Cost-effectiveness analyses: applications in surgery and cardiology
Dijksman, Lea

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HOSPITAL COSTS IN A CONSECUTIVE GROUP OF PATIENTS WITH SURGERY FOR AN AORTIC ANEURYSM: OPEN PROCEDURE OR ENDOVASCULAR

L. M. Dijksman, C. Drijfhout van Hooft, S. van der Tol, M. Schreve, V.J. Leijdekkers, M.G.W. Dijkgraaf, A.C. Vahl

Submitted
ABSTRACT

Introduction

We can conclude from trials and meta-analyses that endovascular aneurysm repair (EVAR) in patients with abdominal aortic aneurysm (AAA) is not cost-effective compared to open repair. However, these trials included selected patient groups. Little is known about cost-effectiveness in consecutive patient series. The purpose of this study is to investigate if EVAR is cost-effective compared to open repair in an average hospital population and to find predictors for higher costs.

Methods

We retrospectively collected a consecutive cohort of primary and electively operated patients with AAA, from 2004-2010 in the OLVG. Confidence intervals of costs were calculated using bias-corrected bootstrapping. Ordinal regression analysis was used to predict if an EVAR-procedure was a predictor for higher total cost, corrected by other possible confounders.

Results

We analyzed 187 consecutive patients. Median costs for all patients were €13,000 per patient. The average cost difference per patient was €2,637 (95% confidence interval: minus €990 to €4,446) with open repair costing less. Two variables were associated with higher costs at higher percentiles of total costs: receiving EVAR-procedure (odds ratio 9.38, 95%CI 3.6-28.9, p<0.001), and age in years (odds ratio 1.03, 95%CI 1.002-1.07, p=0.055). The difference was mainly caused by higher surgery costs (stent graft). The plotted bootstrapped (uncorrected) costs against the number of patients without complications show a probability of 86.2% of EVAR being more effective against higher costs. Patients in the EVAR group being cost-effectiveness would exceed 75% at a willingness-to-pay of 60,000 euro or higher per prevented patient with complications.

Conclusion

Bootstrapped results showed that the probability of EVAR being cost-effectiveness would exceed 75% at a willingness-to-pay of 60,000 euro or higher per prevented patient with complications. Costs for EVAR-procedure were mainly driven by stent graft costs.
INTRODUCTION

Nowadays endovascular treatment (EVAR) is the first choice for surgeons in the treatment of patients with an abdominal aortic aneurysm (AAA) when anatomically opportune. Patients prefer this minimally invasive technique as well. However, it is still unclear if endovascular treatment (EVAR) is a better choice for the long term regarding survival and cost-effectiveness. Major randomized trials were published comparing EVAR with open repair.\textsuperscript{1-6} The EVAR-trials show a benefit in favor of EVAR in the early mortality outcome, but not in the long term outcome (6,904 person-years of follow-up). In a study by Brown and colleagues EVAR was not found to be cost-effective.\textsuperscript{7} The ACE-trial shows no significant difference between EVAR and open repair.\textsuperscript{2} EVAR was shown to be cost-effective in the OVER-trial after the initial hospitalization, but after two years survival, quality of life and costs were not significantly different.\textsuperscript{6} A systematic review from 2009 shows that EVAR can be cost-effective under certain conditions. This minimally invasive technique shows good results on short term. However, the long term effects do not show better results than open repair and there are several reinterventions. With the much higher costs for EVAR it not easy to reach cost-effective results.\textsuperscript{8} The study of Epstein et al, addressing the long-term cost-effectiveness of EVAR versus open repair, constructed a Markov-model using outcome of the EVAR-1, DREAM, OVER and ACE-trials. They showed that EVAR was not cost-effective compared with open repair.\textsuperscript{9}

From these studies it was not known how costs of operations would develop in cohorts of consecutive patients in an unselected hospital population. The study of Mani and colleagues concluded that average costs for consecutive patients were not significantly higher in EVAR patients compared to open repair.\textsuperscript{10} Nevertheless, in this study a case-mix correction was not performed. In the current study, we investigated in a large teaching hospital with a consecutive patient series with AAA, if corrected costs of EVAR are higher than the costs of open repair.

PATIENTS AND METHODS

We included all consecutive patients, operated in the OLVG between January 2004 and December 2010 for AAA. We included only patients with an AAA operated with EVAR or open repair. Patients with revision surgery or secondary procedures were excluded as were patients with a ruptured or acute aneurysm. All pre- and postoperative data were collected from the medical charts. The main research goal was to determine the costs difference and cost-effectiveness of EVAR versus open repair. Costs of patients in EVAR-group are of interest of hospital and insurance company and costs of admission to the hospital and procedure costs are expected to exceed costs of indirect medical costs. Therefore we took a restricted provider
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Perspective (only inpatient hospital costs) and collected costs from the hospital information system. Costs are calculated from admission for surgery until discharge from the hospital. Costs were admission days, laboratory costs, physiotherapy or dietary consults, blood products, radiology, costs of surgery, and intensive care during admission.

The primary outcome measure in the economic evaluation was costs per patient. Secondary outcome was costs per complication outcome. We recorded all surgery, reoperation and diagnostics such as X-ray, sonography, CT scans, and laboratory data. The numbers of days from the primary hospitalization were recorded. Outpatient hospital as well as out-of-hospital care and productivity losses were not taken into account.

Costs were expressed in Euros. All unit costs were calculated from the 2010 financial ledger of the Onze Lieve Vrouwe Gasthuis, taking into account the average input of personnel, use of materials, writing-off of equipment, and medication. Overhead costs by the back-office e.g. depreciation of buildings and equipment, capital costs and departmental administration were added in two steps: first, total front-office costs and volumes (counts of procedures and hospitalizations) were calculated per patient care-related department, and second, overhead costs were attributed to the procedures, pro rata of their contribution to the total volume and front-office costs.

STATISTICS

Differences in patient characteristics of both groups were analyzed using the Student's t-test or Chi-square test. Costs were not normally distributed. The 95% confidence interval of the mean cost-difference was calculated using the bias-corrected nonparametric bootstrapping, drawing 5,000 samples of the same size as the original sample separately for each group and with replacement. Bootstrapped costs were plotted against complication free rates. Univariable and multivariable ordinal logistic regression analyses were performed to determine independent predictors influencing higher total costs. Total costs were divided into percentiles. All variables with a p-value of <0.2 were included in the model. The association with higher costs was reflected in the odds ratio with confidence interval. A p-value of <0.05 was considered significant.
RESULTS

Patient characteristics of 187 included patients are described in table 1. There was a difference between open repair and EVAR in several patient characteristics. The EVAR group included older, male patients, with less hypertension, and with larger infrarenal neck diameter and length. Table 2 shows the clinical outcome. There was no significant difference between EVAR and open repair in complications. Patients with open repair were significantly longer admitted than EVAR patients (median 10 versus 6 days, \( p<0.001 \)). Table 3 shows the (uncorrected) mean costs per patient. The average cost difference was € 2637 (95% CI -461 to 4,975), with higher costs for EVAR. Large differences in costs mainly originated from differences in surgery costs (including stent graft costs), diagnostics and hospital admissions.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>EVAR N=128</th>
<th>open repair N=59</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>112 (88)</td>
<td>45 (76)</td>
<td>0.052</td>
</tr>
<tr>
<td>(History of) Smoking*</td>
<td>45 (51)</td>
<td>24 (53)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hypertension</td>
<td>69 (54)</td>
<td>41 (70)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>16 (13)</td>
<td>11 (19)</td>
<td>0.27</td>
</tr>
<tr>
<td>Age</td>
<td>73.2± 8.2</td>
<td>70.5±7.3</td>
<td>0.03</td>
</tr>
<tr>
<td>AAA diameter in mm</td>
<td>58.9±11.1</td>
<td>64.8±23.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Infrarenal neck diameter 18-32mm*</td>
<td>98 (91)</td>
<td>25 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infrarenal neck length &gt;15mm*</td>
<td>98 (92)</td>
<td>23 (51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glasgow Aneurysm Score n</td>
<td>77.8</td>
<td>76.8</td>
<td>0.52</td>
</tr>
<tr>
<td>ASA score 3 or 4</td>
<td>67 (52)</td>
<td>31 (53)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

All variables are in mean ± standard deviation or number (%). GAS=age + coronary disease (+7) + creatinin >150 (+14) + cerebrovascular disease (+10)* missing values in 53, 37, 35 cases.

We plotted the costs of EVAR and open repair in figure 1. The median costs were €12,851 (range 5,241 – 67,477). Two of the three patients with costs over €40,000 received EVAR. The most expensive patient had open repair and was discharged home in poor condition. This patient was a 76 years old man, ‘unfit’ for open repair because of cardiac and kidney failure, with a ten cm large symptomatic AAA. Six patients (four EVAR) costed over €30,000. Twenty patients (eleven EVAR) - including one diseased patient - costed over €20,000. Thirty-four patients had hospital costs below €10,000. They all had open repair.
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Figure 2 shows the bootstrapping result of the cost-difference between EVAR and open repair to the difference in prevented patients with major complications. This figure shows the majority of the bootstrapping results lying in the upper right quadrant of the figure (86.2%), i.e. more expensive and more effective. The probability of EVAR being cost-effectiveness would exceed 75% at a willingness-to-pay of 60,000 euro or higher per prevented patient with complications. If the willingness-to-pay would be infinite, the probability of EVAR being cost-effectiveness would be 93% per prevented patient with complications.

The multivariable ordinal regression analysis shows EVAR and age to be the only predictors for higher costs. The EVAR-procedure has a 9.38 times higher odds of higher costs than open repair (95% CI 3.6-28.9, p<0.001). Age showed an odds ratio of 1.033, 95% CI 1.002-1.066, p=0.055).

### Table 2. Patient outcome.

<table>
<thead>
<tr>
<th></th>
<th>EVAR N=128</th>
<th>open repair N=59</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications</td>
<td>13 (10)</td>
<td>11 (19)</td>
<td>0.107</td>
</tr>
<tr>
<td>Died</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.140</td>
</tr>
<tr>
<td>Reoperation</td>
<td>9 (7)</td>
<td>7 (12)</td>
<td>0.272</td>
</tr>
<tr>
<td>Admission, days</td>
<td>6 (5-9)</td>
<td>10 (8-15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All variables are in median (25%-75%) or number (%)* *Complications: Myocardial infarct, renal failure, reoperation (bleeding, endoleak type I, etc), major amputation, cerebral infarction, colonic ischemia.*

### Table 3. Mean costs per patient (euro)

<table>
<thead>
<tr>
<th></th>
<th>EVAR N=128</th>
<th>open repair N=59</th>
<th>Cost-difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, total material</td>
<td>10,473 (8,500)</td>
<td>3,606 (400)</td>
<td>6,867 (6,000 to 7,836)</td>
<td></td>
</tr>
<tr>
<td>Intensive care</td>
<td>186</td>
<td>3,230</td>
<td>-3,044 (-4,492 to -600)</td>
<td></td>
</tr>
<tr>
<td>Ward</td>
<td>3,055</td>
<td>4,340</td>
<td>-1,285 (-2,089 to -532)</td>
<td></td>
</tr>
<tr>
<td>Diagnostics</td>
<td>1,246</td>
<td>432</td>
<td>814 (585 to 1,025)</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>108</td>
<td>468</td>
<td>-360 (-555 to -205)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>79</td>
<td>434</td>
<td>-354 (-558 to -183)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15,147</td>
<td>12,510</td>
<td>2,637 (-461 to 4,975)</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 10

Figure 1. Box en Whisker plots of total costs of EVAR and open repair

Figure 2. Cost-effectiveness plane showing difference between EVAR and open repair after 5000 (uncorrected) bootstrap replications.
In our cohort study, the average hospital costs for EVAR were not significantly higher than costs for open repair. This was in accordance with the previous cohort study by Mani and colleagues. However, the average difference of over €2,600 and a 95% confidence interval of (minus 461 to 4,975) showed a trend. After dividing total costs per patient into percentiles and multivariable ordinal regression analysis it showed that EVAR in comparison with open repair was significantly associated with higher costs after correction for age. The odds of higher costs with EVAR were nine times as high as with open repair. In the study of Mani and colleagues, the difference in hospital costs was over €4000. Figure 2 showed that the probability of EVAR being cost-effectiveness would exceed 75% at a willingness-to-pay of 60,000 euro or higher per prevented patient with complications. If the costs of material or stent costs would have been much lower, then this probability of being cost-effective could be achieved at a considerable lower level of willingness-to-pay.

Costs of AAA surgery can be divided into three phases: preoperative diagnostics, treatment costs and follow up. Current practice is for every patient to have a CT-scan preoperatively, before EVAR as well as before open repair. Follow-up costs for EVAR and open repair are almost similar: nowadays the follow up is as much as a yearly duplex-scan. Costs of reinterventions used to be important. EVAR used to show around four times more interventions as open repair, but most of them minimally invasive. In the study of Mani and colleagues the mean costs after 2.5 years are the same. EVAR had more graft revisions, most of them minimally invasive, and open repair showed more incisional hernias and abdominal surgery. Modern techniques reduced the number of graft revisions.

Now it seems of importance to aim at the hospital costs during the initial hospitalization. In this phase most costs are made. The costs of EVAR are mainly caused by the costs of prosthetic material. Cost of a conventional prosthesis for open repair is around €400 and around €8,500 for a stent graft in our hospital. These costs differ largely per country, which makes generalization of the results difficult. The mean hospital costs per patient in our cohort of over €14,000 are low compared to literature: €17,000 to over €23,000. Since the admission time after EVAR is shorter, there is gain in costs. Patients are in better health after discharge as well.

COST-UTILITY

The quality of life in the first months after EVAR is much better than after open repair, but after one year this difference is diminished. Simulation models, based on previous studies, show a slight gain in QALY (0.1) for EVAR patients. Cost-effectiveness ratios are diverse in literature.
The incremental cost-effectiveness ratios (calculated by dividing the difference in costs by the difference in (quality adjusted) survival in both groups) can vary between €170,000 and €200,000 per QALY. A systematic review showed that at the usual cut-off points, EVAR could not be shown to be cost-effective at current stent graft price levels. Markov-modeling costs for EVAR versus open repair showed EVAR unlikely to be cost-effective. For patients ‘unfit’ (=significant cardiac-, lung- and/or renal failure) for open repair, there is some room for cost-effectiveness of EVAR. However, in this patient group there is doubt about operative therapy. We cannot draw definite conclusions with these data. There are patient factors and methodological factors that should be well thought through.

### PATIENT FACTORS

A large part of the current analysis used older patient series with older generation EVAR prostheses. Perioperative results get better all the time for both patient groups. A recent French trial shows a mortality of 0.6% for EVAR and 1.3% for open repair. Both are three times better than older trials. The absolute risk difference is lowered from 3.1% to 0.7%. Assuming pre- and postoperative costs in both surgery methods to be quite similar, and since survival and quality of life are similar after one year [ref], we can focus on hospital costs. These are very high for EVAR due to stent graft costs.

### METHODOLOGICAL FACTORS

Cost-effectiveness analysis can be complex. There is always a discussion if the instruments for measuring quality of life for AAA patients are sufficient, especially if one can prevent early deaths. If we only focus on costs we have to keep in mind that the differences among country can be substantial and will lead to large differences across publications. Nevertheless it seems that surgery costs for EVAR are higher than for open repair, due to material prices. Still, interpretation is difficult because of the applied analysis methods. Calculating the mean costs is necessary to make a statement about costs in healthcare. The usual statistical tests to compare means (e.g. Student’s t-test) are not sufficient to calculate differences, because costs are not normally distributed. Outliers in costs cannot be left out of the analysis, because these are patients with complications in follow up and thus macro-economically important to include in the analysis. It is recommended to calculate the confidence interval of the mean costs with the bootstrap method. With this method the factors influencing the total costs per patient are not taken into account. In cohort and populations studies, dichotomizing the total costs can be a method to adjust for other variables. In our series we cannot show a significant difference in costs per patient, but the bootstrapped (uncorrected) results show a clear trend. This is probably
Cost-effectiveness in cohort EVAR versus open repair

because this study, like many other cost-analyses, is underpowered for the cost outcome. 25 However, when adjusting for age EVAR is a clear predictor for higher costs.

There are several good reasons to continue treating patients with AAA with EVAR. The operation is a prophylactic operation and therefore mortality needs to be as low as possible. The chance of rupture of untreated AAA is on average more than 20% after 4 years with AAA larger than 5 cm. 26 This can go up to 14% per year for patients with AAA of 6 cm and more than 30% per year for patients with AAA of more than 7 cm. 27,28 EVAR seems an effective method as a preventive operation. In some centers an operative mortality of less than 1% can be achieved. Patients prefer EVAR over open repair as well. 29 There is also the societal wish for minimally invasive methods, such as laparoscopic procedures. The quick post-operative recovery is an important factor for this choice.

However, in this time of societal responsible actions, we will have to critically evaluate the procedure. The cost for an endoprosthesis is very high and the procedure costs must be lowered. 8 We need to have a better patient selection to lower the costs of treatment and improve its cost-effectiveness. We expect the following patient groups will have cost-effectiveness in favor of EVAR (with current stent graft prices): elderly, 13 higher expected operative mortality and a large AAA with open repair 8

This study has some limitations. First, the sample size of 187 is relatively small. We found a small (non-significant) effect, but comparable to previous studies. Still, we can see costs are mainly driven by EVAR. Every EVAR in our hospital leads to higher costs due to stent graft prices. There is no effect from the patient characteristics on the difference in higher costs. Second, there were fewer patients with open repair than there were with EVAR. This is, however, inevitable in this consecutive group of patients, since most patients with AAA are anatomically fit for EVAR. In our hospital we have strict criteria for indication for EVAR, whereas the quality of the aneurysm neck is of most importance. For this reason, there are several patients undergoing open repair. Third, this is a retrospective cohort. Selecting patients for open repair or EVAR will have its effect on outcome. Still, we can see a small (non-significant) effect in fewer complications for EVAR even though this patient group is older and contained more males.

We can conclude that EVAR in patients with AAA was associated with higher hospital costs, however not significantly different from open repair. Independent predictors for higher costs were EVAR and age. Bootstrapped results showed the probability of EVAR being cost-effectiveness would exceed 75% at a willingness-to-pay of 60,000 euro or higher per prevented patient with complications.
10. Mani K, Bjoreck M, Lundkvist J, Wanhainen A. Similar cost for


