair for ruptured AAA has been proven to be feasible (5) and is increasingly being adopted as the treatment of choice (6). Several studies showed a reduction in mortality and morbidity rates after endovascular repair compared to rates for open surgery in patients with ruptured AAAs (7-10); however, in other studies this reduction could not be confirmed (11-13). Recently, it was suggested that patients at higher risk for peri-procedural cardiac complications may benefit more from endovascular repair than from open surgery (13).

Due to the rise of endovascular repair, the patient population receiving open surgery has shifted in recent years, and the GAS may no longer be valid in this population. Additionally, the GAS cannot be used to decide whether a patient with a ruptured AAA may benefit more from endovascular repair or from open surgery, as it does not predict outcomes for endovascular repair patients. Whether the current GAS prediction rule is still valid in predicting 30-day mortality after open surgery and whether it can predict 30-day mortality after endovascular repair needs to be determined. Ideally, the GAS should be modified to identify patients who would be better suited for endovascular repair versus open surgery.

The purpose of our study was to validate the GAS in patients with ruptured AAA who were treated with endovascular repair or open surgery. In addition, we aimed to update the GAS into the Dutch Aneurysm Score (DAS) for prediction of 30-day mortality after endovascular repair or open surgery.

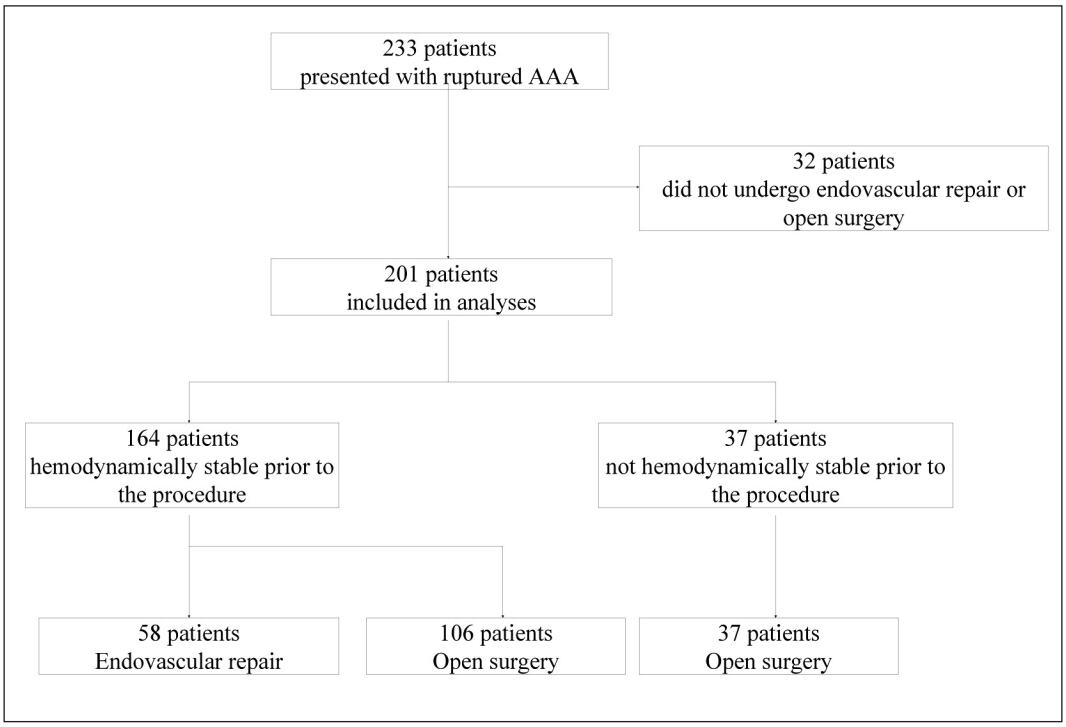
MATERIALS AND METHODS

Patient population

In a prospective multicenter observational study, data were collected on 233 consecutive patients between December 22, 2004 and October 31, 2006 in seven institutions in the Netherlands: Atrium Medical Center, Heerlen (45 patients), Catharina Hospital, Eindhoven (25 patients), Erasmus MC, Rotterdam (40 patients), Medical Spectrum Twente, Enschede (24 patients), Medical Center Rotterdam Zuid, Rotterdam (30 patients), University Medical Center, Groningen (37 patients), and University Medical Center, Nijmegen (32 patients). Patients were included if they pre-

sented with ruptured AAA and were treated with endovascular repair or open surgery (n = 201). A total of 32 of 233 patients (14%) were excluded because they died before AAA repair could be initiated; death was caused by severe comorbidity or the patient refused treatment (Figure 1).

Figure 1: Patient flowchart



Rupture of the AAA was confirmed on CT-scan or angiography prior to the procedure, or by free blood noted during laparotomy. The Institutional Review Board approved this study and waived the obligation to obtain informed consent due to the acute nature of the clinical problem and the observational nature of this study (14).

Protocol

In all participating hospitals, endovascular repair was the preferred treatment in patients with ruptured AAA. Except for in one hospital, the vascular surgeon and/or radiologist who performed endovascular repair of ruptured AAA were available 24 hours a day, 7 days a week. Upon arrival in the hospital, patients who were in a hemodynamically stable condition underwent an abdominal CT-scan or aortic angiography to confirm rupture and to assess whether the AAA was anatomically suited for endovascular repair. Hemodynamically unstable patients (n = 37) were immediately transported to the operating room for open surgery. The definition of "hemodynamically

stable" varied across the participating hospitals. In two hospitals, the attending vascular surgeon made the judgment without explicit criteria. In two other hospitals, the attending vascular surgeon or radiologist considered the patient hemodynamically stable if (s)he gave an adequate verbal reply. In one hospital, the attending vascular surgeon defined hemodynamically stable as a systolic blood pressure of 60 millimeter Mercury or higher, whereas in two other hospitals a systolic blood pressure cutoff of 70 millimeter Mercury was used. After CT-scan or angiography confirmed the presence of a ruptured AAA, the patient was immediately transported to the operating room where endovascular repair was performed if the AAA was anatomically suitable; otherwise, open surgery was performed. The anatomic inclusion criteria for endovascular repair differed between the participating hospitals since they stocked different endovascular devices. The criteria varied between 7 and 15 millimeter for the proximal neck length, between 30° and 90° for the neck angulation, and between 28 and 32 millimeter for the neck diameter. The endografts used were Talent aortouniiliac (AUI) stent-grafts (Medtronic, Santa Rosa, CA), ANACONDA bifurcated endografts (Vascutek, Renfrewshire, Scotland), Cook endografts (Zenith, Bloomington, IN), and Excluder endografts (Gore, Flagstaff, AZ).

Data collection and definitions

Prospectively collected data included: patient characteristics (i.e., age, sex, renal failure, and history of diabetes mellitus, hypertension, angina pectoris, myocardial infarction, congestive heart failure, or cerebrovascular disease), use of medication prior to hospital admission, patients' hemodynamic condition upon presentation to the hospital, shock upon presentation to the hospital, use of CT-scan or angiography prior to the procedure, morphology of the AAA (infrarenal, juxtarenal, or suprarenal), and which treatment was performed (endovascular repair or open surgery). Shock was defined as a systolic blood pressure less than 80 millimeter Mercury. Myocardial disease comprised previous myocardial infarction and/or angina pectoris. Cerebrovascular disease included all previous cerebrovascular accidents and transient ischemic attacks. Renal failure referred to a preoperative creatinine value more of than 160 micromol per liter (i.e., 1.8 milligram per deciliter). A standardized form was used to register these data. In order to obtain information about 30-day mortality, medical records and the computerized database of the participating hospitals were used.

Glasgow Aneurysm Score

The GAS was originally based on 235 patients treated for AAA between January 1980 and December 1989 at 4 hospitals in Glasgow, United Kingdom (1). The GAS was calculated using the following formula: GAS = age in years + 17 for shock + 7 for myocardial disease + 10 for cerebrovascular disease + 14 for renal disease (1). Patients with a GAS less than 70 are considered to have a low risk of mortality after open surgery for AAA, whereas patients with a GAS more than 85 are considered to have a high risk of mortality after treatment for AAA. In the original paper, 'shock' was based on clinical information of tachycardia, hypotension, pallor, and sweating. Myocardial

disease was defined as previous myocardial infarction and/or angina pectoris. Cerebrovascular disease comprised all grades of stroke including transient ischemic attacks. Renal disease included chronic and acute renal failure (1).

Data and statistical analyses

Patient data were entered into a database and checked by one of the authors for completeness (author initials blinded). Missing data regarding continuous variables (i.e., age and systolic blood pressure) were assumed to be missing at random and entered based on the variable means. If data regarding patients' medical history or medication were missing, it was assumed that the risk factor was not present or the medication was not used. In total, the proportion of missing data was less then 2%. Analyses were performed according to the intention-to treat principle.

We validated the GAS using receiver operating characteristics (ROC) curves to determine discriminative ability (i.e., whether the GAS was higher in patients who died). An area under the ROC curve (AUC) of 0.50 indicates no discriminative ability and the closer the AUC is to 1.0, the better the discriminative ability.

In addition, we tested for interactions between risk factors (as determined in the GAS model) and the specific procedure performed in predicting 30-day mortality using logistic regression analysis. Interaction terms were considered potentially relevant if $p < 0.20$.

Based on a previously published approach, the GAS was updated to predict 30-day mortality after either endovascular repair or open surgery (15). In the first step, we estimated new regression coefficients for the GAS variables based on the Dutch data. In the second step, we added patients' hemodynamic stability prior to the procedure and the procedure performed (endovascular repair versus open surgery) to the original GAS variables (15). Regression coefficients for the new variables (i.e. patients' hemodynamic stability and the procedure) and an intercept term were estimated; the GAS was then multiplied by a calibration slope β_{GAS} for overall adjustment of the original GAS regression coefficients. The formula we used was: $(\text{30-day mortality})_{\text{Dutch data}} = \alpha + \beta_{\text{hemodynamic stability}} * (\text{patients' hemodynamic stability}) + \beta_{\text{procedure}} * (\text{procedure}) + \beta_{GAS} * \text{GAS}$. To calculate the adjusted GAS odds ratios, we used the formula: (adjusted GAS odds ratio) = (original GAS odds ratio) * exp (β_{GAS}). In the third step, we performed a multivariable logistic regression analysis on 30-day mortality, including patients' hemodynamic stability prior to the procedure, the procedure performed (endovascular repair versus open surgery), and all individual GAS variables (i.e., age, shock, myocardial disease, cerebrovascular disease, and renal disease), and we estimated new regression coefficients for each variable (15). For each step, the AUC was estimated as a measure of discriminative ability and adjusted for optimism by bootstrapping. We used 200 bootstrap samples drawn with replacement from the original data set. This validation procedure indicates the performance that may be expected in new, but similar patients (16). The AUCs from

the first, second, and third step were compared, and the prediction rule with the highest AUC is presented as the updated prediction rule: the DAS.

Analyses were performed using SPSS for Windows Version 11.0.1 (SPSS Inc., Chicago, IL) and S-Plus Version 6.0 (Insightful Corporation, Seattle, WA).

RESULTS

Patient population

Patient demographics, characteristics and use of medication before admission are listed in Table 1.

The proportion of males was somewhat higher in patients treated with endovascular repair compared with patients treated with open surgery (93% versus 83%, p = 0.05). Shock occurred more often in patients treated with open surgery compared with patients treated with endovascular repair (28% versus 7%, p = 0.001). In addition, the use of statins was somewhat higher in patients treated with endovascular repair compared with patients treated with open surgery (31% versus 19%, p = 0.06). The other characteristics were similar between the treatment groups. All of the 58 patients treated with endovascular repair had infrarenal AAAs. Eighty-three of the 143 patients (58%) treated with open surgery had infrarenal AAAs, 49 (34%) had juxtarenal AAAs, 4 (3%) had suprarenal AAAs, and in 7 patients (5%) the AAA anatomy was not reported.

Outcomes

Thirty-day mortality was 15/58 (26%) for patients treated with endovascular repair and 57/143 (40%) for patients treated with open surgery (p = 0.06). Among patients who were treated with open surgery, 30-day mortality was 39/106 (37%) for those who were hemodynamically stable prior to the procedure and 18/37 (49%) for those who were hemodynamically unstable prior to the procedure (p = 0.20). Two of the 58 patients (3%) treated with endovascular repair died intraoperatively, while 21 of the 143 patients (15%) treated with open surgery died intraoperatively (p = 0.02). The causes of 30-day mortality are listed in Table 2.

Nine of the 58 patients (16%) initially treated with endovascular repair were converted to open surgery.

Validation of GAS

The GAS was less than 70 in 42 patients; between 70 and 75 in 26 patients; between 76 and 85 in 58 patients; and more than 85 in 75 patients (Table 3).

Table 1: Patient demographics and characteristics

	Endovascular repair n = 58	Open surgery n = 143	P-value
Male	54 (93%)	118 (83%)	0.05
Mean age (SD)	73.2 (8.6)	73.5 (7.5)	0.83
Renal failure	8 (14%)	16 (11%)	0.61
Diabetes mellitus	8 (14%)	13 (9%)	0.32
Hypertension	29 (50%)	60 (42%)	0.30
Angina pectoris	6 (10%)	18 (13%)	0.66
Previous myocardial infarction	12 (21%)	35 (25%)	0.57
Heart failure	6 (10%)	14 (10%)	0.91
CVA/TIA	6 (10%)	18 (13%)	0.66
COPD	15 (26%)	30 (21%)	0.45
AAA known before admission	14 (24%)	25 (18%)	0.28
Shock	4 (7%)	40 (28%)	0.001
Medication			
Beta-blocker	19 (33%)	40 (28%)	0.50
Antiplatelet agents	11 (19%)	17 (12%)	0.19
Aspirin	24 (41%)	46 (32%)	0.21
Statins	18 (31%)	27 (19%)	0.06

SD = standard deviation, CVA = cerebrovascular accident, TIA = transient ischemic attacks, COPD = chronic obstructive pulmonary disease, AAA = abdominal aortic aneurysm

The mean GAS among patients who survived 30 days after the initial procedure was 77 for patients treated with endovascular repair and 80 for patients treated with open surgery (p = 0.14). The mean GAS among patients who died within 30 days after the initial procedure was 87 for patients treated with endovascular repair and 88 for patients treated with open surgery (p = 0.81). The AUC for the GAS was 0.686 (95%-confidence interval 0.612 – 0.761).

Interaction

Testing for interaction between risk factors and the type of procedure performed on 30-day mortality showed no relevant interactions (all p-values > 0.20). This means that, considering the included variables, 30-day mortality was always lower if patients with ruptured AAA were treated with endovascular repair instead of open surgery.

Table 2: Causes of 30-day mortality

	Endovascular repair n = 58	Open surgery n = 143
Intraoperative	2 (3%)	21 (15%)
Postoperative		
Cardiovascular*	3 (5%)	8 (6%)
Pulmonary†	3 (5%)	5 (3%)
Renal failure	1 (2%)	1 (1%)
Sepsis	2 (3%)	1 (1%)
Shock‡	2 (3%)	4 (3%)
Coagulopathy	1 (2%)	0 (0%)
Multiorgan Failure	1 (2%)	4 (3%)
Infection	0 (0%)	1 (1%)
No treatment due to patients' comorbidity§	0 (0%)	3 (2%)
Unknown	0 (0%)	9 (6%)
Total deaths	15 (26%)	57 (40%)

* Cardiac causes of death included ventricular fibrillation, myocardial ischemia, progressive heart failure with fatal outcome, continuous hypotension, and cardiac arrest.
† Pulmonary causes of death included acute respiratory distress syndrome, pulmonary embolism, and respiratory insufficiency.
‡ Shock included septic shock, hypovolemic shock, and cardiac shock.
§ Due to patients' comorbidity, no further medical support was given.

Table 3: GAS and the prediction of 30-day mortality

	Endovascular repair		Open surgery		Odds ratio* (95%-CI)
Score	**Number of patients**	**Mortality (%)**	**Number of patients**	**Mortality (%)**	
< 70	17	2 (12%)	25	3 (12%)	1.02 (0.15-6.9)
70-75	8	2 (25%)	18	7 (39%)	1.91 (0.30-12)
76-85	16	3 (19%)	42	17 (41%)	2.95 (0.73-12)
> 85	17	8 (47%)	58	30 (52%)	1.21 (0.41-3.6)
Total	58	15 (26%)	143	57 (40%)	1.90 (0.97-3.7)

GAS = Glasgow Aneurysm Score, CI = confidence interval
* Open surgery versus endovascular repair

Updated prediction rule

In the first step, we estimated new regression coefficients for the GAS variables based on the Dutch data. The AUC adjusted for optimism was 0.673 (Table 4). In the second step, we added 2 new variables to the original GAS variables: patients' hemodynamic stability prior to the procedure and the type of procedure performed (endovascular repair versus open surgery). The

estimation of the intercept, regression coefficients, and calibration slope led to the following formula:

$(30\text{-day mortality})_{\text{Dutch data}} = -4.76 + 0.17 * (\text{patients' hemodynamic stability}) - 0.46 * (\text{procedure}) + 0.051 * \text{GAS}$. The AUC adjusted for optimism was 0.683. The adjusted GAS odds ratios are listed in Table 4.

In the third step, patients' hemodynamic stability prior to the procedure and the type of procedure performed (endovascular repair versus open surgery) were added to the GAS variables, and new regression coefficients were estimated for each variable. The AUC was adjusted for optimism by bootstrapping and was 0.679. Since the second model had the highest optimism-corrected AUC, we used it to calculate the Dutch Aneurysm Score (DAS). Multiplication with the weights in the original GAS and rounding gives the following risk score:

DAS = + 3 if hemodynamically unstable prior to the procedure - 9 for endovascular repair + age in years + 17 for shock + 7 for myocardial disease + 10 for cerebrovascular disease + 14 for renal disease.

Table 4: Multivariable models on 30-day mortality

Variable	Odds ratio (95%-confidence interval)		
	Step 1	**Step 2**	**Step 3**
Patient hemodynamically stable for imaging* followed by open surgery	-	1.00	1.00
Patient not sufficiently hemodynamically stable for imaging* followed by open surgery	-	1.18 (0.53-2.65)	1.70 (0.70-4.13)
Patient hemodynamically stable for imaging* followed by endovascular repair	-	0.63 (0.30-1.33)	0.57 (0.27-1.22)
Age (per decade)	2.39 (1.52-3.75)	2.21 (1.18-4.13)	2.51 (1.57-4.02)
Shock	1.66 (0.80-3.45)	3.82 (2.30-6.37)	1.19 (0.53-2.70)
Myocardial disease	1.76 (0.90-3.44)	1.81 (1.13-2.90)	1.67 (0.84-3.31)
Cerebrovascular disease	1.13 (0.46-2.80)	2.20 (1.19-4.06)	1.16 (0.46-2.90)
Renal disease	2.06 (0.83-5.06)	3.02 (1.55-5.89)	2.17 (0.87-5.42)
Area under the curve	0.673 (0.600-0.746)	0.683 (0.610-0.758)	0.679 (0.608-0.751)

* Computed tomography scan or angiography

Table 5 shows an example of how to calculate the 30-day mortality for a patient with a ruptured AAA for endovascular repair or open surgery.

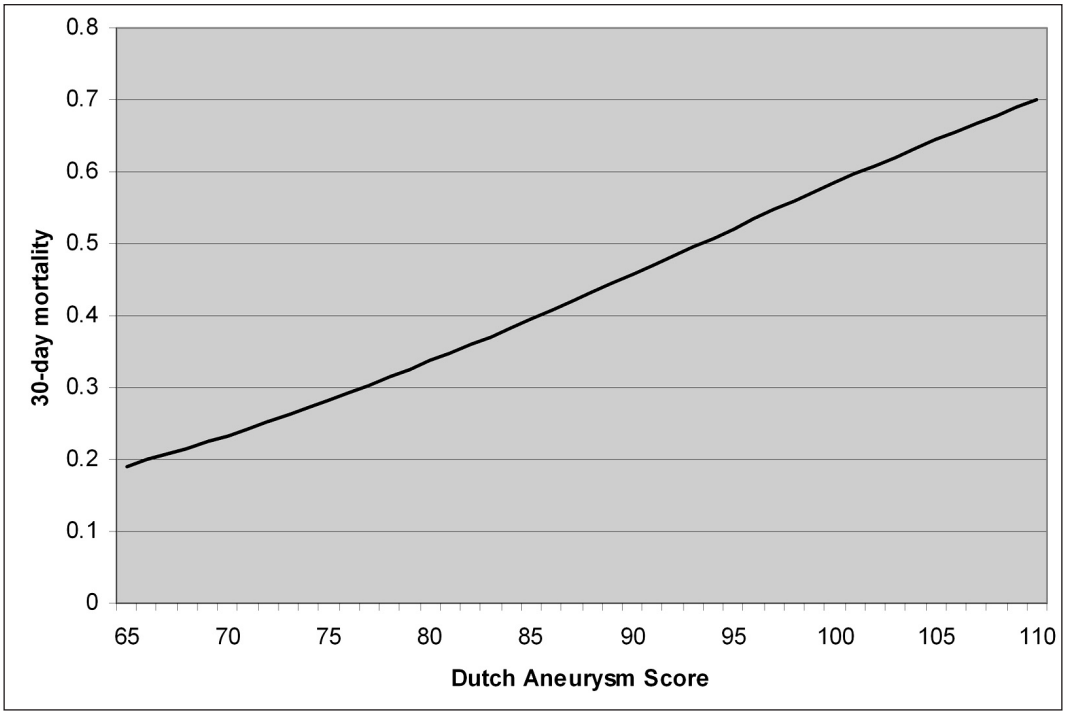
Table 5: How to calculate 30-day mortality after endovascular repair or open surgery for patients with ruptured AAA

Example	**A 72-year old patient with a ruptured AAA, who is sufficiently hemodynamically stable to undergo CT-scan or angiography prior to the procedure, previously had a myocardial infarction, and has a preoperative creatinine value of more than 160 micromol per liter.**		
Steps	**Formulas**	**Endovascular repair**	**Open surgery**
1. Calculate DAS	DAS = + 3 if hemodynamically unstable prior to the procedure* - 9 for endovascular repair + age† + 17 for shock‡ + 7 for myocardial disease§ + 10 for cerebrovascular disease‖ + 14 for renal disease#	DAS = + 0 – 9 + 72 + 0 + 7 + 0 + 14 = 84	DAS = + 0 – 0 + 72 + 0 + 7 + 0 + 14 = 93
2. Calculate linear predictor	Linear predictor = – 4.76 + 0.051 * DAS	Linear predictor = – 4.76 + 0.051 * 84 = – 0.48	Linear predictor = – 4.76 + 0.051 * 93 = – 0.017
3. Calculate 30-day mortality	30-day mortality = 1 – (1 / (1+exp (linear predictor)))	30-day mortality = 1 – (1 / (1+exp (– 0.48))) = 0.38	30-day mortality = 1 – (1/ (1+exp (0.017))) = 0.50

AAA = abdominal aortic aneurysm, CT = computed tomography, DAS = Dutch Aneurysm Score
* The definition for hemodynamic stability differed across the hospitals (see "Methods" section).
† Age in years.
‡ Shock was defined as a systolic blood pressure less than 80 millimeter Mercury.
§ Myocardial disease comprised previous myocardial infarction and/or angina pectoris.
‖ Cerebrovascular disease included all previous cerebrovascular accidents and transient ischemic attacks.
Renal failure referred to a preoperative creatinine value more of than 160 micromol per liter (i.e., 1.8 milligram per deciliter).

Figure 2 shows the 30-day mortality depending on the DAS.

Figure 2: 30-day mortality as a function of the Dutch Aneurysm Score



DISCUSSION

Policies for treatment of AAA have changed since the introduction of endovascular repair for patients with ruptured AAA. Patients who are hemodynamically stable receive a CT-scan or angiography prior to the procedure to assess anatomic eligibility for endovascular repair. Those who are too hemodynamically unstable to undergo imaging are immediately transported to the operating room for open surgery. Therefore, in this prospective multicenter study, we aimed to validate the GAS both in patients with ruptured AAA treated with open surgery and in those treated with endovascular repair. Furthermore, we updated the GAS to predict 30-day mortality after either endovascular repair or open surgery in patients with ruptured AAA. We found that the GAS showed limited discriminative ability in our patient population. In addition, we showed that, considering the included risk factors, 30-day mortality was always lower if patients with ruptured AAA were treated with endovascular repair as opposed to open surgery.

The limited discriminative ability of the GAS may be due to the introduction of endovascular repair in patients with ruptured AAA. When the GAS was developed, open surgery was the only treatment for ruptured AAAs. The limited discriminative ability of the GAS suggests that factors not involved in the GAS influenced mortality after repair for ruptured AAA. In addition, in the evaluation of predictive values of the GAS, we found that patients with a high GAS would benefit less from endovascular repair. This is not consistent with previous findings, suggesting that patients at higher risk for peri-procedural cardiac complications would benefit more from endovascular repair than those at lower risk (13). It should be noted, however, that confidence intervals surrounding the odds ratios were wide.

In the DAS, we added 2 new variables to the GAS variables: patients' hemodynamic stability prior to the procedure and the type of procedure performed. It turned out that patients who were hemodynamic stable prior to the procedure had lower 30-day mortalities than those who were not. This may be due to selection criteria since hemodynamically stable patients are expected to have lower 30-day mortalities than those who are not hemodynamic stable and therefore were immediately transported to the operating room for open surgery (6). Similar to hemodynamically stable patients, hemodynamically unstable patients might better undergo endovascular repair than open surgery if the anatomy allows. Therefore, it remains to be clarified whether hemodynamically unstable patients should undergo imaging prior to the procedure, although most patients appear to be sufficiently stable to do so (17).

Furthermore, the DAS showed that patients who underwent endovascular repair had lower 30-day mortalities than those who underwent open surgery. Again, this may be due to selection criteria since all endovascular repair patients were by definition hemodynamically stable, while 26% of open surgery patients were not. In addition, the interaction terms between GAS variables

and the therapeutic procedure performed were not associated with 30-day mortality. This suggests that given the particular set of risk factors in our model, endovascular repair was always preferable with respect to 30-day mortality.

Two studies that validated GAS in patients with ruptured AAA treated with open surgery reported better validity than our study (2, 3), and one study reported worse validity (4). It should be noted that these studies were performed in patients treated with open surgery, whereas in our study patients treated with open surgery as well as patients treated with endovascular repair were included.

Our study had several limitations. The definitions of risk factors were slightly different from the original GAS. In addition, since the intent is for the model to be predictive, the GAS only included patient characteristics that can be known upon patients' presentation to the hospital or shortly thereafter. Consequently, we did not collect data on the AAA anatomy, such as neck length, neck diameter, and neck angulation. Furthermore, our prediction rule is not based on a randomized controlled trial, and the selection for endovascular repair was based on patients' hemodynamic condition and AAA eligibility for endovascular repair. Therefore, selection bias may have affected our results in favor of endovascular repair. The data we used, however, were based on patients who were seen consecutively, and our study represents current clinical practice. Fourth, we had a small sample; therefore, lack of statistical power may have affected our results.

The treatment protocols between the participating hospitals were slightly different. The criteria for patients being hemodynamically (un)stable differed across the hospitals. In addition, the types of endografts used were not the same in all hospitals. As a result, different anatomic criteria were applied across the participating hospitals. It should be noted that in practice, physicians tend to apply more lenient criteria for endovascular repair in case of severe comorbidity in order to avoid open surgery. In order to implement a more uniform treatment policy for patients with ruptured AAAs, similar protocols are needed in the different hospitals. In addition, these protocols enable more precise comparison of endovascular repair with open surgery across the different hospitals.

We recommend ongoing prospective observational and randomized controlled trials in patients with ruptured AAA. Prospective observational studies reflect daily practice and changes in treatment policy over time (18, 19). This is of particular interest in this group of patients, since new types of endografts, which allow for more lenient anatomic criteria, are rapidly becoming available. Randomized controlled trials are needed in order to assess associations between risk factors, the procedure performed, and 30-day mortality, and to avoid selection bias. Furthermore, future studies should investigate which patients should go immediately to the operating room for open surgery and which patients should undergo imaging prior to the therapeutic procedure

to determine anatomic eligibility for endovascular repair. In addition, since patient populations may change over time, the development of a prediction tool is an ongoing process; therefore, we encourage further validation and updating of our prediction rule.

In conclusion, we showed limited discriminative ability of the GAS in patients with ruptured AAAs to be treated with endovascular repair or open surgery. The GAS was updated into the DAS, by adding patients' hemodynamic stability prior to the procedure and the type of procedure performed, which predicts 30-day mortality for patients with ruptured AAA to be treated with either endovascular repair or open surgery.

REFERENCES

1. Samy AK, Murray G, MacBain G. Glasgow aneurysm score. Cardiovasc Surg 1994; 2:41-44.
2. Leo E, Biancari F, Nesi F, et al. Risk-scoring methods in predicting the immediate outcome after emergency open repair of ruptured abdominal aortic aneurysm. Am J Surg 2006; 192:19-23.
3. Korhonen SJ, Ylonen K, Biancari F, Heikkinen M, Salenius JP, Lepantalo M. Glasgow Aneurysm Score as a predictor of immediate outcome after surgery for ruptured abdominal aortic aneurysm. Br J Surg 2004; 91:1449-1452.
4. Tambyraja AL, Fraser SC, Murie JA, Chalmers RT. Validity of the Glasgow Aneurysm Score and the Hardman Index in predicting outcome after ruptured abdominal aortic aneurysm repair. Br J Surg 2005; 92:570-573.
5. Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. Lancet 1994; 344:1645.
6. Visser JJ, Sambeek v, M.R.H.M., Hamza TH, Hunink MG, Bosch JL. Endovascular repair and open surgery in patients with ruptured abdominal aortic aneurysms: systematic review. Radiology 2007; (in press).
7. Franks S, Lloyd G, Fishwick G, Bown M, Sayers R. Endovascular treatment of ruptured and symptomatic abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31:345-350.
8. Larzon T, Lindgren R, Norgren L. Endovascular treatment of ruptured abdominal aortic aneurysms: a shift of the paradigm? J Endovasc Ther 2005; 12:548-555.
9. Castelli P, Caronno R, Piffaretti G, et al. Ruptured abdominal aortic aneurysm: endovascular treatment. Abdom Imaging 2005; 30:263-269.
10. Alsac JM, Desgranges P, Kobeiter H, Becquemin JP. Emergency endovascular repair for ruptured abdominal aortic aneurysms: feasibility and comparison of early results with conventional open repair. Eur J Vasc Endovasc Surg 2005; 30:632-639.
11. Hinchliffe RJ, Bruijstens L, MacSweeney ST, Braithwaite BD. A randomised trial of endovascular and open surgery for ruptured abdominal aortic aneurysm - results of a pilot study and

lessons learned for future studies. Eur J Vasc Endovasc Surg 2006; 32:506-513; discussion 514-505.
12. Peppelenbosch N, Geelkerken RH, Soong C, et al. Endograft treatment of ruptured abdominal aortic aneurysms using the Talent aortouniiliac system: an international multicenter study. J Vasc Surg 2006; 43:1111-1123.
13. Visser JJ, Bosch JL, Hunink MG, et al. Endovascular repair versus open surgery in patients with ruptured abdominal aortic aneurysms: clinical outcomes with 1-year follow-up. J Vasc Surg 2006; 44:1148-1155.
14. Central Committee on Research Involving Human Subjects. In: Available at: http://www.ccmo-online.nl/. Date accessed: February 10, 2006.
15. Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med 2004; 23:2567-2586.
16. Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. Springer: New York, 2001.
17. Lloyd GM, Bown MJ, Norwood MG, et al. Feasibility of preoperative computer tomography in patients with ruptured abdominal aortic aneurysm: a time-to-death study in patients without operation. J Vasc Surg 2004; 39:788-791.
18. Hordijk-Trion M, Lenzen M, Wijns W, et al. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. Eur Heart J 2006; 27:671-678.
19. Lloyd-Williams F, Mair F, Shiels C, et al. Why are patients in clinical trials of heart failure not like those we see in everyday practice? J Clin Epidemiol 2003; 56:1157-1162.

5
COST ANALYSIS WITH 1-YEAR FOLLOW-UP

ABSTRACT

Purpose: To retrospectively assess in-hospital costs and costs of 1-year follow-up of endovascular aneurysm repair and conventional open surgery in patients with an acute infrarenal abdominal aortic aneurysm (AAA), using the resource utilization approach.

Materials and methods: Institutional Review Board approval was obtained and informed consent was waived because we analyzed only patient data documented as part of routine clinical care collected from the medical records. In-hospital costs for all consecutive patients undergoing endovascular (n = 32) or open surgical repair (n = 35) of acute infrarenal AAA from January 1, 2001 until December 31, 2004 were assessed using the resource utilization approach. Patients who did not undergo a computed tomography (CT) scan before the procedure were excluded from the analysis. Costs of 1-year follow-up were complete for 30 patients who underwent endovascular repair and 34 patients who underwent open surgery. Costs were assessed from a healthcare perspective. Mean costs were calculated for each treatment group and compared using the Mann-Whitney U-test, $\alpha = 0.05$. In uni- and multivariable analyses, we investigated the influence of clinical variables on the total in-hospital costs. Costs were expressed in 2003 Euros.

Results: Sex (61 male, 6 female), age (mean 72.0), and comorbidity did not differ between the treatment groups ($p > 0.05$). The mean total in-hospital costs were lower for endovascular repair compared to open surgical repair (€ 20,767 and € 35,470, respectively; $p = 0.004$). The total costs including one-year follow-up were € 23,588 versus € 36,448 for patients who underwent endovascular repair and open surgical repair, respectively ($p = 0.05$). In multivariable analysis, complications had a significant influence on total in-hospital costs (2.27 times higher costs).

Conclusion: Total in-hospital costs and total costs including 1-year follow-up were lower for patients with an acute AAA who underwent endovascular repair compared to open surgical repair.

INTRODUCTION

The exponential growth in technological developments in medicine lead to new treatment options for patients. Especially in the field of radiology and vascular surgery numerous improvements have been made in the past few decades. One of the new treatment options is endovascular repair in patients with an acute infrarenal Abdominal Aortic Aneurysm (AAA). Several studies have reported on the effectiveness of endovascular repair in patients with acute symptomatic or ruptured AAAs (1-7). The results demonstrated a reduction in mortality and morbidity rates compared with open surgery.

Endovascular repair performed electively in patients with an asymptomatic infrarenal AAA was demonstrated to cost more than open surgery (8). In patients with acute AAAs, costs have previously been assessed in patients subjected to open surgery. The results of these studies, however, were quite different from each other reporting total in-hospital costs that varied from $ 13,396 to $ 126,305 (9-15). The methods of these studies varied and were based on small sample sizes. To our knowledge no study has been published yet that reported total in-hospital costs for the treatment of acute infrarenal AAA by endovascular repair and comparing these with open surgery in acute AAA patients.

Furthermore, most studies so far have only taken immediate costs associated with the procedure into account. Costs of follow-up should, however, be considered, as fairly intensive surveillance is needed in patients treated with endovascular aneurysm repair, whereas patients treated with open surgery do not require such an intense surveillance during follow-up (16-20). In addition, costs associated with additional procedures due to failures or complications should be considered. Patients treated with open surgery are expected to undergo more procedures for severe complications immediately following the procedure whereas endovascular treated patients are expected to undergo more procedures for graft failures or complications that may occur later in follow-up. Thus, in order to evaluate the incurred costs of both procedures, it is important to calculate both in-hospital costs and costs during follow-up after the procedure. The objective of our study, therefore, was to retrospectively assess in-hospital costs and costs of 1-year follow-up of endovascular aneurysm repair and conventional open surgery in patients with an acute infrarenal AAA, using the resource utilization approach (21).

MATERIALS AND METHODS

Patients and protocol

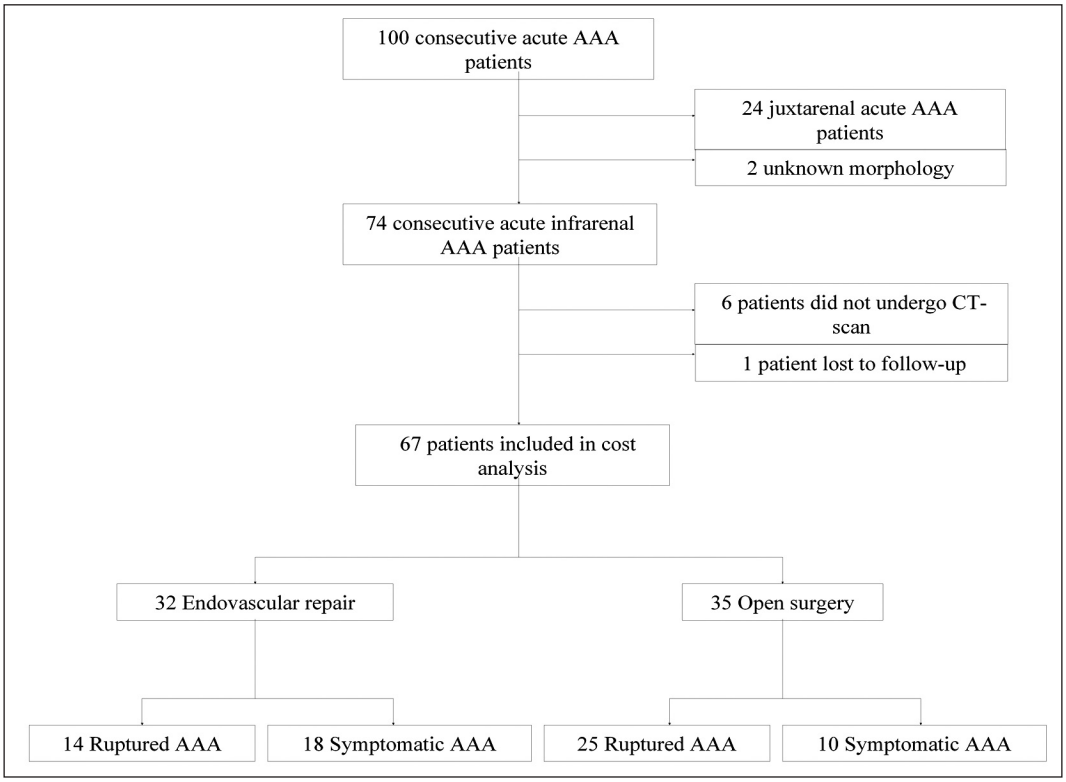
The medical records of all consecutive patients with an acute infrarenal AAA who presented to our academic hospital between January 1, 2001 and December 31, 2004 were reviewed. An acute infrarenal AAA was defined as either an acute symptomatic infrarenal AAA or an acute ruptured infrarenal AAA. We limited our study to admissions beginning in 2001 since endovascular repair of acute abdominal aneurysms became routine practice in our hospital from that time. All patients with an acute infrarenal AAA were retrieved from the medical registry using operation codes. These codes are used for administration purposes and valid for our institution specifically. The data were retrospectively obtained from a computerized database of the hospital and the medical records of all these patients were analyzed. Readmissions were obtained from patients' medical records and the computerized database of our hospital or the hospital they were readmitted to. Institutional Review Board approval was obtained and informed consent was waived because we analyzed only patient data documented as part of routine clinical care and collected from the medical records.

Upon the patient's admission to the hospital, an abdominal ultrasound and/or an abdominal CT-scan was performed. Patients were diagnosed with an acute infrarenal symptomatic or ruptured AAA by the vascular surgeon and the interventional radiologist who were on call. The four vascular surgeons involved had 3, 4, 4, and 5 years of experience in endovascular AAA repair and 4, 10, 30, and 35 years of experience in open AAA repair, respectively, as of 2001. The two interventional radiologists involved had 3 and 5 years of experience in endovascular AAA repair, respectively, as of 2001. Depending on the morphologic anatomy of the aneurysm (e.g., proximal neck shorter than 15 millimeters, angulation more than 90°), the vascular surgeon and the interventional radiologist decided whether to perform endovascular repair or open surgery. Six patients did not receive a CT-scan due to a hemodynamically instable condition. These patients went immediately to the operating room for open surgery and were excluded from the analyses.

The endovascular as well as the open procedure were performed by using commercially available grafts (Cook Zenith, Gore Excluder, Vascutek Sulzer/Terumo). The team that performed open surgery included one vascular surgeon (4 involved, average 4 years of experience in endovascular AAA repair and 20 years of experience in open AAA repair, as of 2001), one surgery fellow (3 involved, average 1 year of experience in endovascular AAA repair and 3 years of experience in open AAA repair), one anesthesiologist (6 involved, average 15 years of experience), one anesthesiology fellow (2 involved, average 2 years of experience), and two operating room nurses (10 involved, 10 years of experience). When an endovascular procedure was performed, the same team was present plus one radiologist (2 involved, average 4 years of experience) and one radiologic technologist (4 involved, average 4 years of experience).

In our study period, 100 patients presented at the Vascular Unit with an acute AAA (Figure 1).

Figure 1: Flowchart of patients with an acute Abdominal Aortic Aneurysm included in the analyses.



Twenty-four patients with a juxtarenal AAA were excluded from the analyses, because these patients were not eligible for endovascular repair. Two patients had an AAA of unknown origin. One patient was lost to follow-up because this patient was transported to another hospital immediately after open surgery for acute AAA. As mentioned above six patients who were too unstable did not undergo CT-scanning prior to the procedure. To make the patients in the endovascular and open surgical treatment group more comparable, these 33 patients were excluded from the analyses. Therefore, in our analyses we included 67 patients with an acute infrarenal AAA, of whom 32 underwent endovascular repair and 35 open surgery (Figure 1).

Costs

Direct hospital costs of all patients were assessed using the resource utilization approach by multiplying resource utilization with the cost per unit of resource (21, 22). We assessed the in-hospital costs and costs during 1-year follow-up from a health care perspective.

Total in-hospital costs were determined by preoperative costs, costs of the procedure, costs of the intensive care unit (ICU) and ward, costs of the postoperative diagnostic tests, costs of postoperative blood products, and costs of additional procedures. All costs included personnel costs, use of equipment, use of material, investment during use, maintenance, administration and other overhead costs. To calculate the actual costs of the diagnostic tests and procedure related items, we retrieved data from the Financial Unit of the Department of Radiology, the Financial Unit of the operating rooms, and the Financial Unit of Surgery. To increase generalizability among hospitals, we used costs reported in the "Dutch manual for cost-analysis in health care" (23) to assess the costs, for example, of the ward (€ 476 per day) and the ICU (€ 1,684 per day). Finally, in the absence of actual costs for tests and procedures due to failures and complications, charges were obtained from the 'National Health Tariffs Authority'. In the Netherlands, these charges are estimated based on actual costs. Therefore, it was not necessary to adjust these charges with a cost-to-charge ratio.

Preoperative costs included use of the emergency room and radiological diagnostic tests performed prior to the procedure, such as an abdominal ultrasound or CT-scan. Procedure costs of the endovascular and surgical treatment included costs for use of the operating room, anesthesiology, personnel, materials such as grafts, catheters, sterilized gauzes, needles, and blood products. Costs of the ward and ICU stay included costs of physician consultations, nurses, materials, and medication. Costs of postoperative diagnostic tests included CT-angiography, abdominal ultrasound, sigmoidoscopy, and bronchoscopy. Costs of postoperative blood products included use of packaged cells, fresh frozen plasma, and platelets. Costs of additional procedures included procedures such as tracheostomy, Hartmann-procedure, and surgical evacuation of an access site hematoma or infection due to the treatment of the acute AAA.

For 64 patients 1-year follow-up was completed. Thirty patients underwent endovascular repair, 34 patients were treated by open surgery. For three patients, of whom two underwent endovascular repair and one open surgery, we could not complete the full 1-year follow-up because they were treated for an acute AAA less than a year ago. These patients were excluded from the calculations of total costs including 1-year follow-up even if they died peri-procedurally. Following the procedure, during the 1-year follow-up, three patients treated with endovascular repair died due to non-aneurysm related causes, namely pulmonary infection, heart failure, and malignancy. Costs of 1-year follow-up included scheduled follow-up physician visits and costs of diagnostic tests. For patients who underwent endovascular repair, physician visits and CT-scans were scheduled 3, 6, and 12 months after the initial procedure. For patients who underwent open surgery, physician visits were only scheduled on clinical indication. Also, costs of readmissions due to failures and complications of the treatment of the acute AAA were assessed. These costs included costs of diagnostic tests, ward stay, and procedures during readmission and were determined as described above. All costs were calculated in 2003 Euros.

Data and statistical analysis

Patient and lesion characteristics between the patients who underwent endovascular and open repair were compared using the Student t-test, Mann-Whitney U-test, $\chi 2$-test and Fisher's Exact Test (two-sided, $\alpha = 0.05$). For each patient, we calculated the total in-hospital costs and the costs of 1-year follow-up. In 7 patients (10%) we missed a few items related to the preoperative costs such as use of the abdominal ultrasound; these missing values were imputed using the mean-imputation method (24). Data to assess all other cost items were complete. Consistent with intention-to-treat analyses, the mean in-hospital costs were calculated by taking all patients ($n = 67$) into account, including patients who died. Costs during follow-up were calculated taking all patients into account ($n = 64$). In order to increase the precision of the 95% confidence interval of the mean, we used the bootstrap resample method. The costs of patients who received endovascular repair versus open surgery were compared using the Mann-Whitney U-test (two-sided, $\alpha = 0.05$).

In univariable analyses, we tested which variables had a significant influence on the natural logarithm of the total in-hospital costs ($\alpha = 0.10$). Because the distributions of the costs were skewed, we used the natural logarithm. The variables tested were age, sex, comorbidity (i.e., cardiovascular or respiratory disease), ruptured versus symptomatic AAA, open versus endovascular repair, in-hospital complications due to the treatment of the acute AAA, and in-hospital death. We defined in-hospital complications as myocardial infarction, respiratory insufficiency, pneumonia, renal failure, ischemia of the sigmoid, sepsis, abdominal haematoma, and urinary tract infection. The significant variables ($\alpha = 0.10$) from the univariable analyses were included in a multivariable regression analysis. On the basis of this multivariable model, the mean difference in total in-hospital costs for endovascular versus open surgery was calculated using the formula:

$$\Delta\text{Total in-hospital costs} = (\text{Total in-hospital costs})_{\text{Open surgery}} - (\text{Total in-hospital costs})_{\text{Endovascular repair}} = e^{(C+\beta r*Fr+\beta o*Fo+\beta c*Fc)} - e^{(C+\beta r*Fr+\beta o*Fo+\beta c*Fc)}$$

where,

- C = constant
- βr = β ruptured versus symptomatic AAA
- Fr = fraction of patients who had a ruptured AAA
- βo = β open versus endovascular repair
- Fo = fraction of patients who underwent open surgical repair
- βc = β complications
- Fc = fraction of patients who had a complication

Because studies showed that the clinical outcome and anatomic suitability to treat patients with an acute AAA with an endovascular approach may be different for symptomatic and ruptured

AAA (25, 26), subgroup analysis for in-hospital costs in patients with a ruptured AAA was performed.

Analyses were performed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA), SPSS for Windows Version 11.0.1 (SPSS Inc., Chicago, Il), and S-Plus Version 6.0 Professional Release 1 (Insightful Corporation, Seattle, WA).

RESULTS

In our study group, we included 61 (91%) men and 6 (9%) women. Baseline patient demographics were not different between the two treatment groups (Table 1).

Table 1: Patient demographics and admissions

	Endovascular repair n = 32	Open surgical repair n = 35	P-value
Male	28 (88%)	33 (94%)	0.29
Mean age (SD)	71.3 (9.9)	72.6 (10.0)	0.57
Comorbidity*	22 (69%)	23 (68%)	0.63
Ruptured AAA	14 (44%)	25 (71%)	0.02
General anesthesia	16 (50%)	35 (100%)	< 0.001
ICU admission	15 (47%)	31 (89%)†	< 0.001
In-hospital complications	11 (34%)	19 (54%)	0.14
In-hospital mortality	4 (13%)	9 (26%)	0.22
Readmissions in follow-up‡	2 (7%)	4 (12%)	0.68
Admission time: mean (SD), median			
Duration procedure in minutes	169 (53), 157	239 (70), 230	< 0.001
Postoperative days in the ICU	3.0 (8.0), 0.15	9.4 (14.4), 1.9	< 0.001
Postoperative days on the ward	7.7 (10.3), 6.0	12.7 (14.9), 9.0	0.07
Postoperative days in hospital	10.7 (15.7), 6.5	22.1 (24.3), 14.8	0.003

SD = standard deviation, AAA = abdominal aortic aneurysm, ICU = intensive care unit
* Comorbidity = cardiovascular or respiratory disease; comorbidity data was not available for one patient who underwent open surgical repair, which changed the denominator to 34 patients for open surgical repair.
† Four patients were not admitted to the ICU as they died intraoperatively.
‡ Follow-up data were available for 30 endovascular repair treated patients and 34 open surgical treated patients; readmissions included: embolisation endoleak, leakage of the wound, back pain suspected for aneurysm related problems, endovascular repair of an aneurysm of the femoral artery, and anal blood loss.

Fourteen (44%) of the 32 patients who underwent endovascular repair had a ruptured AAA, whereas 25 (71%) of the 35 patients who underwent open surgery had a ruptured AAA

(p = 0.02). Fifteen (47%) of the 32 patients who underwent endovascular repair were admitted to the ICU, whereas 31 (89%) of the 35 patients who underwent open surgery were admitted to the ICU. Frequencies of in-hospital complications and in-hospital mortality were lower in the endovascular group (34% versus 54% (p = 0.14) and 13% versus 26% (p = 0.22) for endovascular and open repair, respectively). The mean postoperative stay in the ICU was lower after endovascular than after open repair (3.0 days vs. 9.4 days, respectively; p < 0.001). None of the patients who were treated with an endovascular repair underwent conversion to open surgery.

In-hospital costs

The mean total in-hospital costs were lower in patients who underwent endovascular repair compared to patients who underwent open surgery (€ 20,767 and € 35,470, respectively; p = 0.004; Table 2).

Table 2: Mean in-hospital costs of acute AAA repair

	Endovascular repair (n = 32) Costs (€)* (min-max)	Open surgical repair (n = 35) Costs (€)* (min-max)	P-value
Preoperative costs	386 (279-455)	411 (349-492)	0.10
Costs procedure	9829 (2863-16931)	9181 (1222-24484)	0.14
Costs ICU	5048 (0-57168)	15822 (0-91883)	< 0.001
Costs ward	3674 (0-24752)	6052 (0-36176)	0.07
Costs postoperative diagnostic tests:			
- Radiology Department	393 (0-1673)	520 (0-1853)	0.65
- Other Departments	957 (68-7969)	2275 (0-11767)	< 0.001
Costs postoperative blood products	141 (0-1432)	684 (0-7728)	0.03
Costs additional procedures	338 (0-6593)	525 (0-5467)	0.17
Total in-hospital costs	20767 (6644-78983)	35470 (1674-131536)	0.004
95%-confidence interval	15479-29355	25933-48245	

AAA = abdominal aortic aneurysm, ICU = intensive care unit
* In 2003 Euros

The distribution of these costs for both treatments was skewed to the right, although the range of total in-hospital costs of patients who underwent endovascular repair was smaller than of patients who underwent open surgery (Figure 2a and 2b).

More specifically, preoperative costs were higher in patients who underwent open surgery (Table 2). This was mainly because these patients visited the emergency room (as opposed to being

Figure 2a: Distribution of total in-hospital costs of endovascular repair in patients treated for acute Abdominal Aortic Aneurysms

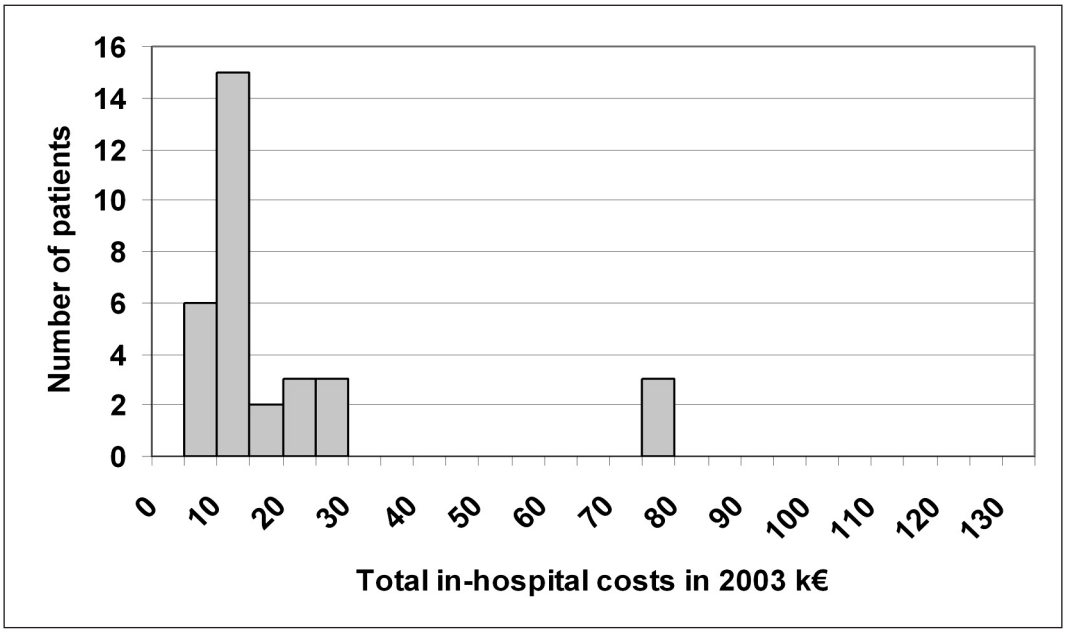
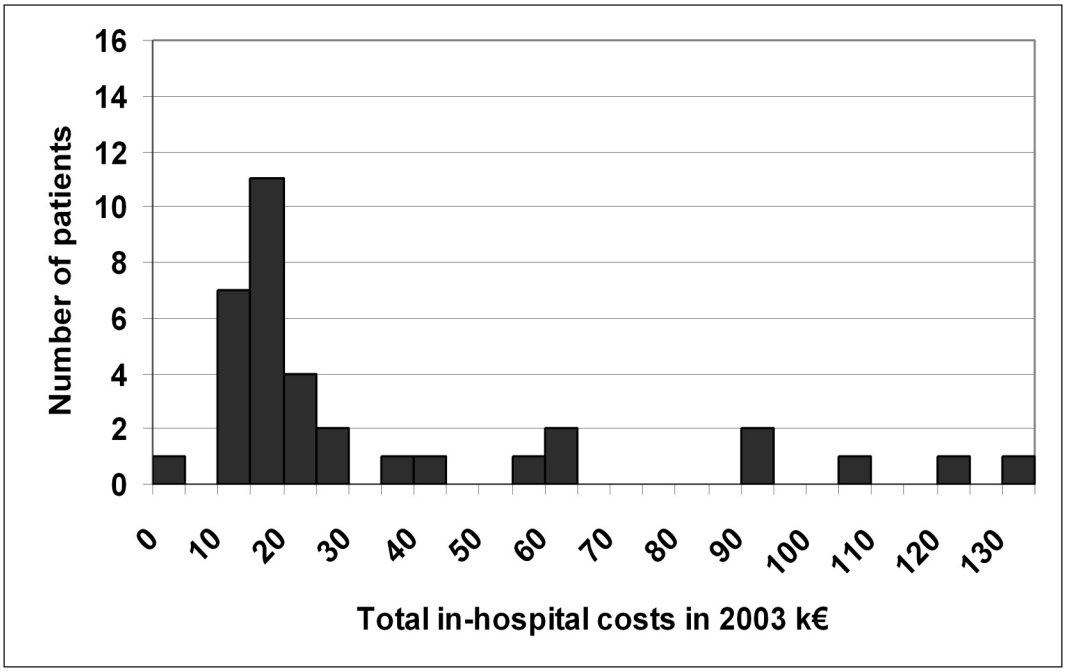


Figure 2b: Distribution of total in-hospital costs of open surgery in patients treated for acute Abdominal Aortic Aneurysms



admitted through the outpatient clinic) more often than patients who underwent endovascular repair. The largest difference within the hospital costs between the treatment groups was found in the costs of the ICU (€ 5,048 versus € 15,822 for endovascular repair and open surgery, respectively; $p < 0.001$).

Procedure costs

The mean total procedure costs were not different between the two treatment groups (€ 9,829 versus € 9,181 for endovascular repair and open surgery, respectively; $p = 0.14$; Table 3).

Table 3: Mean procedure costs of acute AAA repair

	Endovascular repair (n = 32) Costs (€)* (min-max)	Open surgical repair (n = 35) Costs (€)* (min-max)	P-value
Operating room	1492 (699-2700)	2118 (354-3842)	< 0.001
Anesthesiology	1578 (740-2856)	2240 (375-4063)	< 0.001
Personnel	721 (338-1304)	1023 (171-1856)	< 0.001
Material	5617 (501-11446)	734 (322-932)	< 0.001
Blood products	421 (0-2428)	3066 (0-14099)	< 0.001
Total procedure costs	9829 (2863-16931)	9181 (1222-24484)	0.14

AAA = abdominal aortic aneurysm
* In 2003 Euros

All procedural cost items were lower for endovascular repair ($p < 0.001$), except for the material costs; this was mainly due to the price of the stent graft itself, which varied between € 3,515 and € 10,944 (mean € 5,281), whereas the cost of a graft for open surgery was less than € 1,000.

Follow-up costs

The total costs during 1-year follow-up were higher for endovascular repair compared to open surgery (€ 2,012 versus € 694; $p = 0.003$; Table 4).

Costs of diagnostic tests performed by the Radiology Department were higher for endovascular repair. Total costs including in-hospital costs and 1-year follow-up were lower for endovascular repair than for open surgery (€ 23,588 versus € 36,448; $p = 0.05$).

Analyses of covariates

Univariable analyses showed no significant associations between the total in-hospital costs and age, sex, comorbidity, and in-hospital death. However, ruptured versus symptomatic AAA, open versus endovascular repair, and complications were associated with increased total in-hospital costs (Table 5).

Table 4: Mean costs during 1-year follow-up in patients treated for acute AAA repair

	Endovascular repair (n = 30) Costs (€)* (min-max)	Open surgical repair (n = 34) Costs (€)* (min-max)	P-value
Visits	287 (0-600)	276 (0-800)	0.52
Costs diagnostic tests:			
- Radiology Department	338 (0-840)	27 (0-210)	<0.001
- Other Departments	11 (0-107)	22 (0-103)	0.13
Readmissions: costs procedures†	82 (0-2465)	36 (0-1207)	0.91
Readmissions: costs diagnostic tests:			
- Radiology Department	7 (0-210)	31 (0-587)	0.35
- Other Departments	18 (0-525)	36 (0-1010)	0.23
Readmissions: costs ward	1269 (0-23800)	266 (0-4284)	0.56
Total costs during 1-year follow-up	2012 (0-24325)	694 (0-6610)	0.003
95% confidence interval	676-4987	393-1384	
Total costs including 1-year follow-up	23588 (8770-79293)	36448 (1674-132136)	0.05
95% confidence interval	18187-33691	27693-51508	

AAA = abdominal aortic aneurysm
* In 2003 Euros
† Readmissions included: embolisation endoleak, leakage of the wound, back pain suspected for aneurysm related problems, endovascular repair of an aneurysm of the femoral artery, and anal blood loss.

Table 5: Univariable analyses on the natural logarithm of total in-hospital costs of acute AAA repair

	β- coefficient	Relative cost ratio*	Incremental costs†	Standard error	P-value
Age	0.002	-	-	0.01	0.85
Sex (female versus male)	-0.43	0.65	- 7318	0.33	0.20
Comorbidity‡	0.05	1.05	948	0.09	0.59
Ruptured versus symptomatic AAA	0.50	1.64	9750	0.19	0.01
Open versus endovascular repair	0.42	1.51	8393	0.19	0.03
Complications	0.92	2.50	20218	0.16	< 0.001
In-hospital death	- 0.13	0.88	- 2516	0.24	0.60

AAA = abdominal aortic aneurysm
* These numbers represent the relative costs due to the specific variable and were retrieved by transforming the β-coefficient using the formula e^{β} with β=β variable
† These numbers represent the incremental costs for the index versus the reference group and were calculated using the formula $e^{c+\beta}$-e^{c} with C=constant and β=β variable
‡ Comorbidity = cardiovascular or respiratory disease

In the multivariable regression procedure, the variables ruptured versus symptomatic AAA and open versus endovascular repair were not significantly associated with costs (Table 6).

Table 6: Multivariable regression analysis on the natural logarithm of total in-hospital costs of acute AAA repair

	β-coefficient	Relative cost ratio*	Standard error	P-value
Constant	9.33	-	0.14	< 0.001
Ruptured versus symptomatic AAA	0.21	1.24	0.17	0.20
Open versus endovascular repair	0.19	1.21	0.16	0.24
Complications	0.82	2.27	0.16	< 0.001

AAA = abdominal aortic aneurysm
* These numbers represent the relative costs due to the specific variable and were retrieved by transforming the β-coefficient using the formula e^{β} with β=β variable

The variable complications was associated with the total in-hospital costs, that is patients with complications incurred 2.27 times more total in-hospital costs than patients with no complications. On the basis of this model, the mean difference in total in-hospital costs for endovascular versus open repair, with adjustment for ruptured versus symptomatic AAA and complications, was € 3,903, in favor of endovascular repair.

Ruptured AAAs

Regarding our subgroup analysis in patients with ruptured AAAs (Table 7), the mean total in-hospital costs for patients with a ruptured infrarenal AAA were lower for those who underwent endovascular repair (€ 28,163 versus € 42,609; p = 0.06).

DISCUSSION

Endovascular repair has become an important and increasingly performed alternative to open surgery in patients with an acute AAA. The principal finding of our study was that the total in-hospital costs for endovascular repair were lower than for open surgery. In addition, total costs including the initial hospital costs and costs of 1-year follow-up were also lower for endovascular repair.

The most important cause for the difference in total in-hospital costs between endovascular and open repair were the costs of the ICU. Approximately half of the patients (15/32, 47%) who underwent endovascular repair were admitted to the ICU, whereas 31 (89%) of the 35 patients who underwent open surgery were admitted to the ICU. The length of stay in the ICU also played an

Table 7: Mean in-hospital costs and length of hospitalstay for ruptured AAA

	Endovascular repair (n = 14) Costs (€)* (min-max)	Open surgical repair (n = 25) Costs (€)* (min-max)	P-value
Preoperative costs	373 (279-418)	414 (349-492)	0.01
Costs procedure	9606 (2863-16931)	10048 (1222-24484)	0.81
Costs ICU	10786 (0-57168)	20853 (0-91883)	0.15
Costs ward	4624 (0-24752)	6226 (0-36176)	0.53
Costs postoperative diagnostic tests:			
- Radiology Department	509 (0-1673)	603 (0-1853)	0.85
- Other Departments	1733 (68-7969)	2913 (0-11767)	0.09
Costs postoperative blood products	296 (0-1432)	943 (0-7728)	0.23
Costs additional procedures	237 (0-1671)	609 (0-5467)	0.52
Total in-hospital costs	28163 (6644-78983)	42609 (1674-131536)	0.06
95%-confidence interval	17890-46565	29479-60592	
Admission time mean (SD), median			
Postoperative days on ICU	6.4 (11.3), 0.9	12.4 (16.1), 5.5	0.14
Postoperative days on ward	9.7 (14.6), 4.0	13.1 (17.3), 9.0	0.53
Postoperative days in hospital	16.1 (22.4), 6.8	25.5 (28.0), 14.8	0.19

ICU = intensive care unit, SD = standard deviation
* In 2003 Euros

important role, which was shorter for patients treated with endovascular repair than for patients who underwent open surgery (3.0 days vs. 9.4 days, respectively; $p < 0.001$).

Another finding of our study was that mean total costs of the procedures itself did not differ. However, the component costs were quite different between the procedures. Costs of the operating room, anesthesiology and personnel were higher in patients who underwent open surgery, caused by the longer procedure time in these patients. The higher costs of materials in patients who underwent endovascular repair were mainly caused by the use of expensive endografts. The high costs of blood products in patients who underwent open surgery, was caused by the large amount of blood loss in these patients. These differences cancelled out, leading to similar total costs of the procedures.

Furthermore, our study showed that costs of 1-year follow-up were higher for endovascular repair compared to open surgery. This was to be expected since regular CT-scans were performed to identify possible endoleaks, graft migration or other complications related to the endovascular repair (16, 19, 20). In addition, patients who undergo endovascular repair probably will have more complications in the long run due to these graft related failures.

Our univariable analyses showed a significant effect on total in-hospital costs of three variables: ruptured versus symptomatic AAA, open versus endovascular repair, and complications. When the three significant variables were included in a multivariable analysis, however, only complications was significant. This suggests that the demonstrated association between the variable ruptured versus symptomatic AAA and the total costs and the association between the type of repair and the total costs is explained by whether complications occurred. The difference in total in-hospital costs between the two treatments derived from the multivariable analysis, should be interpreted with caution, because the model had an R^2 of 0.39, meaning that only 39% of the variation was explained by the model.

In other studies, that determined the total in-hospital costs of open surgery in patients with ruptured AAAs, the results were quite different than our results (9-15). The most important reason for this was the large variation in the average length of stay in the ICU and on the ward reported. Furthermore, a limitation of these studies was the relatively small sample sizes compared to our study. Studies in which the total in-hospital costs for elective endovascular repair and open surgery were assessed in patients with asymptomatic AAAs showed that costs of both treatment options were lower than the costs assessed in our study in patients with an acute AAA. This was as expected due to the shorter stay in the hospital, especially in the ICU, of patients who underwent elective aneurysm repair (8, 12).

Our study has several limitations. The main problem was that the data were not based on a randomized controlled trial; therefore selection bias may be present. Also the sample size was relatively small and the follow-up was limited to 1 year. The small sample size made it hard to distinguish between statistically significant and insignificant findings. Therefore, we reported the p-values so that the reader can determine whether a finding is significant or not. In our cost comparison of endovascular and open repair in acute infrarenal AAA patients, we did not adjust for the indication of endovascular versus open surgical repair (i.e., anatomy of the aneurysm) in the included patients because this data was unfortunately not well documented (27). We did, however, limit the analyses to patients that were potentially eligible for either endovascular or open surgery and in whom selection of the type of repair was determined by anatomic morphologic considerations. Patients with an AAA with a proximal aneurysm neck shorter than 15 millimeter or an angulation of more than 90º were not considered suitable for endovascular repair. Therefore, it remains unclear whether the difference in costs occurred due to the procedure performed or to the anatomy of the aneurysm.

Another limitation was that substantially more patients with ruptured AAAs received open surgery. Therefore, we performed a subgroup analysis in patients with a ruptured AAA. Although mean total in-hospital costs for these patients did not differ, open surgery was at least € 14,000 more expensive than endovascular repair. It may be possible that we did not demonstrate sta-

tistical significance because of the large range in total in-hospital costs and the limited number of patients.

Another limitation of our study is the possible limited generalizability of the results to other countries. We used unit costs from Dutch guidelines and hospitals. However, our results may be generalized to other countries by using methods like regression techniques and Markov decision models (21, 28, 29). In these models, differences in costs of medical treatments between countries due to factors like demography, epidemiology, culture, applicability of health care, differences in medical practice, difference in resource use, funding of health care, and absolute and relative price differences can be taken into account (21, 28, 29). Furthermore, a limitation was that we used charges for tests and procedures performed due to failures and complications. In the Netherlands, however, these charges are estimations of the actual costs and therefore very similar. Furthermore, these charges accounted for less than 10% of the total in-hospital costs, which is considered acceptable in a cost accounting study (23).

To decide whether patients with an acute AAA, who are eligible for endovascular repair, should preferably be treated with this procedure, costs as well as effects should be taken into account. To deal with the limitations of this study, namely the non-randomization, small sample size, and limited follow-up, more research in this area should be considered.

In conclusion, total costs including in-hospital costs and 1-year follow-up in acute infrarenal AAA patients were lower for endovascular repair than for open surgery.

REFERENCES

1. van Sambeek MR, van Dijk LC, Hendriks JM, et al. Endovascular versus conventional open repair of acute abdominal aortic aneurysm: feasibility and preliminary results. J Endovasc Ther 2002; 9:443-448.
2. Veith FJ, Ohki T. Endovascular approaches to ruptured infrarenal aorto-iliac aneurysms. J Cardiovasc Surg (Torino) 2002; 43:369-378.
3. Verhoeven EL, Prins TR, van den Dungen JJ, Tielliu IF, Hulsebos RG, van Schilfgaarde R. Endovascular repair of acute AAAs under local anesthesia with bifurcated endografts: a feasibility study. J Endovasc Ther 2002; 9:729-735.
4. Yilmaz N, Peppelenbosch N, Cuypers PW, Tielbeek AV, Duijm LE, Buth J. Emergency treatment of symptomatic or ruptured abdominal aortic aneurysms: the role of endovascular repair. J Endovasc Ther 2002; 9:449-457.
5. Peppelenbosch N, Yilmaz N, van Marrewijk C, et al. Emergency treatment of acute symptomatic or ruptured abdominal aortic aneurysm. Outcome of a prospective intent-to-treat by

EVAR protocol. Eur J Vasc Endovasc Surg 2003; 26:303-310.
6. Resch T, Malina M, Lindblad B, Dias NV, Sonesson B, Ivancev K. Endovascular repair of ruptured abdominal aortic aneurysms: logistics and short-term results. J Endovasc Ther 2003; 10:440-446.
7. Scharrer-Pamler R, Kotsis T, Kapfer X, Gorich J, Sunder-Plassmann L. Endovascular stent-graft repair of ruptured aortic aneurysms. J Endovasc Ther 2003; 10:447-452.
8. Bosch JL, Lester JS, McMahon PM, et al. Hospital costs for elective endovascular and surgical repairs of infrarenal abdominal aortic aneurysms. Radiology 2001; 220:492-497.
9. Chew HF, You CK, Brown MG, Heisler BE, Andreou P. Mortality, morbidity, and costs of ruptured and elective abdominal aortic aneurysm repairs in Nova Scotia, Canada. Ann Vasc Surg 2003; 17:171-179.
10. Seiwert AJ, Elmore JR, Youkey JR, Franklin DP. Peter B. Samuels Award. Ruptured abdominal aortic aneurysm repair: the financial analysis. Am J Surg 1995; 170:91-96.
11. Ascher E, Scheinman M, DePippo P, Yorkovich W. Ruptured versus elective abdominal aortic aneurysm repair: outcome and cost. Ann Vasc Surg 1999; 13:613-617.
12. Bagia JS, Robinson D, Kennedy M, Englund R, Hanel K. The cost of elective and emergency repair of AAA in patients under and over the age of 80. Aust N Z J Surg 1999; 69:651-654.
13. Patel ST, Korn P, Haser PB, Bush HL, Jr., Kent KC. The cost-effectiveness of repairing ruptured abdominal aortic aneurysms. J Vasc Surg 2000; 32:247-257.
14. Tang T, Lindop M, Munday I, Quick CR, Gaunt ME, Varty K. A cost analysis of surgery for ruptured abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2003; 26:299-302.
15. Aune S, Laxdal E, Pedersen G, Dregelid E. Lifetime gain related to cost of repair of ruptured abdominal aortic aneurysm in octogenarians. Eur J Vasc Endovasc Surg 2004; 27:299-304.
16. Laheij RJ, Buth J, Harris PL, Moll FL, Stelter WJ, Verhoeven EL. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR). Br J Surg 2000; 87:1666-1673.
17. van Marrewijk C, Buth J, Harris PL, Norgren L, Nevelsteen A, Wyatt MG. Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: The EUROSTAR experience. J Vasc Surg 2002; 35:461-473.
18. Verhagen HJ, Prinssen M, Milner R, Blankensteijn JD. Endoleak after endovascular repair of ruptured abdominal aortic aneurysm: is it a problem? J Endovasc Ther 2003; 10:766-771.
19. Prinssen M, Wixon CL, Buskens E, Blankensteijn JD. Surveillance after endovascular aneurysm repair: diagnostics, complications, and associated costs. Ann Vasc Surg 2004; 18:421-427.
20. Tolia AJ, Landis R, Lamparello P, Rosen R, Macari M. Type II Endoleaks after Endovascular Repair of Abdominal Aortic Aneurysms: Natural History. Radiology 2005.
21. Drummond MF, O'Brien B, Stoddart GL, GW T. Methods for the Economic Evaluation of Health Care Programmes. New York: Oxford University Press, 1997.
22. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. New York: Oxford University Press, 1996.

23. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg: College voor zorgverzekeringen, 2004.
24. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. Health Econ 2003; 12:377-392.
25. Lee WA, Huber TS, Hirneise CM, Berceli SA, Seeger JM. Eligibility rates of ruptured and symptomatic AAA for endovascular repair. J Endovasc Ther 2002; 9:436-442.
26. Wilson WR, Fishwick G, Sir Peter RFB, Thompson MM. Suitability of ruptured AAA for endovascular repair. J Endovasc Ther 2004; 11:635-640.
27. Reichart M, Geelkerken RH, Huisman AB, van Det RJ, de Smit P, Volker EP. Ruptured abdominal aortic aneurysm: endovascular repair is feasible in 40% of patients. Eur J Vasc Endovasc Surg 2003; 26:479-486.
28. Drummond MF, Bloom BS, Carrin G, et al. Issues in the cross-national assessment of health technology. Int J Technol Assess Health Care 1992; 8:671-682.
29. Rutten-van Molken M, Doorslaer v, EKA. Multinationale kosteneffectiviteitsanalysen. In van kosten tot effecten: een handleiding voor evaluatiestudies in de gezondheidszorg, Rutten-van Molken MMPH, Busschbach JJV, Ritten FFH (ed). Maarssen: Elsevier gezondheidszorg, 1999.

6
COST-EFFECTIVENESS AND VALUE OF INFORMATION ANALYSIS

ABSTRACT

Purpose: To evaluate the cost-effectiveness of endovascular repair versus open surgery in the treatment of a ruptured abdominal aortic aneurysm (AAA) and to investigate whether performing further research to obtain additional information is justified.

Materials and methods: A Markov decision model was developed to evaluate long-term survival, quality-adjusted life years (QALYs), and lifetime costs for a hypothetical cohort of patients with ruptured AAA managed with endovascular repair or open surgery. Clinical effectiveness data were derived from a prospective multicenter study and from the literature. Cost data were derived from hospital databases and the literature. Probabilistic sensitivity analyses were performed on uncertain model parameters. Value of information analysis was performed to estimate the benefit of future clinical cost-effectiveness research.

Results: Quality-adjusted life expectancy was higher for endovascular repair than for open surgery (5.42 versus 4.85 QALY), and lifetime costs were lower for endovascular repair than for open surgery ($ 49,344 versus $ 50,765). This means that endovascular repair was superior to open surgery. In sensitivity analysis, the cost-effectiveness was influenced by short-term (i.e., 30-day) complications and mortality after endovascular repair. The value of information analysis indicated that future cost-effectiveness research in patients with ruptured AAA is justified and should concentrate on short-term costs and clinical effectiveness.

Conclusion: Our results suggest that endovascular repair yielded more QALYs and was also associated with lower lifetime costs compared with open surgery in patients with ruptured AAA. In addition, further research is justified and should concentrate on short-term costs and clinical effectiveness.

INTRODUCTION

Patients with a ruptured abdominal aortic aneurysm (AAA) who are hemodynamically stable upon presentation to the hospital are usually evaluated with a CT-scan to assess whether they are eligible for endovascular repair. If the AAA is anatomically suitable for endovascular repair the patient will be treated with this procedure, otherwise the patient will undergo open surgery (1, 2).

Recently, however, no statistical significant difference in 30-day mortality between endovascular repair and open surgery in patients with a ruptured AAA was suggested, when adjusted for patients' hemodynamic condition upon presentation to the hospital (3). In addition, after elective AAA repair, patients treated with endovascular repair had about twice the number of aneurysm-related complications requiring intervention during follow-up compared with patients treated with open surgery (4). Furthermore, costs of endovascular repair compared with open surgery in patients with ruptured AAA tend to be lower in the short term, whereas they may be higher in the long run, due to more intensive surveillance and more reinterventions during follow-up (5).

The first question is whether, from a health policy perspective, current available evidence justifies today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable. The second question is whether additional information is required to inform the decision making process for patients with ruptured AAA in the future (6). Therefore, the objective of this study is to evaluate the cost-effectiveness of endovascular repair compared with open surgery in patients with ruptured AAA and to investigate whether performing future research to obtain additional information is justified.

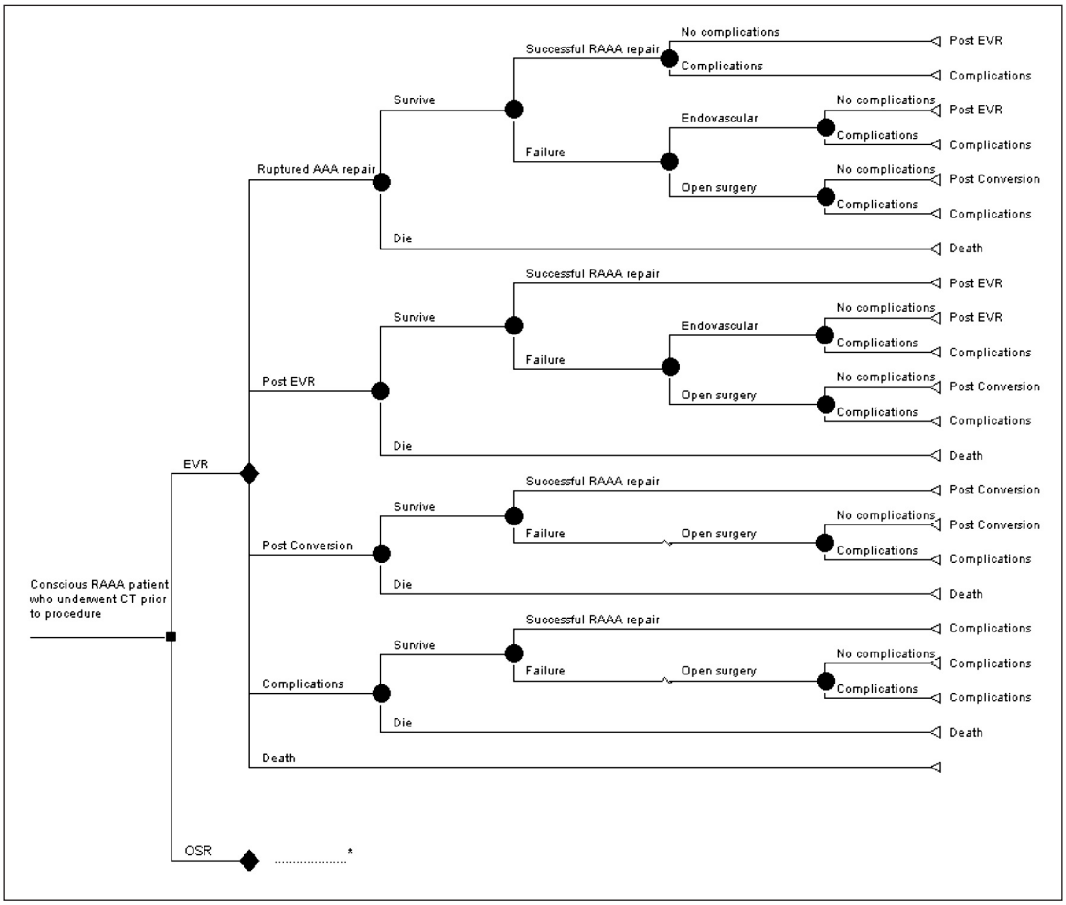
MATERIALS AND METHODS

The model

A Markov cycle tree was developed to model long-term clinical effectiveness and costs of patients treated for ruptured AAA (Figure 1) (7).

All patients underwent a CT-scan prior to the procedure. The strategies compared were endovascular repair and open surgery. During the endovascular procedure, patients died or survived. If patients survived, the initial aneurysm repair could fail or could be successful. In the event of a failure, patients were treated with additional endovascular techniques or were converted to open surgery. Postoperatively all patients were at risk of having complications. During open surgery, patients died or survived. If patients survived, the initial aneurysm repair could fail or could be successful. In the event of a failure, they were treated with additional open surgical

Figure 1: Simplified decision tree of the endovascular repair branch. Complications refer to morbidity of the procedure; failure refers to long-term complications such as endoleak.



* The structure of the open surgical branch was identical to the structure of the endovascular repair branch, except for the endovascular option after failure of the ruptured AAA repair.
■ = decision, ◆= Markov node, ● = uncertain events, ◄ = indicates the end of the cycle-tree and possible transition to another state in the next cycle, CT = computed tomography scan, EVR = endovascular repair, OSR = open surgery, AAA = abdominal aortic aneurysm.

techniques. All patients were at risk of having complications. During follow-up, patients treated successfully with endovascular repair underwent CT-scans after 3, 6, and 12 months, and annually thereafter. Patients treated successfully with open surgery were not subjected to follow-up visits. Patients whose initial endovascular repair failed were treated with endovascular or open surgical techniques. Patients in whom the initial open surgery failed were treated with open surgical techniques.

Procedures considered during follow-up after failure of endovascular repair were percutaneous procedures, such as coil embolisation of an endoleak, and conversions to open surgery (8, 9).

Procedures considered during follow-up after failure of open surgery were open surgical procedures. We assumed that, during follow-up, no more than two open surgical procedures were performed after endovascular repair and open surgery. The model updated patients' clinical status and costs monthly.

The analyses were performed according to the recommendations of the Panel on Cost-Effectiveness in Health and Medicine and performed from the societal perspective. Both costs and effects were discounted at 3% per year (10-12).

Data sources and assumptions

Clinical effectiveness

Short-term (i.e., 30-day) clinical data were obtained from a meta-analysis in which endovascular repair was compared with open surgery in patients with ruptured AAA (3) and a prospective multicenter observational study (4A-study) in which 7 institutions from the Netherlands participated (Tables 1 and 2).

Data were combined using Bayesian evidence synthesis (13). Uncertainty in the parameters of the model was reflected in distributions of each model parameter (Tables 1 and 2) (13). In our prospective multicenter observational study, 164 patients were included. These patients were hemodynamically stable upon presentation to the hospital and underwent a CT-scan or angiography to determine anatomic eligibility of the AAA for endovascular repair. If patients were anatomically suitable for endovascular repair, they were treated with this procedure (n = 58); otherwise they were treated with open surgery (n = 106). Institutional Review Board approval was obtained and informed consent was waived due to the observational nature of the study (14).

Long-term clinical effectiveness data were based on published literature, with a focus on meta-analyses and large clinical studies (Tables 1 and 2). Long-term life expectancy was calculated on the basis of age- and sex-specific mortality rates from U.S. life tables of the general population (15). An excess mortality rate to adjust survival was used for all patients and subsequently for those who had complications (16-20).

Our prospective multicenter observational study demonstrated that the most frequently reported short-term complications were cardiac, pulmonary, renal, and cerebrovascular. These complications had a long-term effect with decreased health related quality-of–life and costs were increased. Data on complications after endovascular repair that may occur after 1-month follow-up were not available. We assumed that the probability to get aneurysm-related complications requiring intervention after 1-month follow-up was equal to the probability to get aneurysm-related complications requiring intervention in electively treated patients with AAA (21).

Table 1: Model probability estimates

Parameter	Base-case	Distribution	Range	Reference
Short-term (30-day)				
Mortality				
Endovascular repair	0.21	Beta	0.15-0.40	4A-study, (3)
Open surgery	0.28	Beta	0.20-0.45	4A-study, (3)
Technical failure requiring intervention				
Endovascular repair*	0.09	Beta	0.05-0.20	4A-study
Open surgery	0.03	Beta	0.001-0.10	4A-study
Procedure related complications				
Endovascular repair†	0.10	Beta	0.05-0.30	4A-study
Open surgery†	0.17	Beta	0.10-0-35	4A-study
Long term (>30-days)				
Mortality				
Relative Risk due to ruptured AAA repair	2	Lognormal	1-4	(16)
Relative Risk of mortality due to myocardial infarction				
First year	4	Lognormal	3-6	(17)
Follow-up (per year)	2	Lognormal	1-3	(17)
Relative Risk of mortality due to pulmonary complications	4	Lognormal	2-7	(18)
Relative Risk of mortality due to renal disease	4	Lognormal	2-6	(19)
Relative Risk of mortality due to stroke				
First year	4	Lognormal	2-6	(20)
Follow-up (per year)	2	Lognormal	2-6	(20)
Annual aneurysm-related complication rates requiring intervention				
Endovascular repair†	0.09	Beta	0.05-0.20	(46)
Open surgery	0.02	Beta	0.005-0.05	(47)
Discount rate	0.03	-	0.01-0.05	(10)

AAA = abdominal aortic aneurysm
* Percutenous treatment 100%; open surgery 0%. (4A-study)
† Percutenous treatment 88%; open surgery 12 %.

Health-related quality of life

Since most patients are asymptomatic before rupture, quality of life weights before treatment were equal to those in the general population (22). Short-term quality of life adjustments were approximated by reducing a person's quality of life by 10% for the first month after endovascular repair and by 30% for the first two months after open surgery. In addition, quality of life was reduced by 5% during the day that a patient treated with endovascular repair had to undergo scheduled CT-scan. Quality of life weights after recovery from treat-

Table 2: Model costs and quality of life estimates

Parameter	Base-case	Distribution	Range	Reference
Costs (U.S. $ 2005)				
Endovascular repair	38296	Lognormal	24327-63320	(5)
Open surgery	57940	Lognormal	40086-82394	(5)
Percutaneous treatment during follow-up	7284	Lognormal	3642-10926	(28)
Relaparotomy during follow-up	19024	Lognormal	9512-28536	(4)
Follow-up imaging	865	Lognormal	432-1297	(5)
Annual costs of complications				
Non-fatal myocardial infarction				
First year	22778	Lognormal	11389-34167	(29)
Follow-up (per year)	1541	Lognormal	770-2311	(29)
Pulmonary complications	5929	Lognormal	2964-8893	(30)
Renal disease, dialysis dependent				
First year	17772	Lognormal	8886-26658	(31)
Follow-up (per year)	8445	Lognormal	5233-15698	(31)
Stroke				
First year	35383	Lognormal	17692-53075	(32)
Follow-up (per year)	13178	Lognormal	6589-19767	(32)
Quality of life reduction coefficients				
Non-fatal myocardial infarction	0.91	Uniform	0.81-0.98	(25)
Pulmonary complications	0.91	Uniform	0.81-0.98	(26)
Renal disease, dialysis dependent	0.68	Uniform	0.58-0.78	(26)
Stroke	0.61	Uniform	0.51-0.71	(27)

ment were similar to those before treatment (23, 24). For patients with irreversible complications, long-term quality of life adjustments were made by multiplying each year of life, adjusted for age- and sex-specific values in the general population, by a coefficient that ranged from 0.61 to 0.91 depending on the type of complication (Table 2) (25-27).

Cost data

Cost data included costs of procedures, morbidity, and imaging during follow-up (Table 2) (4, 5, 28-32). Data on initial procedure costs and imaging during follow-up were derived from a retrospective cost analysis on ruptured AAAs (5). Data on morbidity costs were derived from the literature with a focus on large clinical studies (4, 28-32). All costs were converted to year 2005 U.S. dollars on the basis of the Medical Care Component of the Consumer Price Index (33). If costs were reported in Euros, they were converted into U.S. Dollars using a currency rate of 1 Euro =

1.25 U.S. dollars (34). If in the literature the year in which costs were expressed was not reported, we assumed that they were expressed in the year prior to publication.

Procedure costs included costs of preoperative care, costs of the procedure itself, cost of intensive care unit stay, cost of regular ward stay, cost of diagnostic in-hospital tests, cost of blood products, and costs of additional procedures. Costs of follow-up imaging in patients treated with endovascular repair included hospital costs for imaging and physician costs. All of these items contain costs of personnel, use of equipment, use of material, investment during use, maintenance, administration, and overhead. We assumed that costs of a (re)laparotomy during follow-up due to failure of the initial procedure were equal to an elective repair of the AAA.

Patient time costs during hospital stay were calculated by multiplying the daily wage rate for all men ($ 144 per day) by the number of days spent in the hospital (33). The number of days spent in the hospital was based on the prospective multicenter observational study, described above, and was 13 days after endovascular repair and 18 days after open surgery. Patient time costs for follow-up imaging were calculated by multiplying the daily wage rate by 0.5.

Data analysis

In the base-case (i.e., initial) analysis, we evaluated a cohort of 70-year old males with ruptured AAA who underwent a CT-scan prior to the procedure (i.e., the decision to treat the patients with endovascular repair or open surgery was based on the AAA anatomy and not on the patients' hemodynamic condition). Quality-adjusted life years (QALYs), lifetime costs, and net health benefits (NHB) were calculated for these patients. The NHB was calculated using the formula: $NHB_{procedure} = E_{procedure} - ((C_{procedure}) / WTP)$. $E_{procedure}$ = QALYs associated with procedure, $C_{procedure}$ = costs associated with procedure, and WTP = willingness to pay = $ 75,000.

We performed sensitivity analyses on uncertain model parameters, such as 30-day mortality, complication rates, procedure costs, follow-up imaging costs, and health-related quality of life weights. Threshold analyses using net health benefit as outcome were performed to determine the value of the variables at which the optimal treatment strategy changed. We considered $ 75,000 per QALY gained the threshold WTP (35).

Analyses were performed using TreeAge Pro 2006 (Boston, MA) and Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA).

Value of information (VOI) analysis

VOI analysis estimates the difference between the expected value of a decision based on current available evidence and the expected value of a decision based on perfect information. This difference indicates the value of future research. For this analysis, costs and effects were transformed

into one composite outcome, net monetary benefits (NMB), which is the monetary equivalent of effectiveness (36). The NMB was calculated using the formula: NMB = WTP * $E_{procedure}$ – $C_{procedure}$. WTP = willingness to pay = $ 75,000, $E_{procedure}$ = QALYs associated with procedure, and $C_{procedure}$ = costs associated with procedure. VOI analysis techniques were used to calculate the expected value of perfect information (EVPI) by performing 100,000 Monte Carlo simulations. The EVPI was defined as the difference between the expected value of the decision based on existing information and the expected value of the decision based on perfect information. Next, the population EVPI was estimated, which was the total EVPI per patient multiplied by the total number of patients that would benefit from the decision over the lifetime of the technology. It was estimated that in The Netherlands about 200 patients with ruptured AAA are eligible for both endovascular repair or open surgical treatment annually and would therefore benefit from future research in this area (37). The lifetime of the technology was estimated to be 5 years. The discount rate used was 3% per year. Furthermore, to identify what type of research would be of interest (e.g., short-term or long-term outcomes), we assessed the EVPI for particular parameters, the expected value of partial perfect information (EVPPI). The EVPPI was defined as the difference between the expected value of the decision based on existing information and the expected value of the decision based on perfect information on particular parameters (38-41). Analyses were performed using TreeAge Pro 2006 (Boston, MA).

RESULTS

Base-case analysis

Quality-adjusted life expectancy was 0.57 QALY higher for endovascular repair than for open surgery (5.42 versus 4.85 QALY). Lifetime costs were lower for endovascular repair than for open surgery ($ 49,344 versus $ 50,765). Using base-case estimates, endovascular repair yielded more QALYs gained and cost less than open surgery (i.e., endovascular repair dominated open surgery) (Table 3).

Table 3: Costs and clinical effects for endovascular repair versus open surgery in patients with ruptured AAA

	Total lifetime costs (U.S dollars)*	QALE (years)*	NHB (QALY)
Endovascular repair†	49,344	5.42	4.76
Open surgery	50,765	4.85	4.17

QALE = quality adjusted life expectancy, NHB = net health benefits, QALY = quality adjusted life years
* Discounted at 3% per year.
† Endovascular repair dominated open surgery.

Sensitivity analysis

The influence of varying 30-day mortality rates for both procedures was evaluated by substituting a wide range of values for these parameters (Table 1 and 2). If the procedure related complication rate after endovascular repair was < 0.22, endovascular repair remained cost-effective compared with open surgery (Table 4).

Table 4: Threshold values for which endovascular repair was cost-effective compared with open surgery in patients with ruptured AAA (incremental cost effectiveness ratio for endovascular repair versus open surgery, willingness to pay (WTP) was $75,000 per QALY).

Parameter	EVR dominant	ICER < $75,000 per QALY	ICER > $75,000 per QALY	OSR dominant
Short-term (30-day) procedure related complications EVR	≤ 0.12	≥ 0.13 and ≤ 0.22	≥ 0.23 and ≤ 0.27	≥ 0.28
Short-term (30-day) procedure related complications OSR	≥ 0.14	≤ 0.13	-	-
Short-term (30-day) mortality EVR	≤ 0.29	≥ 0.30 and ≤ 0.31*	-	≥ 0.32†
Short-term (30-day) mortality OSR	≤ 0.40	≥ 0.41	-	-
Costs initial procedure EVR	≤ $45,000	> $45,000	-	-
Costs initial procedure OSR	> $56,000	≤ $56,000	-	-

EVR = endovascular repair, ICER = incremental cost effectiveness ratio, QALY = quality-adjusted life year, OSR = open surgery
* Open surgery yielded more QALYs and cost more than endovascular repair; endovascular repair was cost-effective given a WTP of $75,000 per QALY.
† Open surgery yielded more QALYs and cost more than endovascular repair; open surgery was cost-effective given a WTP of $75,000 per QALY.

If 30-day mortality after endovascular repair was ≤ 0.29, endovascular repair was superior to open surgery. If 30-day mortality after endovascular repair was ≥ 0.30 and ≤ 0.31, endovascular repair was cost-effective compared with open surgery. If 30-day mortality after endovascular repair was ≥ 0.32, open surgery was cost-effective compared with endovascular repair. The model was insensitive to any other substitution of parameters given a WTP of $ 75,000 per QALY.

Value of information analysis

The EVPI was $ 5,836 per patient and the population EVPI was approximately $ 5 million for a WTP of $ 75,000 per QALY. This means that if the societal WTP equals $ 75,000 per QALY, the value of perfect information concerning the choice of treatment with endovascular repair versus open surgery in patients with ruptured AAA, is estimated to be $ 5 million for the Dutch population. Using a WTP of $ 120,000 per QALY, the population EVPI was approximately $ 4 million (Figure 2).

The EVPPI for short-term clinical risks (i.e., 30-day mortality and procedure-related complications) was $ 484,032 (Figure 3).

Figure 2: Population expected value of perfect information (EVPI) for the decision between endovascular repair and open surgery in patients with a ruptured abdominal aortic aneurysm for the Dutch population.

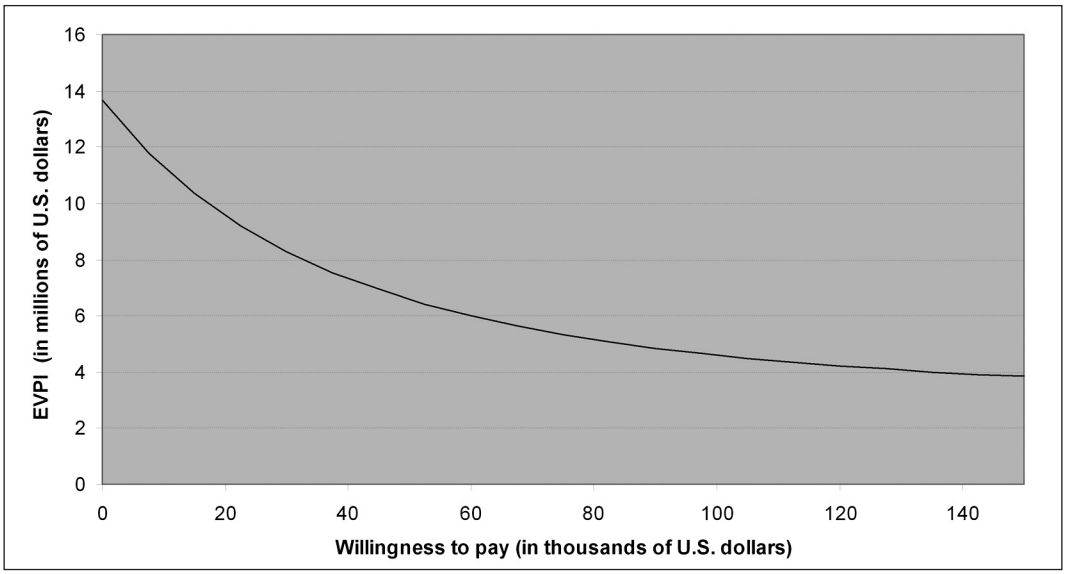
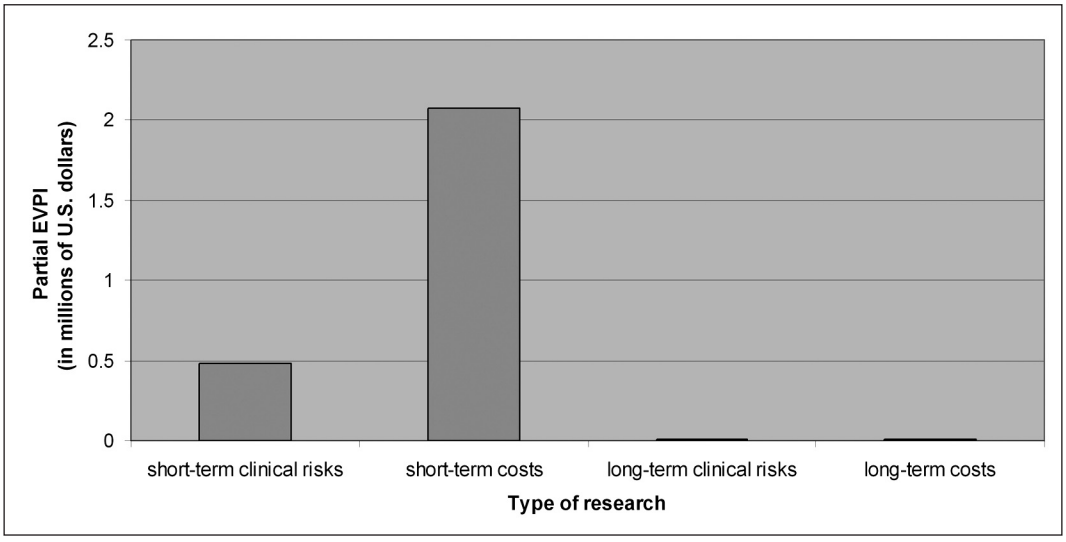


Figure 3: Expected value of partial perfect information (EVPPI) for different types of research in the Dutch population.



The EVPPI for short-term costs (i.e., costs of the initial procedure and procedure-related complications) was $ 2,073,618. The EVPPI for long-term clinical risks (i.e., long-term mortality and reinterventions rates) was practically $ 0. The EVPPI for long-term costs (i.e., costs of procedure-related complications and reinterventions) was also practically $ 0.

DISCUSSION

In this study, we evaluated whether, from a health policy perspective, current available evidence justifies today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable. Treatment with endovascular repair was associated with an increase in QALYs compared with open surgery and a decrease in lifetime costs. In addition, we investigated whether additional information should be obtained in order to make better decisions in the future for patients with ruptured AAA. Our results suggest that it is justified to initiate further research in this area. Furthermore, we concluded that future research should concentrate on short-term (i.e., 30-day) costs and clinical effectiveness.

On the basis of the parameters used in our model, endovascular repair had higher QALYs and lower costs than open surgery. Sensitivity analysis showed that our results were sensitive to short-term (i.e., 30-day) complications and mortality after endovascular repair and open surgery for the initial ruptured AAA repair, given a WTP of $75,000 per QALY. It should be noted, however, that the ability of the operator to perform endovascular repair or open surgery may have an impact on the short-term complication and mortality rates and therefore may affect the results of our model. In addition, our results were sensitive to costs of the initial endovascular repair or open surgery. This indicates that costs of the endografts may affect the results of our model.

The population EVPI of about $5 million indicates that more research is justified. For the USA with a much larger population than the Netherlands, the population EVPI would be even higher. The population EVPPI indicated that the most relevant information in future research could be obtained from research that evaluates short-term (i.e., 30-day) costs and clinical effectiveness. The recommended study design for future research is a randomized controlled trial comparing endovascular repair with open surgery in patients with ruptured AAA. It should be noted that in practice, surgeons tend to apply more lenient criteria for endovascular repair in case of severe comorbidity in order to avoid open surgery. This practice should be considered when designing randomized controlled trials in patients with ruptured AAA since it may affect generalizability of these studies. We found that the additional value of research on long-term costs and clinical effectiveness would be relatively small. It should be noted, however, that in our model we based the probability to get long-term complications after endovascular repair for ruptured AAA on data from patients treated for asymptomatic AAA; therefore the uncertainty for long-term re-

search was small. This assumption, however, seems to be justified as suggested by Oranen et al. (21). In addition, recent literature suggests that current developments in endografts might result in better performance and better outcome and that the indication for secondary interventions after endovascular repair is changing (42-44).

Several studies compared endovascular repair with open surgery in patients with asymptomatic AAAs. In patients treated electively for AAA, endovascular repair was associated with more complications and reinterventions during follow-up compared with open surgery (4, 45). Therefore, after 4 years of follow-up, endovascular repair was not cost-effective compared with open surgery in patients electively treated for AAA (4). In our study, the higher costs during follow-up after endovascular repair were compensated by lower costs of the initial procedure for endovascular repair compared with open surgery.

Our study had several limitations. The parameters in our model were derived from non-randomized observational studies. Therefore, our results may be subject to selection bias. In addition, several assumptions were made. For example, we assumed that follow-up after endovascular repair for ruptured AAA was similar to follow-up after endovascular repair for elective AAA. This may have led to an underestimation of the aneurysm-related complications during follow-up for endovascular repair, and therefore an underestimation of the lifetime costs for endovascular repair. Furthermore, we assumed a maximum number of procedures performed after failure of the initial procedure. In performing sensitivity analyses, however, we investigated the influence of these assumptions on the base-case outcomes and found that the model was insensitive to the annual aneurysm-related complication rate for both procedures. In addition, in the VOI the number of patients that is expected to benefit from additional research was a highly influential parameter in the population EVPI. It is not clear whether country-specific or the worldwide population should be used as the population that may benefit from further research. Furthermore, the lifetime of a technology is another highly influential, uncertain parameter in the VOI. Finally, the population EVPI depends on the WTP. To be on the conservative side we used the country-specific population, a fairly short lifetime of the technology, and calculated the population EVPI for varying WTP which demonstrated a high expected benefit from performing further research.

More research seems to be justified based on our results. Our VOI analysis suggested that information on short-term costs and clinical effectiveness is a key feature in future research. Therefore, the authors recommend that, as mentioned above, besides clinical effectiveness, costs will be subject of investigation in all research that will be performed in patients with ruptured AAA.

In conclusion, our results, which were based on the best available data, suggest that endovascular repair is more effective and costs less compared with open surgery in patients with ruptured

AAA. Therefore, current available evidence justifies today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable. In addition, further research is justified and should concentrate on short-term costs and clinical effectiveness of endovascular repair versus open surgery in patients with ruptured AAA.

REFERENCES

1. Visser JJ, Bosch JL, Hunink MG, et al. Endovascular repair versus open surgery in patients with ruptured abdominal aortic aneurysms: clinical outcomes with 1-year follow-up. J Vasc Surg 2006; 44:1148-1155.
2. Peppelenbosch N, Geelkerken RH, Soong C, et al. Endograft treatment of ruptured abdominal aortic aneurysms using the Talent aortouniiliac system: an international multicenter study. J Vasc Surg 2006; 43:1111-1123.
3. Visser JJ, Sambeek v, M.R.H.M., Hamza TH, Hunink MG, Bosch JL. Endovascular repair and open surgery in patients with ruptured abdominal aortic aneurysms: systematic review. Accepted for publication in Radiology (In press).
4. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005; 365:2179-2186.
5. Visser JJ, van Sambeek MR, Hunink MG, et al. Acute abdominal aortic aneurysms: cost analysis of endovascular repair and open surgery in hemodynamically stable patients with 1-year follow-up. Radiology 2006; 240:681-689.
6. Fenwick E, Palmer S, Claxton K, Sculpher M, Abrams K, Sutton A. An iterative bayesian approach to health technology assessment: application to a policy of preoperative optimization for patients undergoing major elective surgery. Med Decis Making 2006; 26:480-496.
7. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993; 13:322-338.
8. Verzini F, Cao P, De Rango P, et al. Conversion to open repair after endografting for abdominal aortic aneurysm: causes, incidence and results. Eur J Vasc Endovasc Surg 2006; 31:136-142.
9. Tonnessen BH, Sternbergh WC, 3rd, Money SR. Mid- and long-term device migration after endovascular abdominal aortic aneurysm repair: a comparison of AneuRx and Zenith endografts. J Vasc Surg 2005; 42:392-400; discussion 400-391.
10. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
11. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. Jama 1996; 276:1339-1341.
12. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996; 276:1253-1258.

13. Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Med Decis Making 2002; 22:290-308.
14. Central Committee on Research Involving Human Subjects. Available at: http://www.ccmo-online.nl/main.asp?pid=1. Date accessed: February 10, 2006.
15. National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/lftbls/life/1966.htm. Date accessed: October 25, 2006.
16. van Dongen HP, Leusink JA, Moll FL, Brons FM, de Boer A. Ruptured abdominal aortic aneurysms: factors influencing postoperative mortality and long-term survival. Eur J Vasc Endovasc Surg 1998; 15:62-66.
17. Bronnum-Hansen H, Jorgensen T, Davidsen M, et al. Survival and cause of death after myocardial infarction: the Danish MONICA study. J Clin Epidemiol 2001; 54:1244-1250.
18. Frostad A, Soyseth V, Haldorsen T, Andersen A, Gulsvik A. Respiratory symptoms and 30-year mortality from obstructive lung disease and pneumonia. Thorax 2006.
19. Annual Data Report 2006. United States Renal Data System: Available at: http://www.usrds.org/. Date accessed: October 25, 2006.
20. Bronnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. Stroke 2001; 32:2131-2136.
21. Oranen BI, Bos WT, Verhoeven EL, et al. Is emergency endovascular aneurysm repair associated with higher secondary intervention risk at mid-term follow-up? J Vasc Surg 2006; 44:1156-1161.
22. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making 2006; 26:391-400.
23. Tambyraja AL, Fraser SC, Murie JA, Chalmers RT. Quality of life after repair of ruptured abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2004; 28:229-233.
24. Hinterseher I, Saeger HD, Koch R, Bloomenthal A, Ockert D, Bergert H. Quality of life and long-term results after ruptured abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2004; 28:262-269.
25. Kuntz KM, Tsevat J, Goldman L, Weinstein MC. Cost-effectiveness of routine coronary angiography after acute myocardial infarction. Circulation 1996; 94:957-965.
26. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. Med Care 2000; 38:583-637.
27. Hallan S, Asberg A, Indredavik B, Wideroe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. J Intern Med 1999; 246:309-316.
28. Steinmetz E, Rubin BG, Sanchez LA, et al. Type II endoleak after endovascular abdominal aortic aneurysm repair: a conservative approach with selective intervention is safe and cost-effective. J Vasc Surg 2004; 39:306-313.

29. Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. Am J Cardiol 1998; 81:1110-1115.
30. Hilleman DE, Dewan N, Malesker M, Friedman M. Pharmacoeconomic evaluation of COPD. Chest 2000; 118:1278-1285.
31. Hamel MB, Phillips RS, Davis RB, et al. Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Ann Intern Med 1997; 127:195-202.
32. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. Stroke 1996; 27:1459-1466.
33. Bureau of Labor Statistics. Available at: http://data.bls.gov/PDQ/servlet/SurveyOutputServlet. Accessed August 30, 2006.
34. FXHistory: historical currency exchange rates. Available at: http://www.oanda.com/convert/fxhistory. Date accessed: December 28, 2006.
35. Azimi NA, Welch HG. The effectiveness of cost-effectiveness analysis in containing costs. J Gen Intern Med 1998; 13:664-669.
36. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998; 18:S68-80.
37. Centraal Bureau voor de Statistiek. Available at: http://statline.cbs.nl/StatWeb/start.asp?lp=search. Date accessed: October 11, 2006.
38. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999; 18:341-364.
39. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. Med Decis Making 1998; 18:95-109.
40. Claxton K, Neumann PJ, Araki S, Weinstein MC. Bayesian value-of-information analysis. An application to a policy model of Alzheimer's disease. Int J Technol Assess Health Care 2001; 17:38-55.
41. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. Med Decis Making 2004; 24:207-227.
42. van Marrewijk CJ, Leurs LJ, Vallabhaneni SR, Harris PL, Buth J, Laheij RJ. Risk-adjusted outcome analysis of endovascular abdominal aortic aneurysm repair in a large population: how do stent-grafts compare? J Endovasc Ther 2005; 12:417-429.
43. Brewster DC, Jones JE, Chung TK, et al. Long-term outcomes after endovascular abdominal aortic aneurysm repair: the first decade. Ann Surg 2006; 244:426-438.
44. Silverberg D, Baril DT, Ellozy SH, et al. An 8-year experience with type II endoleaks: natural history suggests selective intervention is a safe approach. J Vasc Surg 2006; 44:453-459.
45. Blankensteijn JD, de Jong SE, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005; 352:2398-2405.
46. Drury D, Michaels JA, Jones L, Ayiku L. Systematic review of recent evidence for the safety and

efficacy of elective endovascular repair in the management of infrarenal abdominal aortic aneurysm. Br J Surg 2005; 92:937-946.

47. Adam DJ, Fitridge RA, Raptis S. Late reintervention for aortic graft-related events and new aortoiliac disease after open abdominal aortic aneurysm repair in an Australian population. J Vasc Surg 2006; 43:701-705; discussion 705-706.

7
GENERAL DISCUSSION

GENERAL DISCUSSION

The aim of this thesis was to determine the optimal treatment for patients with ruptured abdominal aortic aneurysm (AAA) using a decision-analytic approach. From both a medical and an economic perspective, we evaluated whether these patients should be treated with endovascular repair or open surgery. This thesis describes the findings from the literature in a systematic way. Furthermore, the clinical effects and a prediction rule that predicts 30-day mortality in patients with ruptured AAA after endovascular repair or open surgery were presented. In addition, we assessed costs for both treatment options. Also, costs and clinical effects were evaluated in a decision analytic model. In this general discussion, the main findings and methodological issues are discussed. Finally, implications for future research are considered.

Main findings

In the western world, the population is aging. People over 65 years are the fastest growing age group in the coming decades. Therefore, it is not surprising that several studies have indicated an increase in abdominal aortic aneurysms (AAAs) and subsequently, ruptured AAAs (1-4).

Ruptured AAA is a life threatening condition that requires immediate intervention in order to avoid death. Mortality in patients with a ruptured AAA treated with open surgery remains high, in spite of the exponential growth in technological developments in medicine (5). Since 1994, endovascular aneurysm repair in patients with a ruptured AAA has proven to be feasible and has become an important and increasingly performed alternative to open surgery in patients with ruptured AAA (6-18).

Since the introduction of endovascular repair for patients with ruptured AAA, the treatment policy for these patients changed. Due to the minimal invasive nature of endovascular repair, most physicians assume that endovascular repair is the best treatment for these patients. In sufficiently equipped hospitals, patients who are hemodynamically stable receive a CT-scan or angiography prior to the procedure to assess anatomic eligibility for endovascular repair. If patients are anatomically suitable they are treated with this procedure, if not, they are treated with open surgery. Those who are hemodynamically too unstable are immediately transported to the operating room for open surgery (19).

We systematically evaluated published studies comparing endovascular repair with open surgery in patients with ruptured AAA and adjusted for differences in inclusion criteria among the studies. We found that 30-day mortality after adjustment for patients' hemodynamic condition upon presentation was not statistically significant for endovascular repair compared with open surgery in patients with ruptured AAA.

Furthermore, in a clinical study we found that 30-day mortality and morbidity were similar for endovascular repair and open surgery in patients with ruptured AAA; this similarity was sustained after one-year follow-up (20). In the absence of randomization, we focused our comparison on hemodynamically stable patients to make the treatment groups more homogeneous and the comparison as valid as possible.

To identify patients that may benefit more from endovascular repair than others, we stratified according to risk for cardiac complications after the procedure. Our results suggested that patients with lower risk for cardiac complications had a better chance to survive and had less morbidity after open surgery than after endovascular repair. In contrast, patients with higher risk for cardiac complications were better off with endovascular repair than with open surgery.

The Glasgow Aneurysm Score (GAS) is a prediction rule recommended to predict in-hospital mortality after open surgery for patients with ruptured and unruptured AAA (21). In our study, the GAS showed limited discriminative abilities in patients with ruptured AAA treated with endovascular repair or open surgery. The limited discriminative ability of the GAS may be due to the introduction of endovascular repair in patients with ruptured AAA. When the GAS was developed, only open surgery was applied to treat ruptured AAAs. In addition, the limited discriminative ability of the GAS suggests that factors not involved in the GAS influenced mortality after repair for ruptured AAA. We modified the GAS into a prediction rule that predicts 30-day mortality after endovascular repair or open surgery by adding patients' hemodynamic stability prior to the procedure and the type of procedure performed to the GAS variables. We showed that, considering the included risk factors, 30-day mortality was always lower if patients with ruptured AAA were treated with endovascular repair as opposed to open surgery, although these results were not statistically different.

In-hospital costs for endovascular repair seemed to be lower than for open surgery (22). The most important cause for this difference was the costs of the ICU. Patients who underwent endovascular repair were admitted to the ICU less often than patients treated with open surgery. In addition, the length of stay in the ICU and in the hospital also played an important role, which was shorter for patients treated with endovascular repair than for patients who underwent open surgery. Costs of the procedures itself did not differ. However, the component costs were quite different between the procedures. Costs of the operating room, anesthesiology and personnel were higher in patients who underwent open surgery, caused by the longer procedure time in these patients. The higher costs of materials in patients who underwent endovascular repair were mainly caused by the use of expensive endografts. The high costs of blood products in patients who underwent open surgery, was caused by the large amount of blood loss in these patients. These differences cancelled out, leading to similar total costs of the procedures.

Furthermore, costs of one-year follow-up were higher for endovascular repair compared with open surgery. This was to be expected since regular CT-scans were performed to identify possible endoleaks, graft migration or other complications related to the endovascular repair (23-25). In addition, patients who undergo endovascular repair probably will have more re-interventions in the long run due to these graft related failures (26). Overall, however, total costs, including in-hospital costs and costs of one-year follow-up, were lower for endovascular repair than for open surgery.

Using results from the above studies, we evaluated whether, from a health policy perspective, current available evidence justifies today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable, using a decision analytic model. Treatment with endovascular repair was associated with an increase in QALYs compared with open surgery and a decrease in lifetime costs. In addition, we investigated whether additional information should be obtained in order to make better decisions in the future for patients with ruptured AAA. Our results suggest that it is justified to initiate further research in this area. Furthermore, we concluded that future research should concentrate on short-term (i.e., 30-day) costs and clinical effectiveness.

Overall, from the patients' perspective, we were able to demonstrate lower short-term mortality after endovascular repair compared with after open surgery, although this difference was not statistically different. It is likely that some patients will benefit from endovascular repair whereas others may not. On one hand, patients with severe comorbidity are likely to benefit from endovascular repair, as suggested in chapter 3. On the other hand, patients with an AAA anatomy unsuitable for endovascular repair are unlikely to benefit from this procedure. Therefore, proper selection is needed in order to give patients the best available treatment.

Furthermore, from a health policy perspective, it is likely that endovascular repair is cost-effective compared with open surgery. Therefore, current available evidence justifies today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable.

Methodological considerations

To determine effectiveness of treatments, a randomized controlled clinical trial is the recommended study design. In this thesis, however, only observational research was included. With this approach, several problems exist and therefore caution must be exercised when interpreting the results of this thesis.

In the systematic review, no randomized controlled clinical trials were included and only observational studies were available. Observational studies are prone to selection bias. The effect of this bias is likely to be in favor of endovascular repair since all patients treated with this proce-

dure were in a hemodynamically stable condition upon presentation to the hospital as opposed to those who were treated with open surgery. In addition, as with many reviews, definitions and protocols varied across the studies, sometimes definitions or data were not reported. Furthermore, the systematic review may have been affected by publication bias (i.e., the greater likelihood of publication of positive results or results based on large sample sizes). Small studies with higher mortality rates for endovascular repair than for open surgery seemed to be underrepresented, which may have favored endovascular repair. In addition, uncertainty remains concerning the long-term effectiveness of endovascular repair for patients with a ruptured AAA.

In the clinical analysis, the patients were not randomly assigned to endovascular repair and open surgery but selection was based on patients' hemodynamic condition and anatomic suitability for endovascular repair. Therefore, selection bias may be present. In addition, the sample sizes of both treatment groups were small and follow-up was limited to one year. Consequently, long-term effectiveness of endovascular repair versus open surgery in patients with ruptured AAA remains unclear.

Prediction rules can be used to predict mortality after a procedure. Our aim was to validate the GAS and to modify this into a prediction rule that can be used for both endovascular repair and open surgery in patients with ruptured AAA. The definitions of risk factors were slightly different from the original GAS. Furthermore, the data for the prediction rule was not based on a randomized controlled trial; therefore selection bias may have affected our results. In addition, the treatment protocols between the participating hospitals were slightly different. The criteria for patients being hemodynamically (un)stable differed across the hospitals. In addition, the types of endografts on stock were not similar for all hospitals. As a result, different anatomic criteria were applied across the participating hospitals. Observational studies, however, may be a better representation of daily clinical practice than randomized controlled trials .

In the cost analysis, the main problem was that the data were not based on a randomized controlled trial; therefore selection bias may be present. Also the sample size was relatively small and the follow-up was limited to one year. The small sample size made it hard to distinguish between statistically significant and insignificant findings. Another limitation of this study was the possible limited generalizability of the results to other countries as different accounting systems are used across countries.

Decision-analytic models can evaluate cost-effectiveness (30). In these models, however, assumptions have to be made since reality is complex. Another limitation of such models is that the input parameters come from multiple sources. In the model we developed, all data of the above studies was used. These data, however, were derived from non-randomized observational studies making the results subject to selection bias. An advantage of these models is that strat-

egies can be compared with lifetime follow-up. In the value-of-information (VOI) analysis, the number of patients that is expected to benefit from additional research was a highly influential parameter in the population EVPI. It is not clear whether country-specific, continent-specific, or the worldwide population should be used as the annual population to benefit. Furthermore, the lifetime of a technology and the societal willingness-to-pay were highly influential, uncertain parameters in the VOI.

As far as we know, one randomized controlled trial is ongoing (31) but it may take years before results are available. As endovascular repair is increasingly performed, data of solid research are needed at this time. Several biases are present, however, decisions have to be made and therefore, presenting the available evidence in a structured way contributes to the decision-making process in patients with ruptured AAA.

Future directions

Based on results from our value-of-information analysis, more research on endovascular repair versus open surgery in patients with ruptured AAA seems justified. It should be noted, however, that this conclusion is only valid if effects and costs of both treatment options remain unchanged. In addition, in the value of information calculations, the improvement of treatments, such as better endografts, was not taken into account.

Our results suggested that information on short-term costs and clinical effectiveness is a key feature in future research. Therefore, we recommend that, besides clinical effectiveness, costs will be subject of investigation in all research that will be performed in patients with ruptured AAA. Furthermore, more data on follow-up than currently available seems to give no expected improvement on the decision whether patients should be treated with endovascular repair or open surgery.

In addition, more research focusing on selection criteria and survival chances needs to be performed. A predictive tool may be used to identify patients who may benefit from endovascular repair and those who are unlikely to benefit from this procedure. Furthermore, future studies should investigate which patients should go immediately to the operating room for open surgery and which patients should undergo imaging prior to the therapeutic procedure to determine anatomic eligibility for endovascular repair. Similar to hemodynamically stable patients, hemodynamically unstable patients might better undergo endovascular repair than open surgery if the anatomy is suitable. Therefore, it remains to be clarified whether hemodynamically unstable patients should undergo imaging prior to the procedure, although most patients appear to be sufficiently stable to do so (32). In addition, since patient populations may change overtime, the development of a prediction tool is an ongoing process; therefore we encourage further validation and adjustment of our new prediction rule.

Furthermore, we recommend ongoing prospective observational research in patients with ruptured AAA. Prospective observational studies reflect daily practice and changes in treatment policy overtime (28, 29). This is of particular interest in this group of patients, since new types of endografts, requiring more lenient anatomic criteria, are becoming rapidly available. Observational studies are needed alongside randomized clinical trials since they provide additional information about clinical practice . Whereas randomized trials assess efficacy under controlled conditions in highly selected patients, observational studies assess effectiveness as observed in daily clinical practice.

The recommended study design for future research is a randomized controlled trial comparing endovascular repair with open surgery in patients with ruptured AAA. It should be noted that in practice, surgeons tend to apply more lenient criteria for endovascular repair in case of severe comorbidity in order to avoid open surgery. This practice should be considered when designing randomized controlled trials in patients with ruptured AAA since it may affect generalizability of these studies. Whatever study will be undertaken, generalizability and a limited time horizon are always limitations that have to be dealt with. Nevertheless, especially in a field where rapid technology improvements are expected to be made, it should be questioned whether a randomized trial is the ultimate way of performing research since generalizability of that research will be limited.

Whereas this thesis rather focused on the curative part of the ruptured AAAs, it is always better to prevent than to cure. Therefore, future research regarding ruptured AAAs should take prevention of AAA into account. A recently published study showed that angiotensin converting enzyme (ACE) inhibitors may be related to a lower chance of rupture of the AAA (33). This research highlights the need for further investigation in prevention of rupture of the AAA. Furthermore, probably the most gain in survival in patients with ruptured AAA can be obtained by the introduction of a screening program in patients at risk to develop an AAA (34). Nowadays, families in which AAAs were previously diagnosed undergo abdominal ultrasounds regularly to detect a possible AAA at an early stage. In addition, all males over the age of 65 are likely to benefit from screening for AAA (35).

In summary, the results of this thesis demonstrate that endovascular repair and open surgery are feasible in patients with ruptured AAA. With the current knowledge, it seems justified to treat all anatomically eligible patients with a ruptured AAA with endovascular repair. Further research in this area is justified and should concentrate on short-term (i.e., 30-day) clinical effectiveness and costs. In addition, the development of a prediction tool to identify patients who may benefit from endovascular repair and those who are unlikely to benefit from this procedure is an ongoing process; therefore, we encourage further validation and updating of our prediction rule.

REFERENCES

1. Filipovic M, Goldacre MJ, Roberts SE, Yeates D, Duncan ME, Cook-Mozaffari P. Trends in mortality and hospital admission rates for abdominal aortic aneurysm in England and Wales, 1979-1999. Br J Surg 2005; 92:968-975.
2. Best VA, Price JF, Fowkes FG. Persistent increase in the incidence of abdominal aortic aneurysm in Scotland, 1981-2000. Br J Surg 2003; 90:1510-1515.
3. Gillum RF. Epidemiology of aortic aneurysm in the United States. J Clin Epidemiol 1995; 48:1289-1298.
4. Reitsma JB, Pleumeekers HJ, Hoes AW, et al. Increasing incidence of aneurysms of the abdominal aorta in The Netherlands. Eur J Vasc Endovasc Surg 1996; 12:446-451.
5. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. Br J Surg 2002; 89:714-730.
6. Greco G, Egorova N, Anderson PL, et al. Outcomes of endovascular treatment of ruptured abdominal aortic aneurysms. J Vasc Surg 2006; 43:453-459.
7. Franks S, Lloyd G, Fishwick G, Bown M, Sayers R. Endovascular treatment of ruptured and symptomatic abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31:345-350.
8. Vaddineni SK, Russo GC, Patterson MA, Taylor SM, Jordan WD, Jr. Ruptured abdominal aortic aneurysm: a retrospective assessment of open versus endovascular repair. Ann Vasc Surg 2005; 19:782-786.
9. Larzon T, Lindgren R, Norgren L. Endovascular treatment of ruptured abdominal aortic aneurysms: a shift of the paradigm? J Endovasc Ther 2005; 12:548-555.
10. Kapma MR, Verhoeven EL, Tielliu IF, et al. Endovascular treatment of acute abdominal aortic aneurysm with a bifurcated stentgraft. Eur J Vasc Endovasc Surg 2005; 29:510-515.
11. Hechelhammer L, Lachat ML, Wildermuth S, Bettex D, Mayer D, Pfammatter T. Midterm outcome of endovascular repair of ruptured abdominal aortic aneurysms. J Vasc Surg 2005; 41:752-757.
12. Alsac JM, Desgranges P, Kobeiter H, Becquemin JP. Emergency endovascular repair for ruptured abdominal aortic aneurysms: feasibility and comparison of early results with conventional open repair. Eur J Vasc Endovasc Surg 2005; 30:632-639.
13. Lee WA, Hirneise CM, Tayyarah M, Huber TS, Seeger JM. Impact of endovascular repair on early outcomes of ruptured abdominal aortic aneurysms. J Vasc Surg 2004; 40:211-215.
14. Resch T, Malina M, Lindblad B, Dias NV, Sonesson B, Ivancev K. Endovascular repair of ruptured abdominal aortic aneurysms: logistics and short-term results. J Endovasc Ther 2003; 10:440-446.
15. Reichart M, Geelkerken RH, Huisman AB, van Det RJ, de Smit P, Volker EP. Ruptured abdominal aortic aneurysm: endovascular repair is feasible in 40% of patients. Eur J Vasc Endovasc Surg 2003; 26:479-486.
16. Peppelenbosch N, Yilmaz N, van Marrewijk C, et al. Emergency treatment of acute symptom-

atic or ruptured abdominal aortic aneurysm. Outcome of a prospective intent-to-treat by EVAR protocol. Eur J Vasc Endovasc Surg 2003; 26:303-310.
17. Castelli P, Caronno R, Piffaretti G, et al. Ruptured abdominal aortic aneurysm: endovascular treatment. Abdom Imaging 2005; 30:263-269.
18. Brandt M, Walluscheck KP, Jahnke T, Graw K, Cremer J, Muller-Hulsbeck S. Endovascular repair of ruptured abdominal aortic aneurysm: feasibility and impact on early outcome. J Vasc Interv Radiol 2005; 16:1309-1312.
19. Visser JJ, Sambeek v, M.R.H.M., Hamza TH, Hunink MG, Bosch JL. Endovascular repair and open surgery in patients with ruptured abdominal aortic aneurysms: systematic review. Radiology 2007; (in press).
20. Visser JJ, Bosch JL, Hunink MG, et al. Endovascular repair versus open surgery in patients with ruptured abdominal aortic aneurysms: clinical outcomes with 1-year follow-up. J Vasc Surg 2006; 44:1148-1155.
21. Samy AK, Murray G, MacBain G. Glasgow aneurysm score. Cardiovasc Surg 1994; 2:41-44.
22. Visser JJ, van Sambeek MR, Hunink MG, et al. Acute abdominal aortic aneurysms: cost analysis of endovascular repair and open surgery in hemodynamically stable patients with 1-year follow-up. Radiology 2006; 240:681-689.
23. Laheij RJ, Buth J, Harris PL, Moll FL, Stelter WJ, Verhoeven EL. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR). Br J Surg 2000; 87:1666-1673.
24. Prinssen M, Wixon CL, Buskens E, Blankensteijn JD. Surveillance after endovascular aneurysm repair: diagnostics, complications, and associated costs. Ann Vasc Surg 2004; 18:421-427.
25. Tolia AJ, Landis R, Lamparello P, Rosen R, Macari M. Type II endoleaks after endovascular repair of abdominal aortic aneurysms: natural history. Radiology 2005; 235:683-686.
26. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005; 365:2179-2186.
27. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. Cardiovasc Drugs Ther 2002; 16:75-77.
28. Lloyd-Williams F, Mair F, Shiels C, et al. Why are patients in clinical trials of heart failure not like those we see in everyday practice? J Clin Epidemiol 2003; 56:1157-1162.
29. Hordijk-Trion M, Lenzen M, Wijns W, et al. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. Eur Heart J 2006; 27:671-678.
30. Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. Ann Intern Med 1999; 130:709-718.
31. Acute endovascular treatment to improve outcome of ruptured aortoiliac aneurysms. ISRCTN66212637 Available at: http://www.trialregister.nl. Date accessed: April 23, 2007.
32. Lloyd GM, Bown MJ, Norwood MG, et al. Feasibility of preoperative computer tomography in patients with ruptured abdominal aortic aneurysm: a time-to-death study in patients with-

out operation. J Vasc Surg 2004; 39:788-791.
33. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. Lancet 2006; 368:659-665.
34. Lindholt JS, Juul S, Fasting H, Henneberg EW. Preliminary ten year results from a randomised single centre mass screening trial for abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2006; 32:608-614.
35. Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 2002; 360:1531-1539.

8
SUMMARY

SUMMARY

This thesis describes studies on the evaluation of endovascular repair versus open surgery in patients with ruptured abdominal aortic aneurysm (AAA). In **chapter 1**, the rationale for this research is presented. Since in the western world, the population is aging, it is expected that the incidence of abdominal aortic aneurysms will increase and consequently, ruptured AAAs. Ruptured AAA is a life threatening condition that requires immediate intervention. The condition can be treated with endovascular repair or open surgery. Therefore, the aim of this thesis was to investigate whether endovascular repair or open surgery would be the preferred treatment in this group of patients from a decision-analytic approach, taking clinical effectiveness as well as costs into account.

To enable comparison of the results of endovascular repair with open surgery in patients with a ruptured AAA from the literature, it is important to systemically evaluate the published studies and to adjust for differences in inclusion criteria among the studies. In **chapter 2**, we performed a systematic review of studies that compared endovascular repair with open surgery in the treatment of patients with a ruptured AAA. We found that, after adjustment for patients' hemodynamic condition upon presentation, a benefit in 30-day mortality for endovascular repair compared with open surgery for patients with a ruptured AAA was observed but was not statistically significant.

In **chapter 3**, we compared the clinical outcomes of treatment after endovascular repair and open surgery in patients with ruptured infrarenal AAAs including one-year follow-up. It turned out that in our study with a highly selective population, mortality and morbidity might be similar for patients with a ruptured infrarenal AAA treated with endovascular repair compared with open surgery, even after one-year follow-up. In addition to the aneurysm anatomy, other criteria may be needed for endovascular repair to improve clinical outcomes.

The Glasgow Aneurysm Score (GAS) is a prediction rule to predict in-hospital mortality after open surgery for patients with ruptured and unruptured AAA. The GAS, however, was developed in patients treated with open surgery only, whereas nowadays, endovascular repair is the preferred treatment for repair of ruptured AAA in many European hospitals. In **chapter 4**, the GAS was validated in patients with ruptured AAA treated with endovascular repair or open surgery. In addition, our aim was to modify the GAS into an updated prediction rule that predicts 30-day mortality after endovascular repair or open surgery. We found that the GAS showed limited discriminative ability in our patient population. In addition, we showed that, considering the included risk factors, 30-day mortality was always lower if patients with ruptured AAA were treated with endovascular repair instead of with open surgery.

To evaluate the incurred costs of both endovascular repair and open surgery, it is important to calculate both in-hospital costs and costs during follow-up after the procedure. **Chapter 5** describes the retrospectively assessment of in-hospital costs and costs of one-year follow-up of endovascular repair and open surgery in patients with an acute infrarenal AAA, using the resource utilization approach. We found that total costs including in-hospital costs and one-year follow-up in patients with acute infrarenal AAA were lower for endovascular repair than for open surgery.

From a health policy perspective, it should be questioned whether current available evidence justifies today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable. In addition, it is of interest whether additional information is required to inform the decision making process for patients with ruptured AAA in the future. Therefore, in **chapter 6**, we evaluated the cost-effectiveness of endovascular repair compared with open surgery in patients with ruptured AAA and investigated whether performing future research to obtain additional information is justified. We concluded that endovascular repair was more effective and less costly compared with open surgery in patients with ruptured AAA. Therefore, current available evidence does justify today's policy to treat patients with ruptured AAA with endovascular repair if anatomically suitable. In addition, further research is justified and should concentrate on short-term costs and clinical effectiveness of endovascular repair versus open surgery in patients with ruptured AAA.

In **chapter 7** the main findings were summarized of the preceding chapters and placed in a broader context. In addition, methodological considerations and future research were discussed.

SAMENVATTING

SAMENVATTING

Dit proefschrift beschrijft studies over de evaluatie van de endovasculaire behandeling versus open chirurgie in patiënten met een geruptureerd aneurysma van de abdominale aorta (AAA). In **hoofdstuk 1** wordt de achtergrond van dit onderzoek beschreven. Doordat in de Westerse wereld de bevolking in een hoog tempo vergrijst, is de verwachting dat de incidentie van AAA's en daarmee van geruptureerde AAA's zal toenemen. Een geruptureerd AAA is een levensbedreigende aandoening die onmiddelijk ingrijpen noodzakelijk maakt. De patiënt kan worden behandeld met een endovasculaire behandeling of met open chirurgie. Daarom is de doelstelling van dit proefschrift te onderzoeken, vanuit een medisch besliskundige benadering waarin zowel klinische effecten als kosten in beschouwing worden genomen, of endovasculaire behandeling danwel open chirurgie de voorkeur verdient in patiënten met een geruptureerd AAA.

Om de resultaten van de endovasculaire behandeling en open chirurgie in patiënten met een geruptureerd AAA uit de literatuur met elkaar te kunnen vergelijken, is het belangrijk om de gepubliceerde studies systematisch te evalueren en te corrigeren voor verschillen in inclusiecriteria tussen de verschillende studies. In **hoofdstuk 2** hebben we de resultaten van een systematisch literatuur onderzoek gepresenteerd van studies die de endovasculaire behandeling en de open chirurgische behandeling in patiënten met een geruptureerd AAA met elkaar vergeleken. We vonden dat, na correctie voor de conditie van de patiënt op het moment dat hij/zij zich presenteerde in het ziekenhuis, er spake was van een voordeel in 30-dagen mortaliteit. Dit verschil was echter niet statistisch significant.

In **hoofdstuk 3** vergeleken we de klinische uitkomsten na endovasculaire behandeling en open chirurgie in patiënten met een geruptureerd infrarenaal AAA, inclusief 1 jaar follow-up. Uit onze studie, met een sterk geselecteerde populatie, bleek dat mortaliteit en morbiditeit wellicht gelijk zijn voor patiënten met een geruptureerd AAA die endovasculair behandeld zijn in vergelijking met open chirurgie, ook na 1 jaar follow-up. Bovendien bleek dat, naast de anatomie van het aneurysma, waarschijnlijk andere criteria nodig zijn om de klinische uitkomsten van de endovasculaire behandeling verder te verbeteren.

De Glasgow Aneurysm Score (GAS) is een predictieregel die de ziekenhuis mortaliteit na open chirurgie voor patiënten met een geruptureerd en een niet-geruptureerd AAA voorspelt. Echter, de GAS is ontwikkeld in patiënten die allen met open chirurgie zijn behandeld, terwijl tegenwoordig de endovasculaire behandeling de behandeling van voorkeur is in veel Europese ziekenhuizen voor patiënten met een geruptureerd AAA. In **hoofdstuk 4** is de GAS gevalideerd in patiënten met een geruptureerd AAA die behandeld zijn met endovasculaire behandeling of open chirurgie. Bovendien was onze doelstelling om de GAS te modificeren in een bijgewerkte predictieregel die de 30-dagen mortaliteit na endovasculaire behandeling of open chirurgie

voorspelt. We vonden dat de GAS beperkte discriminerende mogelijkheden had in onze patiënten populatie. Bovendien toonden we aan dat, gegeven de geïncludeerde risicofactoren, de 30-dagen mortaliteit lager was als patiënten met een geruptureerd AAA endovasculair werden behandeld in plaats van met open chirurgie.

Om alle kosten van de endovasculaire behandeling en open chirurgie te evalueren is het belangrijk om zowel de ziekenhuiskosten als de kosten tijdens follow-up na de procedure te berekenen. **Hoofdstuk 5** beschrijft de retrospectieve bepaling van de ziekenhuiskosten en de kosten van 1 jaar follow-up van de endovasculaire behandeling en open chirurgie in patiënten met een acuut infrarenal AAA met behulp van de 'resource utilization' aanpak. We vonden dat de totale kosten, inclusief de ziekenhuiskosten en de kosten van 1 jaar follow-up, lager waren voor de endovasculaire behandeling dan voor open chirurgie.

Vanuit een beleidsperspectief in de gezondheidszorg dient men zich af te vragen of het beschikbare bewijs het hedendaags beleid rechtvaardigt om patiënten met een geruptureerd AAA endovasculair te behandelen als ze anatomisch geschikt zijn voor deze behandeling. Bovendien is het interessant te weten of aanvullende informatie is vereist om het beslissingsproces voor patiënten met een geruptureerd AAA in de toekomst te optimaliseren. Daarom evalueerden we in **hoofdstuk 6** de kosten-effectiviteit van de endovasculaire behandeling in vergelijking met open chirurgie in patiënten met een geruptureerd AAA en onderzochten we of het uitvoeren van verder onderzoek om extra informatie te verkrijgen is gerechtvaardigd. We concludeerden dat de endovasculaire behandeling effectiever en goedkoper was dan open chirurgie. Daarom rechtvaardigt het beschikbare bewijs het hedendaags beleid om patiënten endovasculair te behandelen als ze anatomisch geschikt zijn voor deze behandeling. Bovendien is verder onderzoek gerechtvaardigd. Dit dient zich te concentreren op de korte termijn (30-dagen) klinische effecten en kosten van de endovasculaire behandeling versus open chirurgie in patiënten met een geruptureerd AAA.

In **hoofdstuk 7** zijn de belangrijkste bevindingen van de voorgaande hoofdstukken samengevat en in een bredere context geplaatst. Bovendien worden de methodologische overwegingen en de mogelijkheden van vervolgonderzoek besproken.

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DANKWOORD

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ABOUT THE AUTHOR

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