SYSTEMATIC REVIEW AND COST-EFFECTIVENESS ANALYSIS OF ELECTIVE ENDOVASCULAR REPAIR COMPARED TO OPEN SURGICAL REPAIR OF ABDOMINAL AORTIC ANEURYSMS

Final report

Prepared for the Ontario Ministry of Health & Long-term Care

by

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DISCLAIMER

This Health Technology Assessment (HTA) report is a review and analysis of existing public literature and an analysis of preliminary field evaluation data. This report was prepared by the Program for Assessment of Technology in Health (PATH) at St. Joseph's Healthcare Hamilton/McMaster University on behalf of the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MOHLTC) for the Ontario Health Technology Advisory Committee (OHTAC).

PATH takes sole responsibility for the final form and content of this report. The statements and conclusions in this interim report are those of PATH and not of the MOHLTC, OHTAC, McMaster University, University of Western Ontario, St. Joseph's Healthcare Hamilton or London Health Sciences Centre.

Please contact PATH at www.path-hta.ca if you are aware of new research findings that should inform the report or would like further information.

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EXECUTIVE SUMMARY

Purpose

In 2003, the Ministry of Health and Long Term Care (MOHLTC) conducted a review of primary studies on endovascular repair (EVAR) for abdominal aortic aneurysms (AAA) as well as a review of previous international and Canadian Health Technology Assessments (HTA). Due to the informational uncertainty associated with the long-term effectiveness of EVAR, the MOHLTC recommended that an Ontario-specific evaluation of the technology was warranted. The MOHLTC provided funding on a one time basis to support a 24-month EVAR evaluation at London Health Science Centre (LHSC) where the Ministry had received previous requests for funding. A condition of this funding was that LHSC would collaborate with the Program for Assessment and Technology in Health (PATH) at St. Joseph's Healthcare Hamilton/McMaster University to design and conduct an observational study or "field evaluation" to support the assessment of the effectiveness and cost-effectiveness of EVAR as compared to open surgical repair (OSR) in Ontario.

The purpose of this research was threefold. First, to provide an evaluation of the scientific literature related to EVAR. Second, to collect Ontario-specific clinical, resource utilization and quality-of-life data related to the use of EVAR and OSR. And finally, to evaluate the cost-effectiveness of endovascular repair compared to open surgical repair for the management of non-ruptured AAA in Ontario.

In 2005, an interim report was provided to the MOHLTC and presented to the Ontario Health Technology Advisory Committee (OHTAC). This report contained an updated systematic literature review, an interim analysis of the "field evaluation" and an initial evaluation of the cost-effectiveness of EVAR versus OSR based on data from a subset of patients recruited into the LHSC study with 1 year follow-up. The purpose of this report is to provide an update on the systematic literature review and report the final findings of the field evaluation and associated economic evaluation.

Background

Clinical Need (Disease, prevalence, treatment)

AAAs, a pathologic dilatation of a segment of the aorta, are a significant health problem in Ontario. It is estimated that the prevalence of AAA ranges from 4.1% to 14.2% in men and between 0.35% and 6.2% in women. The prevalence of AAA is greater in men, increases with age and also is more common to occur in smokers and patients with a history of myocardial infarction, peripheral vascular disease or a family history of AAA.

Aortic aneurysms can remain asymptomatic for years. When symptoms do present they are characterized by back pain or abdominal throbbing usually as a result of pressure on adjacent tissues. The primary risk with AAA is rupture which is associated with significant mortality rates. Current treatment options for AAA include OSR, EVAR and best medical treatment (BMT). The choice of treatment depends on the health of the patient, their ability to undergo surgery, whether the patient is symptomatic and the size, progression rate and morphology of the aneurysm.

New Technology

Endovascular aneurysm repair (EVAR)

EVAR, using covered stent grafts was introduced in 1991. Currently, in Canada, two devices have been approved. The Talent LPS endograft (manufactured by Medtronic) is a self-expanding modular woven monofilament polyester graft with serpentine nitinol stents inlaid into the fabric and 1 cm bare stent at the proximal attachment site. The Zenith endograft (manufactured by Cook) is a modular woven polyester graft supported by self-expanding Z-stents with a bare proximal stent for supra-renal fixation with hooks.

Briefly, the EVAR procedure can be done with the patient under general anaesthesia, regional anaesthesia, or local anaesthesia. This is due to the fact that the procedure involves incisions in the groins to expose the femoral arteries (sometimes a higher small incision is required to expose the iliac arteries if vascular anatomy is not appropriate to allow use of the femoral artery) through which the sheathed endograft is inserted in a retrograde fashion, with catheters and guide wires, and positioned correctly with x-ray guidance, at the top (at the level of the renal arteries) and bottom (iliac arteries) of the aneurysmal segment of the aorta. The sheath is then removed and usually balloon molding of the endograft is used to allow for thorough apposition of the endograft to the vessel wall and achieve endograft fixation. Proper, correct positioning and attachment of the endograft allows blood to pass through it and not through the aneurysm and thus remove pressure from the diseased aortic wall.

Systematic Literature Review

Objectives

A systematic literature review was updated to identify additional comparative studies that describe the clinical efficacy and safety of EVAR versus OSR that have been published since the initial review presented in 2005. As previously, the studies identified in the search were then used to fulfill two purposes for this HTA. The objective was to describe and compare the clinical efficacy and safety of EVAR and OSR as per the Society for Vascular Surgery/American Association

for Vascular Surgery (SVS/AAVS) reporting standards for EVAR. Specific focus of this review was to further characterize the baseline differences in patient characteristics found amongst the clinical literature, predominately composed of observational studies, comparing EVAR to OSR. The second purpose of the systematic literature review was to provide estimates of selected parameters to populate the economic model developed to evaluate the cost-effectiveness of EVAR versus OSR for Ontario.

Methods

The literature search strategies were developed to identify published studies comparing EVAR and OSR. The following literature databases were searched individually: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Evidence Based Medicine (EBM) Reviews (Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CCTR)), and Health and Psychosocial Instruments. English language and human studies between 1990 and 2006 inclusive were selected for review up to November 28, 2006.

Primary clinical reports that discussed EVAR and provided comparative data for elective EVAR versus OSR of AAA were identified. No restriction based on clinical study design was used and non-randomized trials and patient registries were included. However, only publications with unique (non-duplicated) patient data were analyzed.

The outcomes outlined in this report (e.g., mortality, systematic complications, endoleak rates, long-term event rates,) were derived as best as possible following the SVS/AAVS Reporting Guidelines, based on the data provided in the identified primary studies.

Results

The unique primary studies identified from this literature search, including studies previously identified in the interim evaluation and newly identified studies, consisted of 6 randomized controlled trials and 78 non-randomized trials comparing EVAR to OSR. Long-term patient outcomes (greater than 30 days post surgery) were reported in 33.3% (27/78) of the observational trials. The derivation of the outcomes from the SVS/AAVS reporting guidelines was not possible for all studies as the reporting of data was inconsistent from the identified trials. Within the observational studies patients receiving EVAR were generally of a higher surgical baseline risk of mortality and complications.

Field Evaluation

Purpose

The objectives of the field evaluation were two-fold: 1) to prospectively collect clinical outcomes, resource utilization and quality of life information on patients undergoing elective repair (i.e. EVAR and OSR) in an Ontario hospital setting, and 2) to compare EVAR patients, who were at high risk for open surgery (OSR) and anatomically suitable for EVAR, to patients receiving OSR with both low and high surgical risk.

Methods

This non-randomized, prospective, observational study was conducted at LHSC on patients requiring elective repair of an AAA (AAA > 5.5 cm) between August 11, 2003 and April 3, 2005. Patients were followed for a period of one-year post-treatment. The choice of intervention regarding the AAA repair method was determined as per usual LHSC clinical assessment and with discussion with the patient. For patients accepting surgical options, surgical risk and suitability were assessed based on cardiac history and risk factors, the classifications of the SVS and the ASA, as well as the presence of pulmonary and renal diseases, hostile abdomen, technical challenges and thoracic aortic pathology and classified as low or high surgical risk patients.

Demographic, medical, health care resource utilization, cost and quality of life information (SF-36, EQ-5D) were collected from participating patients over a period of 1 year following their elective AAA repair. .

Results

The study enrolled 342 patients with a total of 351 individuals being approached. All of the patients allocated to EVAR (n = 140) were all considered to be high surgical risk. Of the 195 patients allocated to OSR, 52 (26.6%) were considered to be high risk patients and were not suitable for EVAR. Results for patients refusing surgical treatments and who received BMT (n=7) are not discussed in the report.

The mean age of the patients was 75.6 years in the EVAR group and 72.3 years in the OSR group. There were more men than women in both groups (85.7% and 83.6%, respectively). The mean AAA size was similar between the 2 groups (EVAR: 6.2 cm and OSR: 6.1 cm). There statistically significant differences between the overall groups for age (P<.01) employment status (P=.04) and smoking status (P<.01). When comparing the OSR high risk (HR) patients to the EVAR treated patients, no statistically significant differences were found with respect to baseline characteristics except for more women being treated with OSR and a greater rate of peripheral vascular disease in the OSR HR group

(P=.02). Many patients participating in this field evaluation had a cardiac history such as angina (35.7% EVAR, 19.0% OSR LR, 42.3% OSR HR), MI (46% EVAR 24.5% OSR LR, 44.3% OSR HR), arrhythmia (25.0% EVAR, 7.8% OSR LR, 21.6% HR), valvular heart disease (15.7% EVAR vs. 0.7% OSR LR, 9.6% OSR HR), congestive heart failure (9.3%% EVAR, 0% OSR LR 9.6% OSR HR). None of the differences between the EVAR and OSR HR patient groups with respect to cardiac history were statistically significant.

The primary technical success rate (PTSR) was 100% for EVAR and 100% for OSR patients, respectively. Post-procedural type II endoleaks were reported in 67 EVAR patients (47.9%) with no reports of either Type I or Type III endoleaks. Post-operative complications occurred more frequently in the OSR treated patients as compared to the EVAR treated patients. Specifically, comparing the EVAR group to the OSR HR group statistical differences were found with respect to mortality (1 (0.7%) EVAR vs. 5 (9.6%) OSR HR, P<0.01), CHF/pulmonary edema (5 (3.4%) EVAR vs. 9 (17.3%) OSR HR, P<.01), pneumonia (0 EVAR vs. 4 (7.7%) OSR HR and renal failure (5 (3.6%) EVAR vs. 6 (11.5%) OSR HR.

EVAR patients spent less time in the hospital (7.7 days) than OSR LR patients (9.36 days) or OSR HR (16.13 days) patients (P<0.05). Of the EVAR patients 5 (4%) were admitted to an intensive care unit (ICU). In contrast, between 6% (low risk) and 31% (high risk) of OSR patients were admitted to an ICU (P<.05 compared to EVAR patients). The mean procedural time in minutes was statistically significantly lower for EVAR patients (162.4 minutes) than for OSR LR patients (181 minutes) (P<.01) as well as when EVAR patients are compared with OSR HR patients (195.8 minutes) (p<0.01). On average, 26.7% of OSR patients received a blood transfusion (19.6% low risk and 46.2% high risk). Only one of the EVAR patients required a blood transfusion during surgery.

Mid-term mortality (1 year) between the EVAR and the OSR HR were statistically significantly different (7.1% vs. 17.3%, P=.04). Over the one-year period 12 (8.63%) EVAR treated patients developed a new type II endoleak with no other endoleaks, graft migrations, or reinterventions being required.

The initial mean cost of hospitalization for EVAR was $28,139, for OSR LR patients $15,494 and for OSR HR $31,181. A higher number of medical resources consumed during the one-year follow-up in the EVAR patients resulted in a statistically significantly higher cost of follow-up $5,181 compared to OSR LR $1,899 and OSR HR ($2,171) (P<.05).

The total average one year healthcare costs for the EVAR group was $33,320, $17,393 for the OSR LR patients and $33,352 for the OSR HR patients. The difference in total costs (EVAR-OSR HR), including productivity costs when comparing the costs for the EVAR patients to OSR LR patients was $10,981 and when comparing EVAR to the OSR HR patient group the total cost difference was -$24.

There was virtually no diifference in the mean one year cost of EVAR and OSR HR groups. EVAR patients were estimated to be $24 less costly ($34,146 vs. +$34,170) cheaper than OSR patients over 1 year. The difference in life years was 0.111 (0.959 vs. 0.848). The difference in adjusted quality adjusted life years (QALYs) between EVAR and OSR was 0.025 (0.848, vs 0.713). In patients with high surgical risk, OSR is dominated by EVAR, costing more and providing less QALY benefit. Cost-effectiveness acceptability curves indicate a large amount of uncertainty in the cost per QALY outcome. When the 1 year results were extrapolated to 10 years the cost per QALY of EVAR compared to OSR was estimted to be $18,616 or less

Discussion

This field evaluation provides valuable insights into both the effectiveness and cost-effectiveness of EVAR in Ontario. The assessment is based on an Ontario specific EVAR program, making the results particularly relevant for health policy decision makers in the province. The analysis of efficacy and cost outcomes from similar high surgical risk patients treated with EVAR or OSR allows for a comparison of the two interventions following 1 year of follow-up. As this is a non-randomized observational study, as with the majority of the literature comparing EVAR to OSR, the results are susceptible to selection bias and should be considered when examining the results. In addition, the study was conducted at a single center and comparisions are limited to high risk patients. Therefore, the generalizability of the results to other populations is unclear.

Conclusion

For patients at a high risk of surgical mortality and complications, EVAR is a safe effective and cost-effective procedure with fewer complications and mortality occurring in EVAR patients compared to OSR patients with similar baseline risk. Reintervention for the management of endoleaks or endograft failure was not required. The total initial hospitalization costs associated with EVAR compared to OSR HR were lower and differences in the mean total annual 1 year costs were negligible.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS ii
EXECUTIVE SUMMARY iii
TABLE OF CONTENTS ix
1. INTRODUCTION 1
1.1. Statement of the Problem 1
1.2. Evaluation of EVAR in Canada 2
1.3. OHTAC recommendations 6
1.4. Change in Practice Patterns in Ontario 7
1.5. Purpose 8
1.6. Report Purpose 8
2. SYSTEMATIC REVIEW OF LITERATURE 9
2.1 Methods 9
2.1.1. Literature Search 9
2.1.2 Data extraction 11
2.1.3 Statistical Analysis 12
2.2 Results 12
2.2.1 Literature search 12
2.2.2 Study characteristics 13
2.2.3 Patient characteristics 14
2.2.4 Comparison of perioperative mortality and complications. 17
2.2.5 Surgical outcomes and local/vascular complications 20
2.2.6 EVAR Specific Outcomes 22
2.2.7 Mid-term Mortality 25
2.3 Discussion 25
3. FIELD EVALUATION STUDY 27
3.1. LHSC Endovascular Aneurysm Program 27
3.2. Rationale and Study Objectives 32
3.3. Methods 32
3.4 Results 34
3.4.1 Baseline Characteristics 34
3.4.2 Clinical Outcomes 37
3.4.2.1 Procedural and Post-operative Outcomes 37
3.4.2.2 Initial clinical outcomes (30 days) 41
3.4.2.3 Mid-term clinical outcomes & resource utilization (1 yr) 44
3.4.3 One-year direct and productivity costs 47
3.4.4 Quality of Life and QALYs 51

3.4.4.1 SF-36 51
3.4.4.2 EQ-5D 56
3.5 Field Evaluation Cost-Effectiveness Analysis 60
3.5.1 Methods 60
3.5.1.1 Costs 60
3.5.1.2 Life Year Gained 60
3.5.1.3 QALYs 60
3.5.1.4 Uncertainty and time horizon sensitivity analysis 61
3.5.2 Incremental Cost-Effectiveness Results 63
3.5.2.1 Time horizon sensitivity analyses 69
4.0 CONCLUSIONS 72
5.0 REFERENCES 73
6.0 APPENDICES 82

TABLES

Table 1: Current and estimated volume of EVAR repair with funding.....8
Table 2: Difference in Patient Characteristics by Study Design & Risk Status.....15
Table 3: Mortality and Systematic Complications.....19
Table 4: Surgical Outcomes.....21
Table 5: Local / Vascular Complications.....21
Table 6: EVAR Outcomes.....23
Table 7: Endoleaks and Limb Ischemia.....24
Table 8: London Health Sciences Centre Endovascular Program Volume.....28
Table 9: London Health Sciences Centre Endovascular Program for Aorto-iliac Aneurysm: Clinical & Technial Outcomes.....29
Table 10: Comparison of EVAR with Open Repair: Risk Stratification Per Leiden Aneurysm Score - LHSC experience.....30
Table 11: Baseline Patient Characteristics.....35
Table 12: Baseline Patient Comorbidities.....37
Table 13: Primary Procedural Outcomes.....39
Table 14: Complications at Time of Surgery.....40
Table 15: Seconary Procedural Characteristics.....41
Table 16: Initial Post-Operative Complications (30 days or to discharge).....43
Table 17: Hospital Length of Stay.....44
Table 18: Mortality and Complications Rates (1 yr).....45
Table 19: One-year Resource Utilization.....47
Table 20: Scheduled Unit Costs.....48
Table 21: Total Average 1-year Costs by Treatment Group.....49
Table 22: Cost-Effectiveness Results.....65
Table 23: Incremental costs, life years, QALYS and Cost-effectiveness Ratios Modeling the Time Horizon of the Study to 10 years.....69

FIGURES

Figure 1: QUORUM diagram 13
Figure 2: Mortality Difference Between OSR and EVAR by Mid-enrollment Time in Years 17
Figure 3: Mid-term Predicted Mortality Difference by Study Design 25
Figure 4: Referral Pattern of Patients Receiving EVAR at LHSC 31
Figure 5: Treatment Algorhythm for Elective Repair 33
Figure 6: Kaplan Meier Surival for EVAR, OSR LR and OSR HR Groups up to 365 Days of Follow-up 46
Figure 7: Mean Initial Hospitalization Costs for AAA Repair by Treatment Group and Presence of Post-Operative Complications 50
Figures 8a-8h: SF-36 Dimension:
Figure 8a: Bodily Pain 52
Figure 8b: Social Functioning 52
Figure 8c: Vitality 53
Figure 8d: General Health 53
Figure 8e: Role Physical 54
Figure 8f: Mental Health 54
Figure 8g: Role Emotional 55
Figure 8h: Physical Functioning 55
Figure 9: Observed EQ-5D Utility measurements over time 57
Figures 10a-10e: Mean responses to individual EQ5D questions:
Figure 10a: Self Care 57
Figure 10b: Usual Activities 58
Figure 10c: Depression & Anxiety 58
Figure 10d: Pain 59
Figure 10e: Mobility 59
Figure 11: Kaplan Meier Survival Curves 63
Figure 12: Mean EQ-5D Utility Scores Over Time (adjusted) 64
Figure 13: Estimated QALYs Over a year for EVAR and OSR HR pts 64
Figure 14: Incremental cost and effect pairs for cost per LYG 66
Figure 15: Incremental cost and effect pairs for cost per QALY 67
Figure 16: CEA curves for LYG and QALYs gained 68

ABBREVIATIONS

AAA	Abdominal aortic aneurysm
AAVS	American Association for Vascular Surgery
ACP	American College of Physicians
ASA	American Society of Anesthesiologists
BCOHTA	British Columbia Office of Health Technology Assessment
BMT	Best medical treatment
CINAHL	Cumulative index to nursing and allied health literature
CCOHTA	Canadian Coordinating Office of Health Technology Assessment
CCTR	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSVS	Canadian Society for Vascular Surgery
CT	Computed tomography
CVD	Cerebrovascular disease
DARE	Database of Abstracts of Reviews of Effects
DSA	Deterministic sensitivity analysis
EBM	Evidenced based medicine
EMBASE	Excerpta Medica database
EQ-5D	EuroQol 5 Dimensions
EVAR	Endovascular aortic aneurysm repair
FDA	US Food and Drug Administration
FE	Fixed effects model
ICER	Incremental cost-effectiveness ratio
LHSC	London Health Sciences Centre
HLD	Hyperlipidemia
HTA	Health Technology Assessment
HTN	Hypertension

ICU	Intensive care unit
IMA	Inferior mesenteric artery
LOS	Length of stay
MAS	Medical Advisory Secretariat
MI	Myocardial infarction
MEDLINE	Medical literature analysis and retrieval system online
MH	Mantel and Haenszel
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
MOHLTC	Ontario Ministry of Health and Long-term Care
n.a.	Not applicable
n.d.	Not done
n.r.	Not reported
n.s.	Not significant
NYHA	New York Heart Association
Or	Operating room
OSR	Open surgical repair
OSR HR	Open surgical repair high surgical risk
OSR LR	Open surgical repair low surgical risk
OVID	OVID Web Gateway
PATH	Program for Assessment of Technology in Health
PSA	Probabilistic sensitivity analysis
PCI	Percutaneous coronary intervention
PTSR	Primary technical success rate
PVD	Peripheral vascular disease
QALY	Quality adjusted life year
QoL	Quality of life
RCT / nRCT	Randomized controlled trial / .non-randomized controlled trial
RE	Random effects model
RR	Relative risk
s.d.	Standard deviation

SF-36	Short Form 36
SVS	Society for Vascular Surgery
TIA	Transient ischemic attacks
tx	Treatment
VATAP	Veterans' Affairs Technology Assessment Program

1. INTRODUCTION

1.1. Statement of the Problem

An abdominal aortic aneurysm (AAA) is a pathologic dilatation of a segment of the abdominal aorta and presents a significant health problem for individuals over the age of 50 in Ontario. By current reporting standards an aneurysm is defined as a permanent localized dilatation of an artery, having at least a 50% increase in diameter compared with the expected normal diameter. It is estimated that the prevalence of AAA ranges from 4.1% to 14.2% in men and between 0.35% and 6.2% in women.[1] The prevalence of AAA is greater in men, increases with age and also is more common to occur in people with a history of myocardial infarction, peripheral vascular disease, smokers and a family history of AAA[1,2] Aortic aneurysms can remain asymptomatic for years. When symptoms do present they are characterized by back pain or abdominal throbbing usually as a result of pressure on adjacent tissues.

The primary risk with AAA is rupture which is associated with significant mortality rates. [3,4]. In Canada, ruptured AAAs are the 13th leading cause of death overall, and the 10th leading cause of death in men over age 55 years. The effectiveness of elective AAA repair means that most deaths from AAA's are theoretically preventable.

Current treatment options for AAA include open surgical repair (OSR), endovascular aneurysm repair (EVAR) and best medical treatment (BMT). The choice of which option to use depends on the health of the patient, their ability to undergo surgery, whether the patient is symptomatic and the size, progression rate and morphology of the aneurysm. Open surgical repair is currently the primary method of repair of AAA in Canada, however, in some jurisdictions, EVAR is becoming the predominate method of managing AAA[5,6] The available clinical literature comparing EVAR to OSR includes some randomized controlled trials but primarily consists of several non-randomized observational studies with some short-term results from randomized controlled trials available.[7-12] However, in the observational trials, the comparability of the baseline characteristics of the

patients receiving EVAR versus those receiving OSR may not always be the same as there is a potential for a selection bias towards patients with higher surgical risk receiving EVAR over OSR.

As these interventions are associated with differences in morbidity and mortality, hospital resource utilization, follow-up times and monitoring, re-intervention rates, complications, recovery times and costs of care, it is essential to compare the relative cost and effectiveness of OSR versus EVAR. Several evaluations of the cost-effectiveness of endovascular repair versus open surgical repair have been reported. [11,13-16]

Therefore, there is a need to conduct a Canadian-based economic evaluation of the treatment options for AAA in order to evaluate the short and long-term cost and outcomes (including quality of life implications) associated with the use of open surgical repair vs. endovascular repair of AAA.

1.2. Evaluation of EVAR in Canada

Previous Canadian health technology assessments (HTA) of elective endovascular repair of AAA were completed prior to 2003 and the clinical studies reviewed by these HTA's were published prior to 2002 [5,17,18]. The first Canadian evaluation of EVAR was completed for the British Columbia Office of Health Technology Assessment (BCOTHA) in 1998 and was initiated as a result of funding requests for this procedure by clinicians in this province.[17]. At the time of the review, no published randomized or non-randomized, controlled trials could be identified that compared EVAR to OSR for AAA. This initial evaluation in Canada in 1998 considered endovascular graft technology as being at an investigational stage and that public funding of EVAR as a replacement for OSR must await technology maturity. Following the report the technology continued to be provided on a compassionate basis to patients with contraindications to OSR.

A second review of EVAR was conducted by the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) in 2002.[5] This review had two primary objectives 1) to examine the status of EVAR utilization in Canada, through a postal survey of vascular surgeons and 2) to critically review the

literature comparing EVAR, OSR or a "wait-and-see" approach in terms of their relative effects on the mortality and morbidity of patients with abdominal aortic aneurysms. Through the postal survey, the report identified that the majority of surgeons (98%) primarily used EVAR for patients with moderate to high surgical risk and appropriate anatomy. Among those surgeons not performing EVAR, 34% (21/62) stated that a lack of resources was the primary reason for not repairing AAA with this method. The analysis of the comparative efficacy & safety of EVAR vs. OSR in the CCOHTA report was based on 22 unique publications (this report identified considerable overlap of patients between various publications). Pooled estimates of perioperative mortality and primary treatment success were determined and a non-significant difference in perioperative mortality was seen between the patients receiving EVAR or OSR (OR: 0.72; 95% CI: 0.44, 1.17; p=0.18). The primary success rate of EVAR was found to be statistically less than that of OSR (OR: 0.17; 95% CI: 0.08, 0.37; p<0.00001). The report concluded that EVAR was still a new technology and that the evidence did not suggest that the technology was appropriate for all patients undergoing elective repair of AAA.

Further evaluation of EVAR was completed by the Medical Advisory Secretariat (MAS) of the Ontario Ministry of Health and Long-term Care (MOHLTC) in 2002 by conducting a scientific literature review and descriptive analysis of unique studies published between January 1998 and February 2002. The purpose of the evaluation was to review the evidence concerning the effectiveness and cost-effectiveness of EVAR in comparison to OSR. The primary conclusions of the report were that EVAR should be considered as an adjunctive technology to OSR, that no definitive conclusion could be made about the long-term effectiveness of EVAR due to the poor quality of the available evidence and that EVAR may be appropriate for treating a subset of patients with AAA who are unfit for OSR. The report acknowledged the potential of EVAR but stated that the long-term effectiveness and cost effectiveness could not be determined at the time and that further evaluation of the technology was required.

In 2003, the MOHLTC upon review of the evidence available at the time and the informational uncertainty associated with the long-term effectiveness of EVAR, felt that further Ontario-specific evaluation of the technology was warranted. Accompanied by a request for funding, the MOHLTC provided funding on a one time basis to support a 24 month EVAR "field evaluation" at London Health Science Centre (LHSC). An important condition of this funding was that LHSC would collaborate with the Program for Assessment of Technology in Health (PATH) at McMaster University to design and conduct an observational study or "field evaluation" to support the evaluation of the effectiveness and cost-effectiveness of EVAR compared to open surgical repair (OSR) in a "real-life" setting in Ontario.

In 2005, the MOHLTC requested that an interim evaluation be conducted by PATH and LHSC, as a part of this project, to provide an initial analysis of the effectiveness and cost-effectiveness of EVAR compared to OSR using data from a subset of patients (n=79) with 1 year follow-up as of December 30, 2003 (23.1% of all enrolled patients). At the time of the interim analysis the patients allocated to EVAR (n = 24) were all considered to be high surgical risk. Of the 55 patients allocated to OSR, 23 (41.8%) were considered to be high risk patients and were not suitable for EVAR.[19]

This interim evaluation found that the primary technical success rate for EVAR and OSR was 100%, respectively. With respect to endoleaks, only type II endoleaks were reported in 9 EVAR patients (37.5%) with no reports of either Type I or Type III endoleaks with only 1 patient (4.2%) requiring an additional endovascular procedure. Additional procedures were required in 11 (20%) OSR patients.[19]

Within this initial subset of patients (n=79) post-operative complications (death, acute myocardial infarction, stroke, pneumonia and renal failure) occurred more frequently in the OSR patient group than the EVAR group with no post-operative complications occurring in the EVAR group and as a result the EVAR patients spent less time in the hospital (6.7 days) than OSR patients (13.27 days) or OSR

high risk (17.9 days) patients. ICU admissions were not required for the EVAR patients. In contrast, between 10% (low risk) and 40% (high risk) of OSR patients were admitted to an ICU. [19]

Overall the initial mean cost of hospitalization between EVAR ($23,525) and OSR patients ($22,129) was primarily attributable to the higher cost of the EVAR procedure being offset by the higher inpatient costs of OSR patients with post-procedural complications. The increased rate of systemic complications in the OSR HR patients however resulted in an initial mean hospitalization cost of $34,308. [19]

A higher number of medical resources consumed during the one-year follow-up in the EVAR patients resulted in a higher cost of follow-up ($7,885) than OSR patients ($4,623), but this difference was not statistically significant. Similarly, there was no statistical difference in terms of total cost of follow-up between OSR patients stratified by surgical risk level. [19]

The total average one year healthcare costs for the EVAR group was $31,410, and $26,752 for all OSR patients. The OSR healthcare costs for the low risk group was $16,509 and for the high risk group $41,036. The difference in total costs (EVAR-OSR), including productivity costs, was $3,926 when comparing the costs for the EVAR patients to all OSR patients and -$9,417 (i.e. EVAR is cost saving) when comparing EVAR and high risk OSR patient groups. The difference in total costs between the low risk OSR and the high risk OSR was $22,835 ($p<0.05$).[19]

Based on the preliminary data collected from these 79 patients, the difference in the mean total one year cost of EVAR versus OSR was estimated at $3,926 ($32,639-$28,713). The difference in quality adjusted life years (QALYs) between EVAR and OSR was 0.066 (0.843-0.777). This led to an incremental cost-effectiveness ratio of EVAR versus OSR of $59,485 per QALY ($3,926/0.066).[19]

Comparing specifically the high risk patient populations, the difference in the mean annual cost of EVAR versus OSR was estimated to be -$9,417 ($32,639-$42,056) and the difference in the adjusted QALYs between the two interventions

was 0.066 (0.843-0.777). Therefore, patients with high surgical risk OSR was dominated by EVAR, costing more and providing less QALY benefit.[19]

1.3. OHTAC recommendations

Following the interim evaluation, OHTAC recommended that 1) hospitals with the required expertise increase access to endovascular repair for abdominal aortic aneurysms in patients who are at high-risk of perioperative morbidity or death from co-morbidities from open surgical repair. Surgical expertise is critical and a surgeon should do a minimum of 50 EVAR procedures to prepare for this surgery and at least one procedure every two weeks to maintain his/her expertise in performing EVAR. 2) a recommendation as to the provision of endovascular repair for abdominal aortic aneurysms in low or moderate risk patients requires additional long-term outcome studies. The use of EVAR in these patients is not recommended at this time and 3) based on the LHSC's protocol, endovascular repair is considered to be the most suitable treatment for patients falling into one or more of the 'high-risk' categories as outlined in Appendix I

The recommendations from OHTAC were similar to the consensus statement of the Canadian Society for Vascular Surgery (CSVS) regarding the use of endovascular repair for the treatment of AAA were released just prior to the presentation of the interim results.[20] The CSVS statement makes four recommendations: 1) EVAR should be the procedure of choice for patients with suitable vascular anatomy who are at intermediate risk (6%-10%) for perioperative morbidity or death with open repair, 2) for patients at low risk (2%-4%), open repair remains the current standard. For those with suitable vascular anatomy for EVAR, the final decision should also take into account the patients wishes. Longer term outcome data are required before EVAR can replace open repair as the treatment of choice for low-risk patients 3) EVAR procedures require specialized training and cooperation between specialists with complementary areas of expertise. They should be performed in centers experienced with aneurysm repair and with sufficient EVAR volume to enable appropriate data collection and auditing of results and 4) appropriate training in

endovascular therapies and interventional procedures is required for vascular surgery trainees. Training programs are needed for existing vascular surgeons and interventional radiologists currently in practice to allow this procedure to be safely implemented and disseminated across the country.[20]

1.4. Change in Practice Patterns in Ontario

The volume of both elective and emergency AAA repair in Ontario has been recently published.[4] In 1999, the annual volume of elective AAA repair, was estimated to be 1538 cases, while the number of cases for emergency repair of AAA the estimate was 319 cases. Assuming that the volume of AAA has not increased significantly since 1999, the total potential case volume in Ontario would be approximately 1900 cases per year. Estimating that approximately 40% of patients requiring abdominal aortic aneurysm repair would best be treated by EVAR (due to either physiological and/or anatomical high-risk factors), at least 600 EVAR procedures per year should be performed in Ontario.[20,21]

In addition to the LHSC program (which has the largest experience in the province), programs exist in Sudbury (Memorial Hospital), Ottawa (Ottawa Civic Hospital), Hamilton (Health Sciences Centre), and Toronto (Toronto General Hospital and St. Michael's Hospital). Annual EVAR volumes in 2004/05, prior to the interim evaluation were limited, by budgetary constraints, in each of these institutions, with Toronto General Hospital suspending its activity completely as of February 2004, as outlined in Table 1. Estimates of potential volume of EVAR were obtained by an informal survey of the existing Divisions of Vascular Surgery with the ability to perform EVAR (Personal Communication, Dr. G. De Rose, April 2005). The survey asked each program to estimate the potential volume of elective and emergency EVAR procedures that could potentially be completed provided funding was available based on their current case mix. The results of this survey suggest that approximately 635 cases of EVAR annually may be expected if EVAR was an insured and funded medical service in Ontario (Table 1).

Table 1: Current and estimated volume of EVAR repair with funding

	Current total annual volume (2004/05)	Elective procedure volume (estimated)	Emergency procedure volume (estimated)	Total annual volume (estimated)	Estimated annual volume increase
London Health Sciences Centre	110*	135	25	160	50
Hamilton Health Sciences Centre	60	100	25	125	85
Ottawa Civic Hospital	60	80	20	100	40
Sudbury Memorial Hospital	25	35	nr	35	10
St. Michael's Hospital	15	60	nr	60	45
Toronto General Hospital	0	130	25	155	155
Total	270	540	95	635	365

* Funded volume as part of EVAR study. Volume for 2005/06 estimated to be 40 procedures due to decreases in funding as insufficient funding from global hospital budget

nr not reported

1.5. Purpose

The purpose of this project was threefold. First to provide an evaluation of the scientific literature related to EVAR. Second to collect Ontario-specific clinical, resource utilization and quality-of-life data related to the use of EVAR and OSR. and finally to evaluate the cost-effectiveness of endovascular repair compared to open surgical repair for the management of non-ruptured abdominal aortic aneurysms in Ontario.

1.6. Report Purpose

The purpose of this report is to present to OHTAC an updated systematic literature review examining the efficacy of EVAR as compared to OSR, to present the final analysis of the observational field evaluation study evaluating the clinical efficacy and safety of EVAR use at LHSC and finally to estimate the cost-effectiveness of EVAR versus OSR based data from all patients recruited into the study LHSC study.

2. SYSTEMATIC REVIEW OF LITERATURE

The systematic literature review initially conducted as a part of the interim report provided to OHTAC in 2005, was updated to integrate new evidence published since the interim report (e.g. up to November 2006) to further characterize the patient characteristics and clinical outcomes associated with EVAR and OSR for elective treatment of AAA as reported in the scientific literature.

The objective of this review was threefold: 1) to describe and compare the patient characteristics from the identified observational and randomized control trials EVAR and OSR patients; 2) to examine differences in outcome measures between the treatment groups by study design and characteristics; and 3) evaluate trends in mortality and endoleaks rates over time.

2.1 Methods

2.1.1. Literature Search

The literature search strategies were developed to identify papers related to the repair of AAA and the health care interventions to treat the condition, as detailed in Appendix II. The surgical interventions of interest were EVAR and OSR. The goal of the search was to identify clinical studies comparing the two surgical interventions. Specific search strategies for the following literature databases were developed and each database was searched individually via the OVID Web Gateway (OVID Technologies, Inc. New York, NY): MEDLINE, EMBASE, Cumulative index to nursing and allied health literature (CINAHL), Evidence Based Medicine (EBM) Reviews (Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CCTR)), and Health and Psychosocial Instruments. English language and human studies between 1990 and November 2006 inclusive were selected for review. Identification of duplicate citations was completed using Reference Manager, v.10 (ISI

Researchsoft, Thomson Scientific, U.S.A). Randomized controlled trials (RCTs), controlled clinical trials, comparative observational studies, case series studies and population-based registries assessing the efficacy and/or safety of EVAR versus OSR were all included in the review. Excluded were review articles, comments, editorials, guidelines, letters and case reports.

The above searches located studies with and without an abstract available on the database queried. To establish the relevance of each study and all potentially relevant papers obtained, the titles and abstracts (when available) of all search results were screened using predefined criteria to identify publications that discussed the use of EVAR and OSR for the management of Abdominal Aortic Aneurysm (AAA). (Appendix III) When it could not be determined from the citation information available whether an item met the inclusion criteria or not, the full-text item was retrieved.

Citations were included if they examined the repair of non-ruptured AAA repair, of at least a mean AAA diameter of greater than 5 cm, and the publication date was 1991 onwards. Citations were excluded if they reported a mixed patient population including patients with thoracic-abdominal aneurysms, iliac disease, ruptured or infected aorta, emergency aortic repair and patients that received both. If it was uncertain following the review of the title and abstract as to whether a publication provided comparative information, a full text review of the paper was completed. Articles without an abstract were also retrieved in full if the citation was pertinent. No restriction based on clinical study design was used and non-randomized trials and patient registries were included.

Full-text review was then conducted to identify publications with unique patient data using preset criteria (Appendix III). To identify potential overlap in patient data between articles, the names of the authors, their institution, the period of patient enrollment into the study and the study design (i.e. single site results of multicentre study) were recorded in an abstraction data form. Where there was a potential for duplicate reporting of patient results, the most recent publication with the larger sample size was included. At this point, authors were not contacted to

verify potential overlap. Clinical studies regarding the FDA approved clinical trials related to the Ancure device (Guidant) were identified and were excluded from further analysis due to the potential of underreporting of device related events in these studies and the occurrence of patient complications that were identified following investigation of the study results.[22]

2.1.2 Data extraction

For unique comparative clinical studies, data were abstracted using a standard form to record details of the study design and methods, patient baseline characteristics, technical aspects of EVAR and OSR and outcome measures of interest according the SVS reporting standards .[23]

Clinical outcomes were obtained from the studies that described 30 day and post 30 day events. When cumulative evidence was provided (greater than 30 days), the 30 day events were not included in the analysis of the long term outcome data. The studies were classified as multi-centre or single centre. Where the study examined outcomes from a single centre over a period of time greater than one year, annual treatment volume was estimated by dividing the number of patients in the study by the enrollment duration in years. Furthermore, after determining the median surgical volume of institutions performing EVAR, surgical volume was divided into two categories: low volume institutions were identified by having, on average, less than 30 patients per year whereas high volume institutions completed 30 or more procedures per year.

Studies that included only high-risk surgical patients were also identified. High-risk patients were classified as high-risk if they had any one of the following characteristics: age>80, ASA III or IV, or an existing systemic complication (cardiac, pulmonary, renal).[24] Further information was extracted from the studies regarding the suitability of the OSR patients for EVAR, if available.

2.1.3 Statistical Analysis

Statistical analysis was carried out using Microsoft Excel 2002 with comparison of dichotomous outcomes expressed as Odds Ratios (OR). An OR less than 1 indicates a lower rate in EVAR than OSR. Continuous variables were analyzed by ways of Weighted Mean Differences (WMD). A WMD less than zero indicates a lower rate in EVAR than OSR. A level of significance (α) of 0.05 was used to indicate statistical significance.

Meta-regression analyses (including a random effect) were performed on differences in operative mortality between EVAR and OSR with respect to study enrolment time using Stata Statistical Software, release 9.2 (Stata, College Station, Texas, USA).

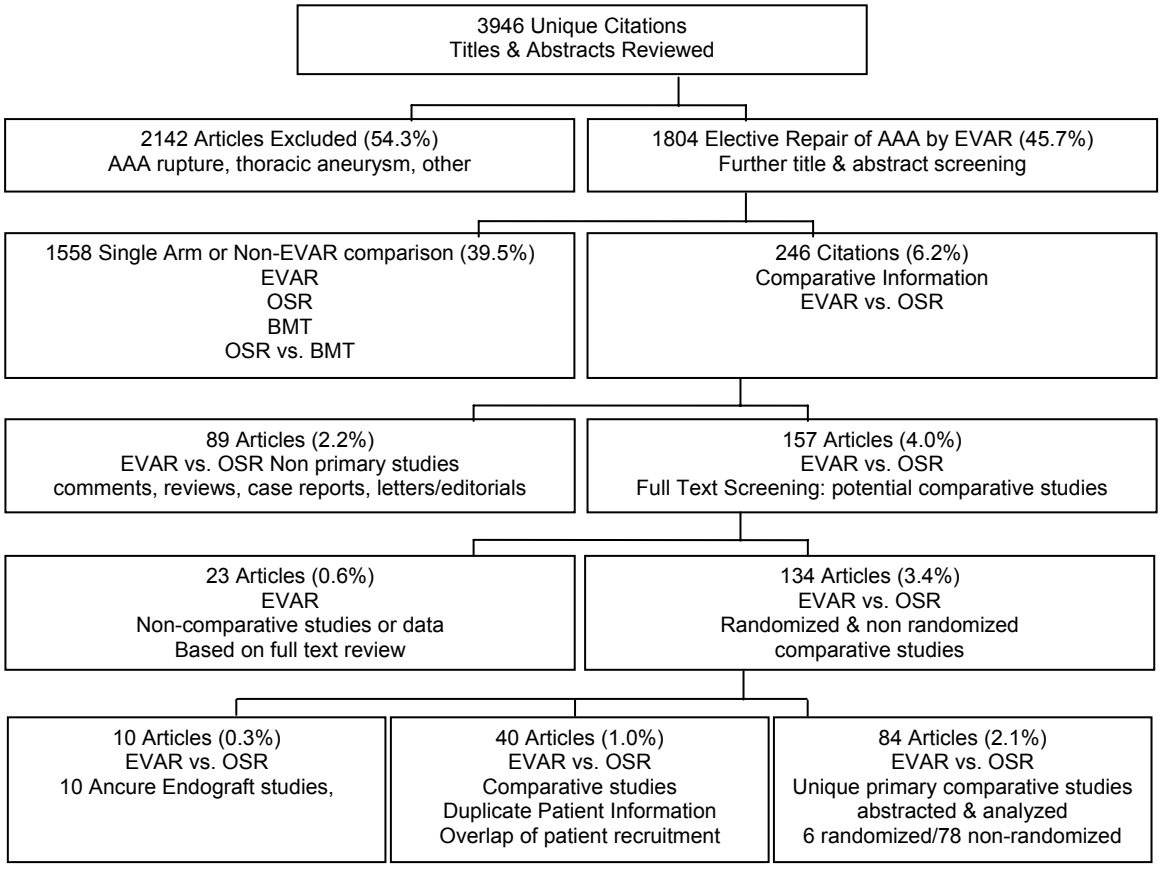
2.2 Results

2.2.1 Literature search

The literature search completed on 20 May 2005 and updated on 28 Nov 2006 identified a combined total of 3,946 unique citations. Available abstracts were searched to establish the relevance of each study to the evaluation and 2,142 studies were excluded as they did not discuss the elective repair of AAA and a further 1558 were excluded because they did not provide comparative information of EVAR versus OSR. 89 articles were excluded as they were case reports, review articles or letters.

Full text review of the remaining 157 articles identified an additional 23 articles that did not include clinical data. Of the remaining 134 articles (3.4% of the initial search) 10 papers were identified as containing Ancure trial data (n=10) and were excluded from further evaluation. The 124 comparative studies were then screened to identify potential duplicate patient data. Through this screening, 40 papers (32.3% of the comparative studies) were identified as containing duplicate information when compared to the other studies. The following evaluation is based on the remaining 84 comparative studies which contain unique patient data comparing EVAR to OSR. (Figure 1)

Figure 1: QUORUM diagram



2.2.2 Study characteristics

These 84 studies included 6 randomized controlled trials consisting of 4 studies reporting short-term outcomes [7-9,12] and 2 long-term studies [10,11]. The other 78 comparative studies were observational evaluations (nRCT) (75 peri-operative and 3 long term only [25-27]). Overall, the identified studies contained data pertaining to 59,188 patients. In the 75 observational studies with peri-operative outcomes reported (initial 30 days), there were 16,407 and 41,238 patients receiving EVAR and OSR, respectively. Of these observational studies, 16 were categorized as multi-centre [6,27-41] and the other 59 papers as single centre evaluations.[14,42-99] Further classification of the single centre studies, based on surgical volume, identified 31 low volume centres[14,42,46,48,49,56-59,67-72,75-

[78,83,84,86,88,90,92-96,99,100], and 28 high volume centres[43-45,47,50,52-55,60-66,73,74,79-82,85,87,89,91,97,98].

Five studies were identified that included information regarding the suitability of the OSR treated patients for EVAR [14,48,61,67,68]. Eight studies specifically examined the efficacy of EVAR high-risk patients only [14,38,53,58,63,72,83,84]. Comparative long-term outcomes (greater than 30 days) were reported in 25 observational studies were long term outcomes of up to 3 years after study enrollment [25-27,29,30,32,34,38,41,45,46,48,52,53,53,56,61,64,67,69,79,83,88,92,99]. Appendices VI & VII present the number of patients identified across all studies that included baseline patient characteristics and clinical outcomes.

Differences between the EVAR and OSR treatment groups for various baseline characteristics and estimates of short-term mortality, systemic complications, procedural outcomes, local/vascular complications and EVAR specific outcomes are described thereafter.

2.2.3 Patient characteristics

The patients enrolled in the EVAR and OSR arms of the 4 RCTs identified in this review had similar baseline characteristics except for pulmonary history (OR = 1.81, P<0.05).[7-9,12] In contrast, in non-randomized studies, patients receiving EVAR were more likely to be male (OR 1.64), have higher ASA III and IV ratings (OR 1.33, 1.49 respectively), and less likely to be ASA I or II (OR 0.20, 0.72). In single or multi-centre studies, as well as in institutions with a high volume, patients receiving EVAR were also more likely than patients receiving OSR to have comorbidities such as smoking history, diabetes, hyperlipidemia, cardiac disease, and peripheral vascular disease (PVD) and less likely to have hypertension (Table 2). In all observational studies, EVAR patients had a higher surgical risk with greater baseline comorbidies than OSR patients

Table 2: Difference in Patient Characteristics by Study Design and Risk Status

	RCT	nRCT	Multi-centre	Single centre	Low volume	High volume	Suitable	High Risk
Studies	4	75	16	59	31	28	5	8
# EVAR patients	791	16,407	12,036	4,371	1,496	2,875	260	332
# OSR patients	752	41,238	36,443	4,795	1,752	3,043	235	352
	WMD.	WMD.	WMD.	WMD.	WMD.	WMD.	WMD.	WMD.
Age (years)	-0.43	-2.02	-2.27	-1.49	-2.03	-1.01	-1.17	-2.84
AAA diameter (cm)	-0.04	0.27	0.15	0.36	0.24	0.54	-0.02	0.16
	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio
Male %	1.13	**1.64 ***	**1.76 ***	**1.44 ***	**1.19 ***	**1.62 ***	1.23	**1.66 ***
ASA I	0.82	**0.20 ***	n.a.	**0.20 ***	**0.21 ***	n.a.	n.a.	n.a.
ASA II	1.21	**0.72 ***	n.a.	**0.72 ***	**0.52 ***	1.19	**0.09 ***	n.a.
ASA III	1.14	**1.33 ***	1.01	**1.33 ***	1.06	**1.53 ***	**2.93 ***	**0.39 ***
ASA IV	n.a.	**1.49 ***	1.04	**2.38 ***	**3.87 ***	**2.13 ***	**12.34 ***	**10.80 ***
Smoking history	1.17	**1.19 ***	**1.20 ***	**1.22 ***	**0.83 ***	**1.57 ***	**1.81 ***	**0.37 ***
Hypertension	1.05	**0.93 ***	**0.92 ***	**0.85 ***	**0.83 ***	**0.86 ***	**1.66 ***	0.97
Diabetes	0.79	**1.28 ***	**1.22 ***	**1.42 ***	1.18	**1.58 ***	1.15	1.74
Hyperlipidemia	0.93	**1.22 ***	0.97	**1.61 ***	**1.29 ***	**1.80 ***	**2.14 ***	n.a.
Cardiac Disease	0.95	**1.84 ***	**2.25 ***	**1.38 ***	1.13	**1.56 ***	**1.39 ***	**1.39 ***
CVD	n.a.	0.89	**0.68 ***	**1.28 ***	0.98	**1.38 ***	n.a.	n.a.
Pulmonary	**1.81 ***	1.01	**0.87 ***	**1.43 ***	**1.64 ***	**1.34 ***	**1.58 ***	1.19
PVD	n.a.	**1.28 ***	**1.21 ***	**1.39 ***	0.77	**2.33 ***	n.a.	1.25
Renal	0.77	0.97	**0.79 ***	**1.27 ***	1.13	**1.31 ***	0.72	1.15
Stroke	n.a.	0.48	**0.20 ***	0.92	n.a.	0.72	n.a.	n.a.

* statistically significant : p-value < 0.05
n.a.: not available,
WMD. (Weighted Mean Difference) (EVAR -OSR). Odds Ratio (EVAR/OSR).
Both WMD and Odds Ratio were calculated with patient weights.

When examining the apparent differences in SVS requirements based on the number of centres involved in the study, multi-centre studies, like the RCTs, appear to present data on patients with similar baseline surgical risk however the frequency of the reporting ASA rating within these studies is low (Appendix VI).

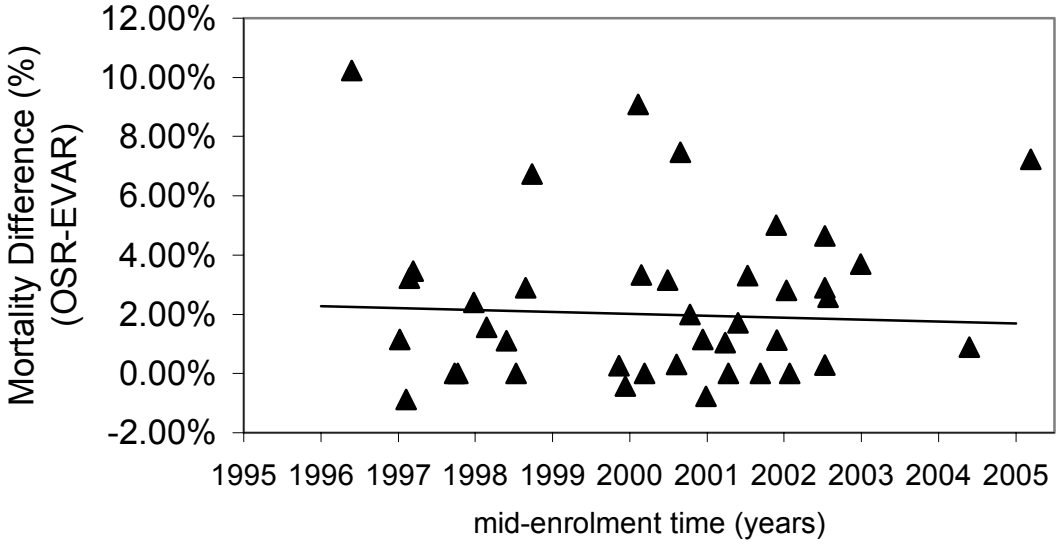
No statistical differences exist between the AAA diameter and age for multi-centre versus single centre evidence. Within the single centre evidence, however, there are more patients with higher level of ASA in EVAR than OSR (ASA I to IV: OR 0.20, 0.72, 1.33, 2.38) and the reporting of the ASA rating is more consistent within the published papers. There are many similarities between the two types of reporting. In EVAR, there are more males, a greater number of individuals with a smoking history, more patients with diabetes, cardiac disease, pvd, and less hypertension. Examining the multi-centre evidence includes less patients receiving EVAR that have CVD, pulmonary, renal disease, while single centre evidence reports the opposite. Fewer patients had stroke in EVAR in multi-centre studies, more hyperlipidemia in EVAR in single centre studies. The differences in baseline characteristics between the EVAR and OSR patients are still apparent when the single centre studies are stratified based on their estimated procedural volume (Table 2).

Only 5 studies stated that both EVAR and OSR patients were anatomically suitable for EVAR. While no statistical differences were found between AAA diameter and age in these studies, there was a much higher rate of ASA III and IV (OR 2.93, 12.34 respectively) in the EVAR patients than in the OSR as compared to the other study designs. Similarly, when examining the baseline characteristics of the 8 studies that have high risk patients only, there were no statistical baseline differences in AAA diameter and age. As observed with EVAR studies reporting patient suitability, there were, statistically significantly more ASA IV patients that received EVAR than in all nRCTs (OR 10.80, $P<0.05$).

2.2.4 Comparison of perioperative mortality and complications.

In all 59 studies, a lower 30-day mortality rate was reported in EVAR than OSR. As shown in Table 3, the mortality difference reported in the nRCTs and in the RCTs was OR = 0.429 and 0.336, respectively. While similar results exist in multi-centre versus single centre evidence, and low volume versus high volume centres, no statistical difference exists in mortality in suitable and high-risk patients. The mortality difference, as determined by meta-analysis, with EVAR having a lower 30 day mortality rate as compared to OSR across the studies (EVAR- OSR; 1.82%; 95% CI 1.61% to 2.03%). When the trends in the difference in peri-operative mortality were determined against the mid-enrolment time of the study there is a small but statistically significant difference that persists over time (Figure 2). The mortality difference has been changing at a rate of 0.066% per year (P<0.001).

Figure 2: Mortality Difference Between OSR and EVAR by Mid-enrollment Time in Years



Within the published RCTs, there were no statistical differences between EVAR and OSR with respect to the occurrence of a myocardial infarction (MI), chronic heart failure (CHF) and arrhythmia, however, not all clinical outcomes were reported in the published papers (Table 3, Appendix X). For observational

studies, lower rates of systemic complications are reported for all measures for EVAR treated patients compared to the OSR group except for limb ischemia which is higher in EVAR (OR 1.866). In multi-centre versus single centre study designs, similar trends in outcome differences between EVAR and OSR are found. Outcomes were also similar in studies coming from both low volume and high volume single centre studies. Of the multi-centre study designs that reported the rate of stroke, EVAR treated patients had a lower perioperative occurrence of stroke as compared to the OSR treated patients (OR 0.196, P<.05). (Table 3).

For the studies that examined EVAR suitable patients and for those that reported results for high risk patients, lesser detail concerning the clinical outcomes recommended by the clinical guidelines were available. Information could be obtained concerning mortality and for general measures of cardiac, pulmonary and renal complications and there were less complications in EVAR than OSR for cardiac (OR 0.076) and pulmonary complications (OR 0.075). (Table 3).

Table 3: Mortality and Systematic Complications

Studies	RCT Odds Ratio 4	nRCT Odds Ratio 75	Multi-centre Odds Ratio 16	Single centre Odds Ratio 59	Low volume Odds Ratio 31	High volume Odds Ratio 28	Suitable Odds Ratio 5	High risk Odds Ratio 8
Mortality	**0.336 ***	**0.429 ***	**0.437 ***	**0.539 ***	**0.508 ***	**0.555 ***	0.797	0.517
Cardiac								
Myocardial Infarction	0.655	**0.401 ***	**0.250 ***	**0.463 ***	0.178	**0.486 ***	--	--
Congestive heart failure	0.159	**0.551 ***	--	0.622	--	0.736	--	--
Arryhthmia	--	**0.198 ***	0.391	0.216	**0.107 ***	**0.262 ***	--	--
Angina	--	**0.047 ***	--	**0.051 ***	--	--	--	--
Unspecified	0.752	**0.473 ***	**0.383 ***	**0.661 ***	0.759	**0.506 ***	0.611	**0.076 ***
Pulmonary								
Failure	--	**0.268 ***	**0.226 ***	**0.263 ***	**0.267 ***	**0.268 ***	--	--
Edema	--	0.375	--	1.233	--		--	--
Pneumonia	--	**0.201 ***	**0.242 ***	**0.164 ***	0.270	**0.160 ***	--	0.306
Pulmonary embolism	--	**0.127 ***	0.657	**0.050 ***	--	**0.057 ***	--	--
Unspecified	--	**0.219 ***	**0.204 ***	**0.255 ***	**0.219 ***	**0.282 ***	**0.105 ***	**0.075 ***
Major	**0.246 ***	**0.288 ***	**0.427 ***	**0.126 ***	--	**0.168 ***	--	--
Moderate	**0.265 ***	--	--	--	--	--	--	--
Renal								
Permanent failure	--	**0.290 ***	**0.102 ***	0.634	0.000	**3.098 ***	--	--
Temporary failure	1.018	**0.553 ***	**0.258 ***	0.717	0.479	0.859	--	0.322
Unspecified	--	**0.396 ***	**0.391 ***	**0.422 ***	0.593	**0.368 ***	0.483	0.314
Stroke & Ischemia								
Stroke	--	0.476	**0.196 ***	0.916	--	0.715	--	--
Transient Ischemia Attacks	**0.321 ***	--	--	--	--	--	--	--
Bowel/colon ischemia	2.047	**0.302 ***	0.197	**0.328 ***	0.871	**0.238 ***	--	--
Limb ischemia	--	**1.866 ***	--	**2.134 ***	2.711	**2.032 ***	--	--
Spinal ischemia	0.506	--	--	0	--	--	--	--
Other ischemia	--	0.511	--	0	--	--	--	0.822

* statistically significant : p-value < 0.05. -- : not available,
WMD. (Weighted Mean Difference) (EVAR -OSR). Odds Ratio (EVAR/OSR). Both WMD and Odds Ratio were calculated with patient weights.

2.2.5 Surgical outcomes and local/vascular complications

Across all types of studies and treatment volume risk status, surgical outcomes were better for EVAR in terms of OR time, blood loss, ICU length of stay (LOS) and hospitalization, but these differences were not always statistically significant (Table 4). For example, the differences between EVAR and OSR surgeries were statistically significant in RCTs (-0.30 hour), in multicentre studies (-1.03) and in high volume (-1.08). Procedural blood loss was statistically lower in the EVAR group across all study designs, low and high volume centres and risk groups.

Independent of the nature of the study, EVAR patients spend statistically less time than OSR patients in hospital. The difference in the total length of hospital stay was highest in suitable patients (12.30 days) and the difference was similar across other categories of studies (4.93 to 6.80 days). No statistical significance was observed in the 79 observational studies with respect to the length of stay in the ICU.

Local/vascular complications were less well reported within the studies, especially for the RCTs (Table 5) but some trends emerged. There was more arterial or graft obstruction, minor groin problems in EVAR, but less hemorrhages and pseudoaneursyms than in OSR. Thromboembolisms were more likely to be moderate in EVAR, while major thromboembolisms occurred in OSR treated patients.

Table 4: Surgical Outcomes

	RCT	nRCT	Multi-centre	Single centre	Low volume	High volume	Suitable	High risk
	WMD.	WMD.	WMD.	WMD.	WMD.	WMD.	WMD.	WMD.
Studies	4	75	16	59	31	28	5	8
Operating Time (hours)	**-0.30 ***	-0.85	**-1.03 ***	-0.80	-0.40	**-1.08 ***	-2.70	-0.39
Blood loss (mL)	**-1243 ***	**-1285 ***	**-1216 ***	**-1306 ***	**-1413 ***	**-1178 ***	**-1629 ***	**-2261 ***
Intensive Care (days)	-4.81	-2.24	**-2.12 ***	-2.32	-2.07	-2.22	**-0.80 ***	**-1.94 ***
Length of Stay (days)	**-5.55 ***	**-5.54 ***	**-5.79 ***	**-5.36 ***	**-5.97 ***	**-4.93 ***	**-12.30 ***	**-6.80 ***

Table 5: Local / Vascular Complications

	RCT	nRCT	Multi-centre	Single centre	Low volume	High volume	Suitable	High risk
	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio
Studies	4	75	16	59	31	28	5	8
Graft infection	0.506	4.646	--	3.518	--	2.458	--	--
Graft thrombosis	--	**3.088 ***	2.242	2.981	--	**3.051 ***	--	--
Aortenteric fistula	--	--	--	--	--	--	--	--
Arterial/graft obstruction	--	**2.853 ***	--	**2.890 ***	1.566	**8.952 ***	2.635	--
Groin minor	--	**2.869 ***	--	**3.035 ***	**3.777 ***	1.735	2.269	--
Groin/wound infection	--	0.871	**0.491 ***	1.197	**2.16 ***	0.977	0.738	--
Hemorrhage - major	**0.165 ***	**0.297 ***	**0.251 ***	**0.288 ***	**0.305 ***	**0.269 ***	1.747	--
Hemorrhage - moderate	--	**0.421 ***	--	**0.421 ***	**0.344 ***	0.577	--	**0.177 ***
Pseudoaneurysm - abdominal	--	**0.151 ***	--	0.209	--	--	--	--
Thromboembolism - major	2.047	**0.229 ***	--	**0.249 ***	0.521	**0.203 ***	--	--
Thromboembolism - moderate	--	**2.435 ***	--	**2.297 ***	1.613	**7.200 ***	--	--
Wound major	1.018	0.570	**0.380 ***	0.230	--	0.232	--	--

* statistically significant : p-value < 0.05: --: not available
WMD. (Weighted Mean Difference) (EVAR -OSR). Odds Ratio (EVAR/OSR).
Both WMD and Odds Ratio were calculated with patient weights.

2.2.6 EVAR Specific Outcomes

More perioperative endoleaks type 1 and type 2 were reported in non-randomized trials (6.27% and 10.57%, respectively) than in RCTs (0% and 5%, respectively) (Table 6). Very few type 3 and type 4 endoleaks were reported in all study designs. More type 1 and type 2 endoleaks were reported in single centre studies than multi-centre studies, while more type 4 were reported in multi-centre studies than single centre studies. High risk patients seem to have a greater rate of type 2 endoleaks than the patients studied in the other publications (26.67%) but a lower rate of type 1 endoleaks (2.22%). The rate of endoleaks was not apparently different between low and high volume centres.

The rate of conversion was similar across studies, risk status and treatment volume. Conversion was lowest in suitable and high risk patients, and higher in RCTS and multi-centre evidence. Graft obstruction was reported to occur more frequently in publications from single centres (1.59%) and low volume centres (5.58%) than compared to the overall rate found in the nRCTs (1.08%). More graft migration was reported in high risk patients (8.33%) than in nRCTs (0.61%).

Table 6: EVAR Outcomes

		RCT	nRCT	Multi-centre	Single centre	low volume	high volume	suitable	high risk
Studies		4	75	16	59	31	28	5	8
Endoleaks		%	%	%	%	%	%	%	%
	type1	0	6.27	4.37	7.89	8.47	7.51	15.00	2.22
	type2	5.0	10.57	8.47	12.11	13.51	11.4	5.00	26.67
	type3	0	0.69	0.67	0.72	0.60	0.79	0	1.11
	type4	0	1.07	2.14	0	0	0	0	0
Conversion		1.81	1.49	1.95	0.98	1.09	0.94	0.38	0.36
Graft obstruction		n.a	1.08	0	1.59	5.58	0	14.46	0
Graft kinks or folds		n.a	0.53	0.64	0.45	1.35	0	0	0
Graft migration		n.a	0.61	0.35	0.86	2.02	0.17	0	8.33

A meta-analysis of long-term trends related to endoleaks is presented in Table 7. The meta-analytic rate of type 1 endoleaks was estimated to be 6.77% across all studies. Examining the reported rate of endoleak relative to the midpoint of the recruitment period indicates that Type 1 endoleaks have been decreasing over time (Table 7). In comparison, the rate of type 2 endoleaks was estimated at approximately 9.78% and has also been decreasing with time. The trends for both type 1 and type 2 endoleaks over time were not statistically significant based on the meta-regression. The rates of type 3 and type 4 endoleaks were lower than that of type 1 and 2 endoleaks (< 1%). The information available from the study reports it appears that there has been an increase in the rate of type 3 endoleaks reported over time and a decrease in the rate of type 4 endoleaks. These rates are both statistically significant from the results of the meta-regression.

Finally with respect to limb ischemia, the reported evidence indicates that it more likely to occur in EVAR treated patients compared to OSR, with an estimated difference of 0.95% (95% CI: 0.94% to 0.96%). The difference in the rate of limb ischemia has been decreasing over time based on the information from the evaluable studies (P<.01) (Table 7)

Table 7: Endoleaks and Limb Ischemia

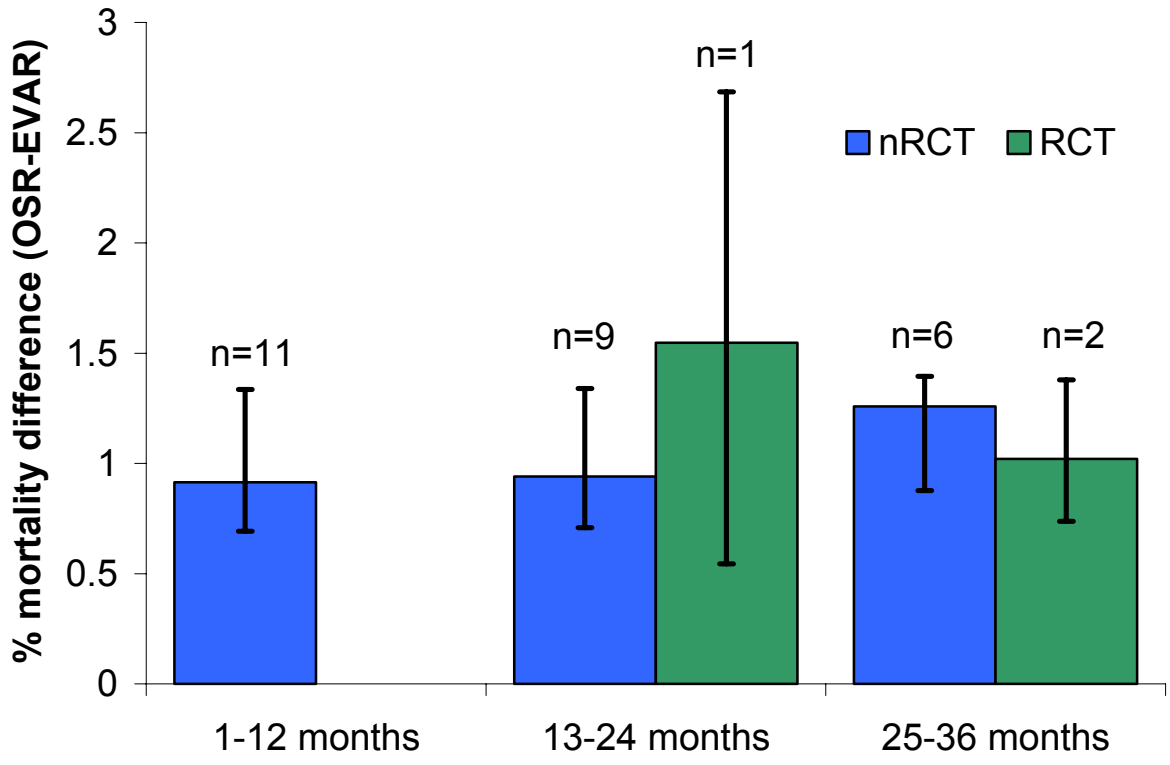
Outcome	Meta-analysis % (95% CI)	Meta-regression trend % (P-value)
Endoleak		
Type 1	6.77% (3.26% to 10.27%)	-0.76% (P=0.39)
Type 2	9.78% (6.76% to 12.79%)	-0.47% (P=0.59)*
Type 3	0.68% (0.43% to 0.94%)	+0.17% (P=0.01)
Type 4	0.33% (0.12% to 0.54%)	-0.22% (P<0.01)
Limb ischemia (EVAR-OSR)	0.95% (0.94% to 0.96%)	-0.02% (P<0.01)

↑ : Coefficient on time trend in meta-regression
* : one outlier with 100% rate of Type 2 Endoleak was removed from analysis.

2.2.7 Mid-term Mortality

No statistical difference in mid-term mortality was found between EVAR and OSR over time (Figure 3). This evidence was based on a total of 6,289 patients with EVAR and 3,547 who received OSR and were followed in comparative nRCT up to a maximum of 36 months. In RCTs, 914 patients received EVAR, and 784 patients received OSR with a mean maximum follow-up time of 28 months.

Figure 3: Mid-term Predicted Mortality Difference by Study Design



2.3 Discussion

In general, the reporting in the published literature of the outcomes suggested in the SVS guidelines is not consistent. Although the identified published literature contains details concerning 59,188 patients, information regarding all of the recommended baseline characteristics and clinical outcomes are not always reported. The literature regarding the comparison of EVAR to OSR, despite the

publication of recent randomized controlled trials[7-9,12,101], is still dominated by a greater number of observational, non-randomized publications. The EVAR patients treated within these observational studies are generally of a higher baseline surgical risk of mortality and post-operative complications as is evaluated in this review and as previously identified in other systematic reviews.[102,103] This analysis has provided an analysis of the differences in baseline characteristics and clinical outcomes between the EVAR and OSR treated patients using recommended guidelines for reporting as the foundation of the data extraction from the identified studies.[23]

Identification of studies that have been conducted specifically in patients that are all are suitable for EVAR and also those studies reporting only outcomes in patients of high surgical risk provide further insight into the use of the procedure in these patient groups. Randomized controlled studies comparing EVAR to OSR in high risk patients have not been conducted to date. In high risk patients, RCT evidence does exist comparing EVAR to best medical treatment.[101] The EVAR2 study compared EVAR to patients initially considered unfit for open surgical repair and found that EVAR treated patients had considerable post-operative mortality and did not improve survival compared to no intervention.[101] The results from EVAR2 however need to be interpreted with caution. The analysis was completed using an intention to treat analysis. Considerable cross-over occurred in the study with 47/172 (27.3%) of the BMT patients being treated with either OSR or EVAR. Furthermore, close to half (9/20 or 45%) of the aneurysm related deaths in the EVAR assigned patients occurred prior to receiving the procedure.

The initial 30-day mortality and post-operative complications with EVAR are lower than that found in OSR treated patients with EVAR having a lower initial mortality and fewer complications. This difference was apparent despite a greater baseline surgical risk. Mid-term survival with EVAR was also identified in this analysis as being comparable to OSR. No long-term mortality and outcome data (greater than 5 years) was identified from comparative studies and this data remains to be published.

3. FIELD EVALUATION STUDY

3.1. London Health Science Centre Endovascular Aneurysm Program

The EVAR program at the London Health Sciences Centre (LHSC) was launched in December, 1997. The rationale for embarking on this endeavour was that this less-invasive method of aneurysm repair would allow for the treatment of patients who might otherwise not be able to have treatment of their life-threatening aortic aneurysm because of prohibitively high perioperative risks associated with standard open repair because of associated heart, lung and/or kidney illnesses. The goals for the program were to:

i) Bring together a group of dedicated medical personnel (e.g surgeons, radiologists and nurses) with specialized skills to perform these procedures.

ii) Evaluate this mode of therapy for the most high-risk patients.

iii) Establish an educational program for the training of vascular surgery trainees and other groups of endovascular specialists throughout the province of Ontario and the rest of Canada.

The LHSC endovascular team currently consists of 4 experienced endovascular surgeons, a dedicated interventional radiologist, a group of specially trained operating room nurses, anaesthesiologists and radiology technicians. The patients are initially assessed by the vascular/endovascular surgeon, with the pre-operative planning for each patient being carried out by the surgeon and the radiologist. The endovascular procedures are carried out in the vascular operating room, equipped with appropriate radiologic imaging equipment. Most procedures are done with the patient under general anaesthesia, but depending on the risk factors, the procedure is also done under regional anaesthesia, with the patient awake. The need for post-operative intensive care is rare. Post-operatively the patients are recovered in the regular post-anaesthetic recovery unit, followed by a few days on the regular vascular surgery ward prior to discharge home.

The program has established guidelines that help determine the anatomical suitability of patients for endovascular aneurysm repair (Appendix I). Patients eligible for EVAR are selected as "high risk" based on selection criteria (Appendix I) that determine high risk on the basis of physiologic parameters and/or anatomical parameters.

Between December 1997 and March 2007 the LHSC endovascular program performed a total of 607 procedures (Table 8). Of these, 499 have been for the elective treatment of infra-renal aortic aneurysms, and 97 for the treatment of thoracic aortic pathology. In fact, EVAR has become the treatment of choice for patients with thoracic aortic pathology, especially traumatic tear of the thoracic aorta, rupture of the thoracic aorta, and thoracic aortic aneurysms at high risk of rupture.

Table 8: London Health Sciences Centre Endovascular Program Volume (December 1997 – March 2007)

Aneurysm Type	Number
Abdominal Aorto-iliac	499
Thoracic Aorta	97
Subclavian Artery	4
Other (Anastomotic, re-do's)	7
Total	607

With respect to EVAR for elective repair of infra-renal aortic aneurysms, the LHSC program has treated 499 patients from December 1997 to March 2007. The technical success (defined as successful deployment of the endograft without Type I endoleaks at the end of the procedure) is 97%, and the 30-day mortality has been 2.6% in these high-risk patients (Table 9). The need for conversion to open repair occurred in 10 patients (2.0%), and all of these occurred in the first two years of LHSC experience (1998-1999) and were primarily due to poor patient selection (based on anatomic criteria). This has not been necessary in the last five years (highlighting the fact that there is a learning curve for these procedures, as documented by the LHSC program).[104] The need

for re-intervention has been 2% (significantly less than reported in multi-center registries).

Table 9: London Health Sciences Centre Endovascular Program for Aorto-iliac Aneurysm: Clinical & Technial Outcomes (December 1997 – April 2005)

Outcome	Number (%)
Successful deployment/technical success (484/499)	97.%
30-day mortality (13/499)	2.6%
Conversion to open repair (10/499)	2.0%
Late graft migration (7/499)	1.3%
Secondary endovascular procedure (10/499)	2.0%
Late aneurysm rupture (2/499)	0.4%

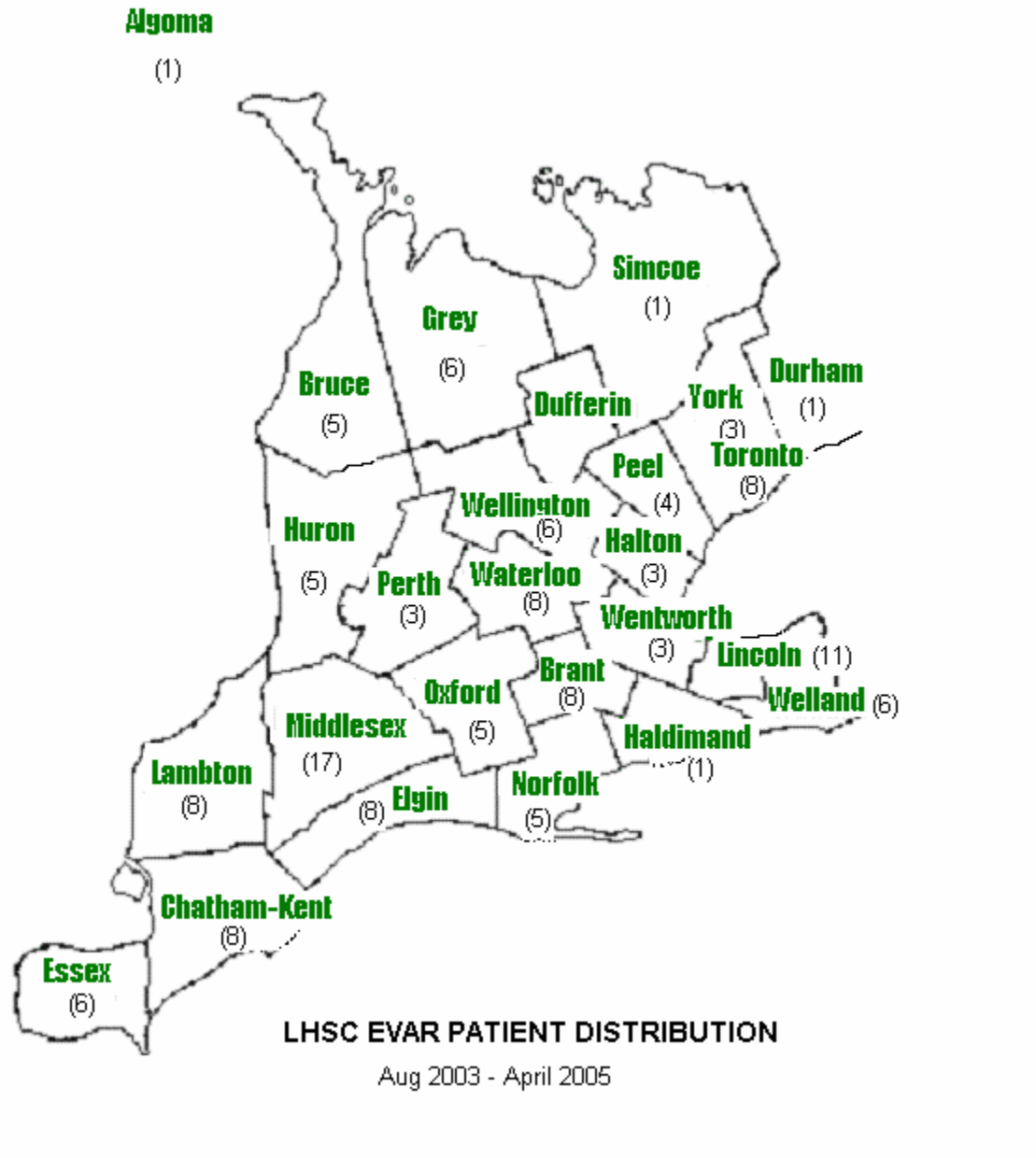
In order to compare the value of EVAR to standard open aneurysm repair, the LHSC group has analyzed the perioperative mortality of all patients undergoing elective repair of an infra-renal aortic aneurysm, by the LHSC team, from September 1999 to December 2004. During this period a total of 871 patients were treated at LHSC, (EVAR – 310 and open surgery – 561). The Leiden Risk Stratification Model was used to stratify patients according to risk factors in order to quantify the prognostic impact of patient's age, gender, cardiac morbidity, renal and pulmonary morbidity.[105] Risk scores are used to estimate surgical mortality. Applying this methodology to the 871 patients treated at LHSC (Table 10) demonstrates that for all risk categories, EVAR was associated with a significantly reduced 30-day mortality rate than predicted for all categories, whereas patients undergoing standard open aneurysm repair the 30-day mortality was in the expected range. (e.g. for the highest risk patients with an expected 30-day mortality of >10%, open repair patients had a mortality of 11.1%, whereas the EVAR patients had a mortality rate of 3.3%).

Table 10: Comparison of EVAR with Open Repair: Risk Stratification Per Leiden Aneurysm Score - LHSC experience (September 1999 – December 2004)

	EVAR (n=310)		OSR (n=561)	
Expected Mortality per Leiden Score	**% of Patients**	**30-Day Mortality**	**% of Patients**	**30-Day Mortality**
<2%	2%	0.0%	13%	0.0%
2-5%	32%	0.0%	61%	3.8%
5-10%	45%	2.9%	20%	8.7%
>10%	21%	3.3%	6%	11.1%

The LHSC endovascular program has treated patients from across the province, but the majority of the patients are from the regions of Southwestern and Central Ontario, traditionally referring patients to the LHSC vascular surgery service for a variety of vascular surgical therapy. The 140 patients receiving EVAR at LHSC from August 2003 to April 2005 are listed as to county of origin as per the map in Figure 4.

Figure 4: Referral Pattern of Patients Receiving EVAR at LHSC



The third goal of the LHSC program was to establish an educational and training resource for endovascular specialists in Canada. Over the years, the LHSC team has trained and mentored teams of surgeons, radiologists and nurses from Halifax, Toronto, Hamilton, Sudbury, Sault Ste Marie, Calgary and Victoria. As well, endovascular surgery training is now a mandatory requirement as per Royal College guidelines for vascular surgery trainees. Thus, the LHSC program is fulfilling an academic need as both a provincial as well as a national resource.

3.2. Rationale and Study Objectives

Current treatment options for AAA include OSR, EVAR or BMT. As these interventions are associated with differences in morbidity, mortality, hospital resource utilization, follow-up procedures, re-intervention rates, complications, recovery times and costs of care, a field evaluation was conducted at LHSC in order to compare EVAR to OSR.

The objectives of the field evaluation were three-fold: 1) to prospectively collect clinical outcomes, resource utilization and quality of life information on patients undergoing elective repair (i.e. EVAR and OSR) in an Ontario hospital setting, 2) to compare EVAR patients who were at high risk of peri-operative complications with open surgical repair (OSR) and anatomically suitable for EVAR, to both high surgical risk and low surgical risk OSR patients and 3) to determine the cost-effectiveness of EVAR versus OSR high risk patients using the data from the field evaluation.

3.3. Methods

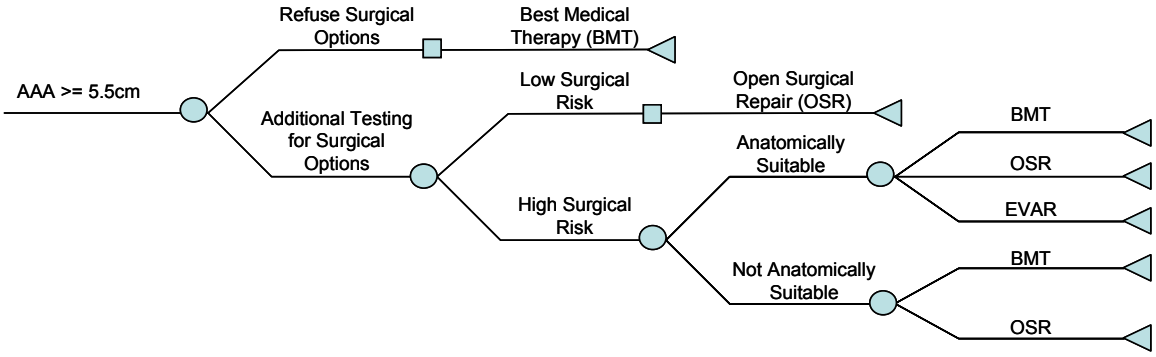
All patients requiring elective repair of an AAA (AAA > 5.5 cm) were invited to participate in this non-randomized, prospective observational study. The study, conducted on an intention-to-treat principle, received ethics approval by the University of Western Ontario Ethics Review Board. Informed consent was obtained from all subjects before study participation.

The method of AAA repair was determined following LHSC clinical criteria for endovascular aneurysm surgery and through discussion with the patient (Appendix I). Individuals not willing to accept surgical options received best medical treatment (BMT). Patients considering surgical options evaluation of surgical risk and suitability were assessed based on cardiac history and risk factors, as well as the presence of pulmonary and renal diseases, hostile abdomen, technical challenges and thoracic aortic pathology (Appendix I). [24]

The repair of AAAs, in patients considered to be of low surgical risk, was completed using OSR. For high risk patients, three treatment alternatives were

considered EVAR, OSR or BMT. High risk patients not anatomically suitable for EVAR were treated using OSR or BMT. For patients anatomically suitable for EVAR, the choice of EVAR or OSR was presented as surgical options. The treatment algorithm for the elective repair of AAAs at LHSC is shown in Figure 5.

Figure 5: Treatment Algorhythm for Elective Repair



At baseline, demographic and medical data (e.g. primary technical success, mortality) as well as quality of life information was collected from participating patients. Subsequent data collection regarding surgical outcomes and resource use were obtained for the peri-operative and post-operative periods.

For surgical patients, subsequent resource utilization data (e.g., hospital admissions, physician visits, procedures, medications) were obtained at 30 days post-surgery and every three months post surgery for 1 year. For patients that received BMT, resource utilization was collected every 3 months for 1 year following enrollment. Data collection was conducted by LHSC research staff during routine clinical visits or over the telephone. Resource utilization information was prospectively collected using a 'telephone assistance card' and study-specific forms depending on the sequence of the assessment and whether the patient was a medical (BMT) or surgical (EVAR or OSR) patient (Appendix IX). Patient specific costs were obtained for the initial hospitalization from the LHSC Case Costing Centre. Unit costs of health care resource utilization for the period following the initial hospitalization were also obtained from LHSC and

multiplied by the observed resource use obtained through the survey data where applicable.

Quality of life was assessed at baseline and at regularly scheduled intervals using two validated quality of life (QoL) instruments: the Short Form-36 Health Survey (SF-36), a generic quality of life questionnaire [106] and the European quality of life questionnaire (EQ-5D), a utility based questionnaire.

Statistical significance was conducted using Chi-square tests for categorical variables and t-tests for continuous variables.

3.4 Results

3.4.1 Baseline Characteristics

Between August 11, 2003 and April 3, 2005, 351 patients were approached to participate in the study, of which 342 subjects were enrolled in the study. Those individuals that were not enrolled consisted of 7 individuals that declined to participate and 2 individuals that had their aneurysm rupture prior to enrollment. Of the enrolled subjects, 140 were treated with EVAR and were considered of high surgical risk for mortality, 195 received OSR and 7 subjects received best medical treatment (BMT). Of the patients undergoing OSR, 52 patients were considered being at a high surgical risk and 143 being of low surgical risk (Table 11). The baseline characteristics by treatment allocation are outlined in Table 11.

Table 11: Baseline Patient Characteristics

	EVAR (n=140)	OSR (n=195)	EVAR vs. OSR	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs. OSR High Risk*
Age	75.6	72.3	P<.01	71.7	74.0	n.s
Gender (male)	85.7%	83.6%	n.s	87.4%	73.1%	P=.04
Work full or part time	5.0%	11.4%	P=.04	13.4%	6.0%	n.s
Smoking Status			P<.01			n.s.
Current	22.8%	39.0%		40.6%	34.6%	
Ever	63.6%	55.4%		53.1%	61.5%	
Never	13.6%	5.6%		6.3%	3.9%	
Mean AAA size in cm (median)	6.2 ()	6.1 ()	n.s.	5.9 ()	6.4 ()	n.s
SVS Grade			P<.01			n.s
I	34.3%	70.8%		83.9%	34.6%	
II	65.7%	29.2%		16.1%	65.4%	
ASA Grade			P=.02			n.s
I	0	0		0	0	
II	1.4%	3.1%		4.2%	0	
III	32.1%	45.9%		50.3%	33.3%	
IV	66.5%	51.0%		45.5%	66.7%	

Overall, the patients treated with EVAR were older than the OSR group (P<0.01) This difference was mainly due to the patients in the OSR low risk group who were younger in age as compared to the EVAR group, 71.7 years vs. 75.6 years, respectively. There was no significant difference in age when comparing the EVAR group to the OSR high risk group. The only difference between the EVAR and the OSR high risk group was observed with respect to gender with more men being treated with EVAR than with OSR high risk patients (P=.04). Only 5.0% of the EVAR patients and 11.4 % of the OSR patients were either employed full or part time at the time of the study (P=.04). However, this difference between the OSR and the EVAR group was not apparent when comparing the OSR high risk group (6.0% employed) to the EVAR group. The mean AAA size was similar between the 2 groups (EVAR: 6.2 cm and OSR: 6.1 cm).

Statistical significance was observed in the SVS grade between the EVAR group and OSR patients (P<.01). Comparing the baseline surgical risk of the patients treated with EVAR (65.7% SVS grade II) to the OSR high risk patients' (65.4% SVS grade II) showed no statistically significant difference. Similarities in

baseline surgical risk was also apparent between the EVAR treated patients and the OSR high risk patients. In terms of assessment of fitness for anaesthesia and surgery with the ASA grade, as there were no statistical differences between the two groups. Approximately one third of the patients were classified as ASA grade III (severe systemic condition limiting activity but not incapacitating) and the two thirds as ASA grade IV (incapacitating systemic disease which is constantly life threatening).

The baseline patient comorbidities in the patients enrolled in the study are provided in Table 12. Significant differences in baseline comorbidities were found between EVAR treated patients and OSR treated patients especially in terms of previous cardiac and respiratory disease history. However, no statistically significant differences in baseline comorbidities were observed between the EVAR treated patients and the OSR high risk patient group except for a higher rate of peripheral vascular disease in the OSR high risk patient group (30.0%) as compared to the EVAR group (10.1%) (P=.02).

With respect to baseline demographics and previous medical history, the EVAR treated patients were generally comparable to the OSR high risk patient group whereas the OSR low risk patient group were younger and had fewer baseline comorbidities.

Table 12: Baseline Patient Comorbidities

	EVAR (n=140) %	OSR (n=195) %	EVAR vs. OSR*	OSR Low Risk (n=143) %	OSR High Risk (n=52) %	EVAR vs. OSR High Risk*
Cardiac History						
Angina	35.7	25.3	P=.04	19.0	42.3	n.s.
MI <6 months previous	2.1	1.6	n.s	0.7	3.9	n.s.
MI >6 months previous	43.9	28.2	P<.01	23.8	40.4	n.s.
Valvular Heart disease	15.7	3.1	P<.01	0.7	9.6	n.s.
Congestive Heart Failure	9.3	2.6	P<.01	0	9.6	n.s.
Arrhythmia	25.0	11.3	P<.01	7.8	21.2	n.s.
Previous Cardiac Interventions						
Angioplasty/Stent	11.4	7.2	n.s.	7.0	7.7	n.s.
CABG	26.4	15.4	P=.01	12.6	23.1	n.s.
Valve Surgery	3.6	1.0	n.s	1.4	0	n.s.
Vascular History						
Hypertension	81.3	74.4	n.s	74.1	75.0	n.s.
Stroke	12.9	4.6	P<.01	4.2	5.8	n.s.
Transient Ischemic Attack	7.9	7.7	n.s	6.3	11.5	n.s.
Peripheral Vascular Disease	10.1	14.2	n.s	8.6	30.0	P=.02
Diabetes History						
Diagnosed diabetes	19.3	13.9	n.s.	11.9	19.2	n.s.
Insulin Dependent	2.9	2.6	n.s.	3.5	0	n.s.
Renal Function			n.s			
Normal	79.1	83.5		84.6	84.0	n.s.
Abnormal (S_{Cr} >250µmol/L)	1.4	1.6		2.1	0	
Dialysis	18.7	14.9		13.2	19.6	
Liver Function			n.s			n.s.
Normal	98.6	99.0		98.6	100	
Pulmonary History						
COPD	35.7	25.9	P=.05	20.4	41.2	n.s.
Emphysema	25.0	11.3	P<.01	8.1	17.3	n.s.
Asthma	2.9	5.6	n.s.	4.9	7.7	n.s.
Other						
Hematologic Disease	5.7	2.6	n.s	2.2	3.9	n.s.
Previous Abdominal Surgery	45.3	30.3	P<.01	28.7	34.6	n.s.
Hostile Abdomen	2.2	1.0	n.s	0.0	3.85	n.s.

*: n.s. means not statistically different

3.4.2 Clinical Outcomes

3.4.2.1 Procedural and Post-operative Outcomes

Three definitions had to be met all together for primary technical success for EVAR: 1) successful introduction and deployment of the device, 2) absence of surgical conversion or mortality and 3) absence of type I or III endoleaks, or graft limb obstruction.[23] For the EVAR treated patients the primary technical success was 100% (140/140) as all patients had successful introduction and deployment

of the endografts during the procedure and there were no surgical conversions, deaths, type I and III endoleaks or graft limb obstructions in this field evaluation (Table 13). Only Type II endoleaks were reported in the EVAR population with 47.9% of EVAR patients demonstrating a type II endoleak on the completion angiogram at the time of the initial procedure. It is important to note that according to experience from many centres as well as LHSC, type II endoleaks do not require an immediate corrective procedure and the majority remain of no clinical significance longterm. The primary technical success was assisted by the completion of 3 (2.1% of patients) unplanned endovascular procedures. Four EVAR patients (2.9%) had to undergo a planned endovascular procedure. Other additional procedures (e.g., inguinal hernia repair) were performed among EVAR patients in only 2 individuals (1.4%).

For OSR patients, primary technical success required replacement or bypass of the aneurysmal segment with a prosthetic graft in the absence of mortality or graft thrombosis either during surgery or during the initial 24-hour postoperative period.[23] Based on these criteria the primary technical success of OSR was 100% (195/195) (Tables 13 & 14). Among the OSR patients, other surgical procedures were required in 10 patients (5.1%). Renal artery revascularization and inferior mesenteric artery reimplantantion was required in 9 (4.6%) and 4 (2.0%) of the OSR patients, respectively. The need for additional procedures between the two treatment groups, EVAR and OSR was not statistically significantly different.

Table 13: Primary Procedural Outcomes

	EVAR (n=140)	OSR (n=195)	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs. OSR	EVAR vs. OSR-HR
Primary Technical Success	140 (100%)	195 (100%)	143 (100%)	48 (100%)	n.s.	n.s.
Procedural death	0	0	0	0	n.s	n.s
Endoleak						
Type I	0	n/a	n/a	n/a	n/a	n/a
Type II	67 (47.9%)	n/a	n/a	n/a	n/a	n/a
Type III	0	n/a	n/a	n/a	n/a	n/a
Type IV	0	n/a	n/a	n/a	n/a	n/a
Additional Procedures						
Conversion to OSR	0	n/a	n/a	n/a	n/a	n/a
Endovascular Procedure						
Planned	4 (2.9%)	n/a	n/a	n/a	n/a	n/a
Unplanned	3 (2.1%)	n/a	n/a	n/a	n/a	n/a
Renal artery revascularization	n/a	9 (4.6%)	8 (5.6%)	1 (1.9%)	n/a	n/a
IMA reimplantation	n/a	4 (2.0%)	2 (1.4%)	2 (3.9%)	n/a	n/a
Other Procedures	2 (1.4%)	10 (5.1%)	8 (5.6%)	2 (3.9%)	n.s.	n.s.

n/a not applicable

Both EVAR and OSR procedures had limited complications at the time of surgery (9/335 or 2.7% of patients) (Table 14). Specifically, there were no procedural graft thromboses, vein or nerve injury and unexpected blood loss was observed in 5 (2.6%) of the OSR patients as compared to none of the EVAR patients. These differences were not significantly different between OSR patients and the EVAR treated patients. A distal popliteal embolus occurred in 1 OSR low surgical risk patient. In the EVAR treated patients 1 patient had an initial misplaced deployment and 1 patient had a twist/kink/obstruction of the endograft that was corrected during the procedure and bladder injury occurred in 1 patient of the 140 treated during the course of the study.

Table 14: Complications at Time of Surgery

	EVAR (n=140)	OSR (n=195)	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs OSR	OSR: Low vs High Risk	EVAR vs OSR High Risk
Complications at Time of Surgery							
Blood Loss (unexpected)	0	5 (2.6%)	3(2.1%)	2 (3.9%)	n.s	n.s	n.s
Graft Thrombosis	0	0	0	0	-	-	-
Nerve Injury	0	0	0	0	-	-	-
Vein Injury	0	0	0	0	-	-	-
Failed Access	0	n/a	n/a	n/a	-	-	-
Access Vessel Complications	0	n/a	n/a	n/a	-	-	-
Failed Deployment	0	n/a	n/a	n/a	-	-	-
Misplaced Deployment	1 (0.7%)	n/a	n/a	n/a	-	-	-
Covered Renal Artery	0	n/a	n/a	n/a	-	-	-
Imperfect Seal	0	n/a	n/a	n/a	-	-	-
Twist/Kink/Obstruction	1 (0.7%)	n/a	n/a	n/a	-	-	-
Complications-Embolisation	0	n/a	n/a	n/a		-	-
Bladder injury	1 (0.7%)	0	0	0	n.s.	n.s	n.s
Distal popliteal embolus	0	1 (0.5%)	1 (0.7%)	0 (0%)	n.s.	n.s.	n.s.

n.s. not significant

Secondary procedural characteristics are outlined in Table 15. The majority of the EVAR patients had a general anaesthesia alone during the procedure (133 or 95%). In contrast, general anesthesia with epidural was given to the vast majority of OSR patients (76.9% low risk OSR and 67.3% high risk OSR). These differences in the use of general anaesthesia with or without epidural were significant between EVAR and OSR patients and between EVAR and high risk OSR patients but not between low and high risk OSR patients (P<.01).

The mean procedural time was statistically significantly lower for EVAR patients (162.4 minutes) than for OSR patients (185 minutes) (P<.01). The mean procedural time for the OSR high risk patients was over 30 minutes longer than those patients treated with EVAR (195.75 minutes vs. 162.4 minutes, respectively, P<.01). Among OSR patients, no statistical difference in procedural time was observed between surgical risk groups. (Table 15)

On average, 26.7% of OSR patients received a blood transfusion (19.6% low risk and 46.2% high risk). In contrast, only 1 EVAR patient required a blood transfusion during surgery. Requirement for blood transfusion were statistically significantly different between each of the treatment groups (P<.01) (Table 15).

Table 15: Seconary Procedural Characteristics

	EVAR (n=140)	OSR (n=195)	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs OSR	OSR: Low vs. High Risk	EVAR vs. OSR High Risk
Anesthesia type					P<.01	n.s.	P<.01
General	133 (95.0%)	50 (25.6%)	33 (23.1%)	17 (32.7%)			
General with Epidural	2 (1.4%)	145 (74.4%)	110 (76.9%)	35 (67.3%)			
Epidural/Spinal	5 (3.6%)	0	0	0			
Local	0	0	0	0			
Surgical Procedure							
Mean Procedural Time (minutes)	162.4	185.0	181.0	195.75	P<.01	n.s.	P<.01
Blood Transfusion (%)	1 (0.7%)	52 (26.7%)	28 (19.6%)	24 (46.2%)	P<.01	P<.01	P<.01

n.s. not significant

3.4.2.2 Initial clinical outcomes (30 days)

The initial 30 day post-operative complications are outlined in Table 16. The 30-day mortality rate was not significantly different between the EVAR and OSR treated patients (i.e. both high and low risk OSR patients). However, the 30 day mortality rate for the OSR high risk treated patients (5 patients, 9.6%) was significantly different as compared to the EVAR treated patients (1 patients, 0.7%) and the OSR low risk (2 patients, 1.4%) (P<.01). Post operative mortality was attributed to cardiac complications, pneumonia, respiratory failure or multi-organ failure as outlined in Table 29.

The post-operative complication rates were in general lower in the EVAR treated patients compared to the OSR treated patients. Specifically, the rates of

congestive heart failure and pulmonary edema (3.4% vs. 12.8%, P<.01), pneumonia (0% vs. 5.6%, P<.01) and paralytic ileus (0% vs. 5.1%, P<.01) occurred more frequently in the OSR patients than EVAR patients. The differences in post-operative complications were primarily attributable to higher rates of complications in the OSR HR treated patients. Statistical differences between the two OSR treated patient groups were found with respect to the rates of renal failure and sepsis (P=.03 for both). Comparing EVAR patients to OSR HR patients, significantly lower rates of CHF/Pulmonary edema (3.4% vs. 17.3%, P<.01), renal failure (3.6% vs. 11.5%, P=.01), pneumonia (0% vs. 7.7%, P<.01), sepsis (0% vs. 5.8%, P=.02) and paralytic ileus (0% vs. 7.7%, P<.01), were observed in the EVAR group. In addition, the OSR HR treated patients had greater need for blood transfusions during the post-operative period as compared to the EVAR treated patients (21.1% vs. 7.9%, P<.05). Other complications which occurred in the patients evaluated are itemized in Table 16.

Table 16: Initial Post-Operative Complications (30 days or to discharge)

Post Operative Complications	EVAR (n=140)	OSR (n=195)	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs OSR	OSR: Low vs High Risk	EVAR vs OSR High Risk
Death	1 (0.7%)	7 (3.6%)	2 (1.4%)	5 (9.6%)	n.s.	p<0.01	P<0.01
Cardiac	1	3	1	2			
Pneumonia		1	1				
Respiratory failure		1		1			
Multi organ failure		2		2			
MI	6 (4.3%)	12 (6.2%)	7 (4.9%)	5 (9.6%)	n.s	n.s	n.s
CHF/Pulmonary Edema	5 (3.4%)	25 (12.8%)	16(11.1%)	9 (17.3%)	P<.01	n.s.	P<.01
Arrythmia	5(3.6%)	13 (6.7%)	8(5.6%)	5(9.6%)	n.s	n.s	n.s.
Stroke	1 (0.7%)	0	0	0	n.s	n.s	n.s
Renal Failure	5 (3.6%)	11 (5.6%)	5 (3.5%)	6 (11.5%)	n.s	P=.03	P=.01
Pneumonia	0	11 (5.6%)	7 (4.9%)	4 (7.7%)	P<.01	n.s	P<.01
Sepsis	0	4 (2.1%)	1 (0.7%)	3 (5.8%)	n.s	P=.03	P=.02
Paralytic Ileus	0	10 (5.1%)	6 (4.2%)	4 (7.7%)	P<.01	n.s	P<.01
Wound Infection/Lymphocele	1 (0.7%)	1 (0.5%)	0	1 (1.9%)	n.s	n.s	n.s
Other Infection	1 (0.7%)	0	0	0	n.s	n.s	n.s
Hemmorrhage/Hematoma	0	1(0.5%)	0	1(1.9%)	n.s	n.s	n.s
Graft Occlusion	0	0	0	0	-	-	-
Blood Transfusion	11(7.9%)	19 (9.7%)	8(5.6%)	11 (21.2%)	n.s	P<.01	p<.05
Vascular Reoperation	1 (0.7%)	4 (2.0%)	3 (2.1%)	1(4.4%)	n.s	n.s	n.s
Embolization	1 (0.7%)	1 (0.5%)	1(0.7%)	0	n.s.	n.s.	n.s.
Urinary Tract Infection	0	2(1.0%)	1(0.7%)	1 (1.9%)	n.s	n.s.	n.s
GI Bleed	0	2(1.0%)	2(1.4%)	0	n.s.	n.s.	n.s.
Other Surgery	1 (0.7%)	4 (2.1%)	1 (0.7%)	3 (5.77%)	n.s.	n.s	n.s
Other Neuro	1 (0.7%)	0	0	0	n.s.	n.s.	n.s.
Other respiratory	0	2 (1.0%)	1(0.7%)	1 (1.9%)	n.s.	n.s.	n.s.
Other	0	1 (0.5%)	0	1(1.9%)	n.s.	n.s.	n.s.

n.s. not significant
n/a not applicable

The implications of the increased rate of post-operative complications in the OSR patients can be further evaluated by examining the duration of the hospitalization following elective AAA repair usng the different treatment options (Table 17). EVAR patients spent significantly less time in the hospital (7.7 days) than OSR patients (11.17 days) or OSR high risk (16.13 days) patients. Four percent of EVAR patients required admission to the intensive care unit (ICU). In contrast,

6% (low risk) and 31% (high risk) OSR patients were admitted to the ICU. Differences in terms of ICU admission were significant in all the comparisons presented in Table 17 (i.e. EVAR versus OSR, OSR low risk versus high risk and EVAR versus OSR high risk). ICU length of stay (LOS) was also statistically different between these groups. For example, the mean ICU LOS was 0.23 days for EVAR patients and 3.21 days for OSR high risk patients (P<.05).

Table 17: Hospital Length of Stay

	EVAR (n=140)	OSR (n=195)	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs OSR	OSR Low Risk vs OSR high risk	EVAR vs OSR High Risk
Length of Stay (LOS)							
Mean length of stay (days)	7.7	11.17	9.36	16.13	p<.05	p<.05	p<.05
Attendance to ICU	5 (4%)	25 (13%)	9 (6%)	16 (31%)	p<.05	p<.05	p<.05
Mean ICU LOS (days)	0.23	1.06	0.27	3.21	p<.05	p<.05	p<.05

3.4.2.3 Mid-term clinical outcomes and resource utilization (1 year)

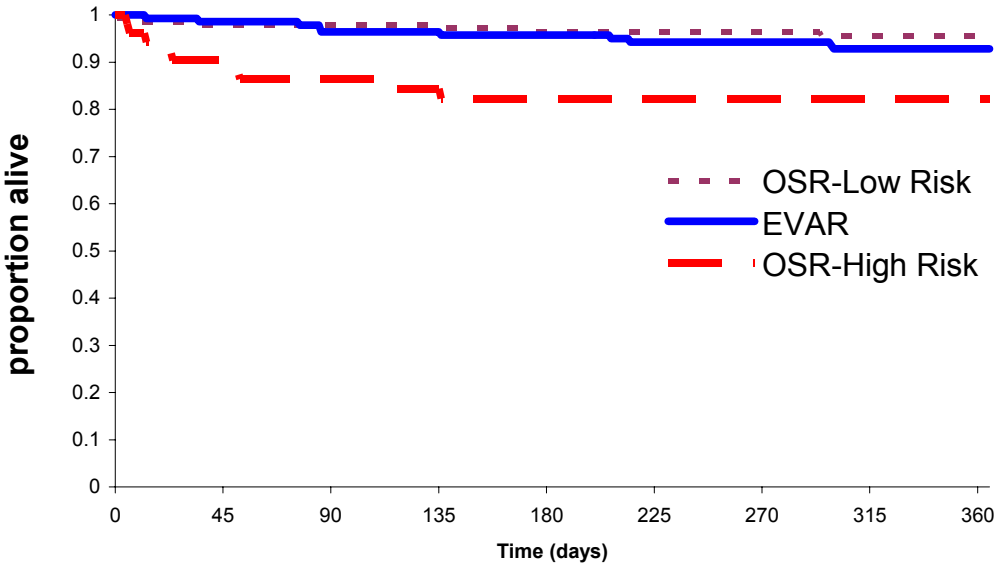
One-year follow-up information with respect to mortality and complication rates is itemized in Table 18. The increased mortality rate observed in OSR High Risk (HR) patients as compared to EVAR individuals persisted out to one year (EVAR 7.1% vs. OSR HR 17.3%, p=.04). The cause of death over the 1 year period for each of the patient groups included cardiac, cerebrovascular, respiratory, renal and oncological causes. Multi-organ failure occurred in 3 patients (1 EVAR and 2 OSR HR treated patients). Over the 1 year period the EVAR patients did not require any reintervention nor were there any cases of aneurysm rupture, graft migration, integrity problems or obstruction of the endografts. Less than 10% of EVAR patients (8.6%) had new type II endoleaks however no re-intervention was necessary (Table 18).

Table 18: Mortality and Complications Rates (1 yr)

	EVAR (n=140)	OSR (n=195)	OSR Low Risk (n=143)	OSR High Risk (n=52)	EVAR vs. OSR	EVAR vs. OSR-HR
1 year mortality	10 (7.1%)	15 (7.7%)	6 (4.2%)	9 (17.3%)	n.s.	P=0.04
Cardiac	2	4	2	2		
Cerebrovascular	1	1		1		
Pneumonia	2	3	2	1		
Respiratory failure		1		1		
Pulmonary fibrosis	1					
Renal failure	1					
Multiple organ failure	1	2		2		
Cancer	2	3	2	1		
Unknown		1		1		
1 year complications						
New Type II endoleaks	12 (8.63%)	n/a	n/a	n/a	n/a	n/a
Reinterventions	0	0	0	0	-	-
Aneurysm Rupture	0	0	0	0	-	-
Graft Migration	0	n/a	n/a	n/a	n/a	n/a
Graft Integrity	0	n/a	n/a	n/a	n/a	n/a
Obstruction-revascularization	0	n/a	n/a	n/a	n/a	n/a
Obstruction-observation	0	n/a	n/a	n/a	n/a	n/a

The Kaplan Meier survival curves for the 3 patient groups are presented in Figure 6.

Figure 6: Kaplan Meier Surival for EVAR, OSR LR and OSR HR Groups up to 365 Days of Follow-up



Over the one year following the the initial hospitalization, the EVAR patients visited specialists (i.e. vascular surgeons and other specialists) more often than OSR patients and had more diagnostic tests (i.e. CT scan) than OSR patients (Table 19). When compared to OSR patients or OSR high risk patients, EVAR patients were more often readmitted to the hospital or to an emergency room. No statistically significant differences were observed between EVAR and OSR patients in terms of follow-up GP visits. Among OSR patient groups, the only statistical difference was observed in the number of specialists visits between low and high risk patients.

With respect to loss of productivity following AAA repair, the mean number of paid days off work for the EVAR group was on average 3.91 days and for the OSR group 7.38 days. The second measure used to capture productivity losses, the average number of hours of care provided by others, indicates that 18.6 hours for EVAR patients and 31.9 hours OSR patients of care were provided by

relatives or others. None of these differences were significant across treatment groups.

Table 19: One-year Resource Utilization

	EVAR	OSR			Differences		
	All (n=140)	All (n=195)	Low Risk (n=143)	High Risk (n=52)	EVAR vs. OSR (all)	OSR High vs. Low Risk	EVAR vs. OSR High Risk
Initial Hospitalization							
Mean Length of Stay	7.7	11.17	9.36	16.13	-3.47*	6.77*	-8.43*
Mean ICU days	0.23	1.06	0.27	3.21	-0.83*	2.94*	-2.98*
Follow-Up. Mean Number of:							
Hospital admissions	0.36	0.18	0.20	0.13	0.18*	-0.07	0.23*
ER visits	0.93	0.46	0.51	0.31	0.47*	-0.20	0.62*
GP visits	6.37	5.74	5.83	5.48	0.63	-0.35	0.89
Specialist visits	4.19	2.15	2.33	1.65	2.04*	-0.68*	2.54*
Vascular Surgeon Visits**	2.61	0.07	0.06	0.10	2.54*	0.04*	2.51*
CT Scans	2.74	1.18	1.27	0.96	1.56*	-0.31	1.78*
Follow-Up (Productivity Costs)							
Mean paid days taken off work	3.91	7.38	8.90	3.32	-3.47	-5.58	0.59
Mean hours of care provided by others	18.6	31.85	35.07	23.0	-13.25	-12.07	-4.40

*Indicates significance at 5% level

**: Vascular surgeons visits are included in specialist visits

3.4.3 One-year direct and productivity costs

Table 20 lists selected 2006 unit costs that were applied to resource utilization data to calculate the mean one year cost of EVAR and OSR. The costs related to initial hospitalization and follow-up were derived from LHSC patient specific data while the unit cost of a vascular surgeon was from the Ontario Schedule of Benefits. The Canadian national hourly wage was used to cost out productivity losses.

Table 20: Scheduled Unit Costs*

Resource Item	Unit cost	Source
Initial Hospitalization	Varies per patient	London Health Science
Follow-up hospitalization		
non-ICU day	$601.20	London Health Science
ICU day	$1446.72	London Health Science
ER visit	$122.95	London Health Science
CT Scan	$285.75	London Health Science
X-ray	$53.42	London Health Science
Vascular surgeon-consult	$112.35	Ontario Schedule of Physician Benefits
Vascular surgeon-assessment	$40.40	Ontario Schedule of Physician Benefits
Hourly wage	$16.75/hour	Statistics Canada

* 2006 Canadian dollars (CAD)

Table 21 presents the total average 1-year cost of EVAR and OSR by main categories (i.e. initial hospitalization costs, follow-up medical costs and productivity costs). The initial costs of hospitalization were $28,139 for EVAR and $19,677 for OSR patients. Despite the fact that EVAR patients spent statistically less time in hospital (Table 17) and generally had a lower post-operative complication rate than OSR patients (Table 18), the overall initial cost of hospitalization was higher due to the cost of the endograft which is approximately $10,000. The mean costs of the initial hospitalization for OSR HR patients however were greater than that of the EVAR treated patients. All the initial hospitalization cost differences between the 3 groups were statistically significant as shown in Table 21.

The average 1-year medical cost of follow-up was statistically greater for EVAR patients ($5,181) than OSR patients ($1,965). This difference ($3,216) was mainly due to the cost associated with hospital readmissions (i.e. $1,343) and diagnostic tests (i.e. $1,258). All the cost differences between EVAR and OSR patients were statistically significant except for the costs associated with GP visits. No statistical differences were observed in terms of total cost of follow-up when OSR patients were stratified by surgical risk level. Productivity losses were

estimated at $835 for EVAR and $1,523 for OSR but these were not statistically different.

As shown in Table 21, the total mean 1-year cost of EVAR patients was $34,146, which compared to $23,165 for all OSR patients resulting in a difference of $10,981. However, when EVAR patients are compared with OSR high risk groups, the difference is negligeable (-$24). Differences in total cost were statistically significant when comparing EVAR versus all OSR patients and when low and high risk OSR patients were compared.

Table 21: Total Average 1-year Costs by Treatment Group

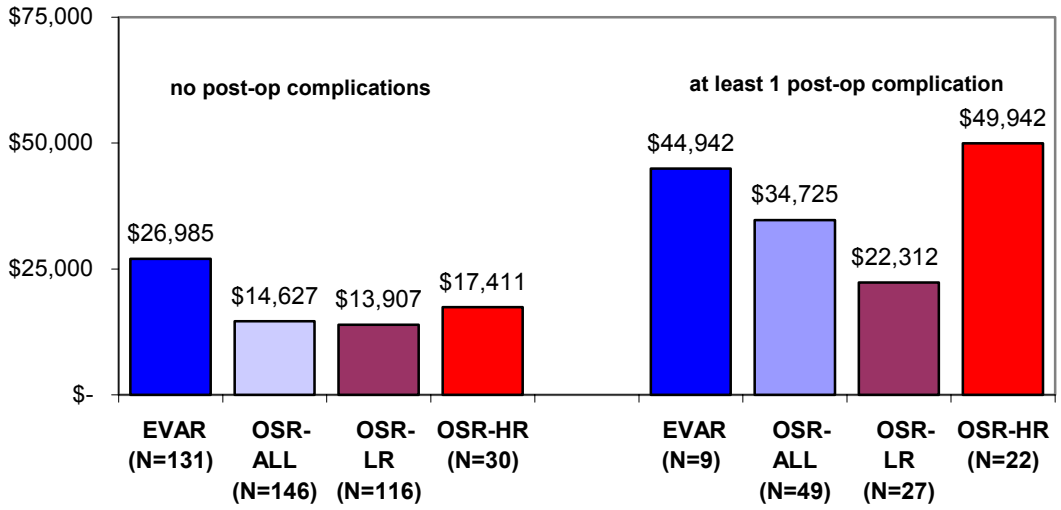
	EVAR	OSR			Differences		
	All (n=140)	**All (n=195)**	**Low Risk (n=143)**	**High Risk (n=52)**	**EVAR vs. OSR(all)**	**OSR High vs. Low Risk**	**EVAR vs. OSR High Risk**
Initial Hospitalization Costs	$28,139	$19,677	$15,494	$31,181	$8,462*	-$15,687*	-$3,042
Follow-Up Medical Cost							
Hospital admissions	$2,318	$975	$874	$1,249	$1,343*	-$375	$1,069*
Tests and procedures	$1,372	$114	$123	$90	$1,258*	$33	$1,282*
ER visits	$115	$56	$63	$38	$59*	$25	$77*
GP visits	$349	$314	$320	$300	$35	$20	$49
Specialist visits	$272	$169	$178	$145	$103*	$33	$127*
Other Health Care Professionals	$755	$336	$332	$348	$419*	-$16	$407*
Sub-Total	$5,181	$1,965	$1,899	$2,171	$3,216*	-$272	$3,010*
Total Healthcare Costs	**$33,320**	**$26,752**	**$17,393**	**$33,352**	**$11,678***	**-$15,959**	**-$32**
Follow-Up. Productivity Costs							
Mean paid days taken off of work	$523	$990	$1192	$433	-$467	$759	$90
Mean hours of care provided by others	$311	$533	$587	$385	-$222	$202	-$74
Sub-Total	**$835**	**$1,523**	**$1,779**	**$818**	**-$688**	**$961**	**$17**
TOTAL	**$34,146**	**$23,165**	**$19,163**	**$34,170**	**$10,981***	**-$15,007***	**-$24**

*: Indicates significance at 5% level

Figure 7 depicts the average costs of initial hospitalization when patients are stratified by presence of major post-operative complications (i.e. mortality, MI,

stroke, CHF, renal failure and pneumonia). In the absence of post-operative complications during the initial hospitalization, the mean hospitalization cost of EVAR was approximately $10,000 more than OSR high risk group. In the presence of post-operative complications for all groups of patients the costs associated with the initial hospitalization increased. This suggests that the high initial hospitalization costs for OSR high risk patients is due to the higher complication rates in this patient group.

Figure 7: Mean Initial Hospitalization Costs for AAA Repair by Treatment Group and Presence of Post-Operative Complications EVAR and OSR



3.4.4 Quality of Life and QALYs

3.4.4.1 SF-36

The first quality of life instrument to be analyzed was the Short-Form 36 (SF-36). Using the scoring method of the SF-36, the eight dimensions of this instrument were computed at every time point (e.g. baseline, discharge and every 3 months) and for each patient group (e.g., EVAR, OSR). The eight dimensions are depicted over the course of the 1 year study in Figures 8-a to 8-h for EVAR patients and for low and high risk OSR patients. The higher is the score, the better the quality of life for the patient.

For 5 dimensions (bodily pain, social functioning, role physical, role emotional and physical functioning), a U-shaped curve was observed with the lowest scores obtained at discharge from hospital. After discharge, the scores increased over time and for OSR patients tended to surpass at the end of the one-year period the initial scores at time of initial hospitalization. In comparison, the scores of EVAR patients at one year were close to the initial baseline scores. After one year, EVAR patients had lower scores compared to OSR patients in terms of bodily pain, social functioning, role physical, role emotional and physical functioning. The scores of the remaining 3 domains (vitality, general health and mental health) did not vary as much over time or by type of treatment.

Figure 8a: SF 36 Dimension: Bodily Pain

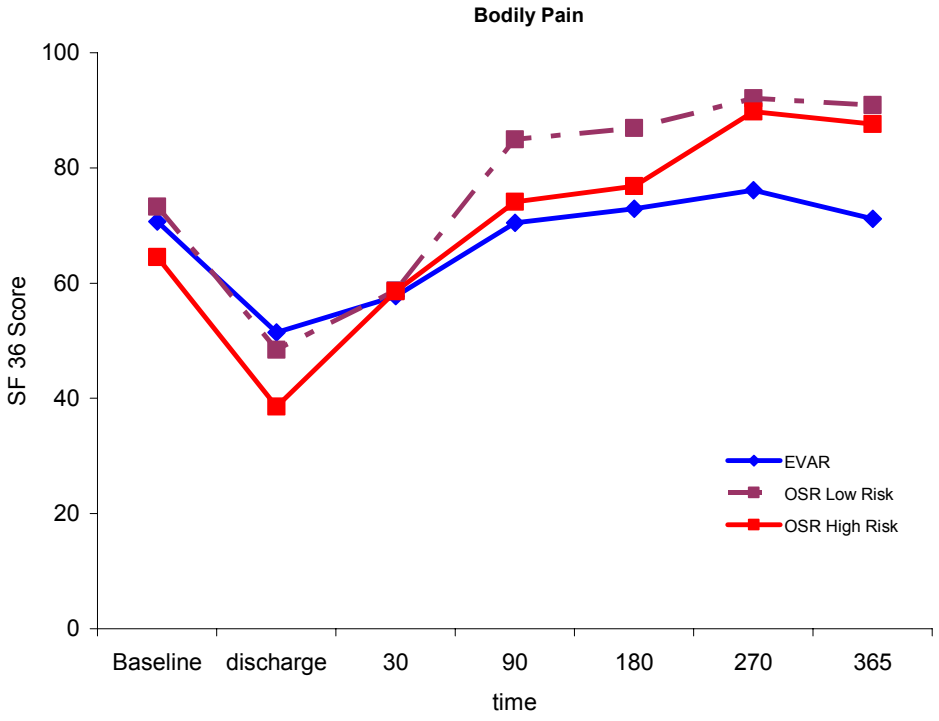


Figure 8b: SF-36 Dimension: Social Functioning

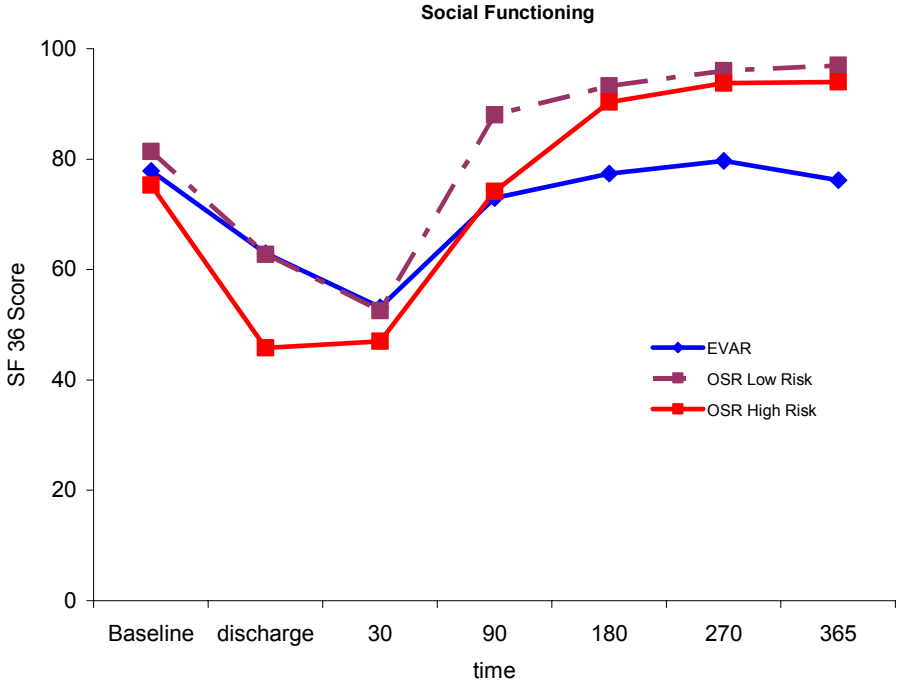


Figure 8c: SF-36 Dimension: Vitality

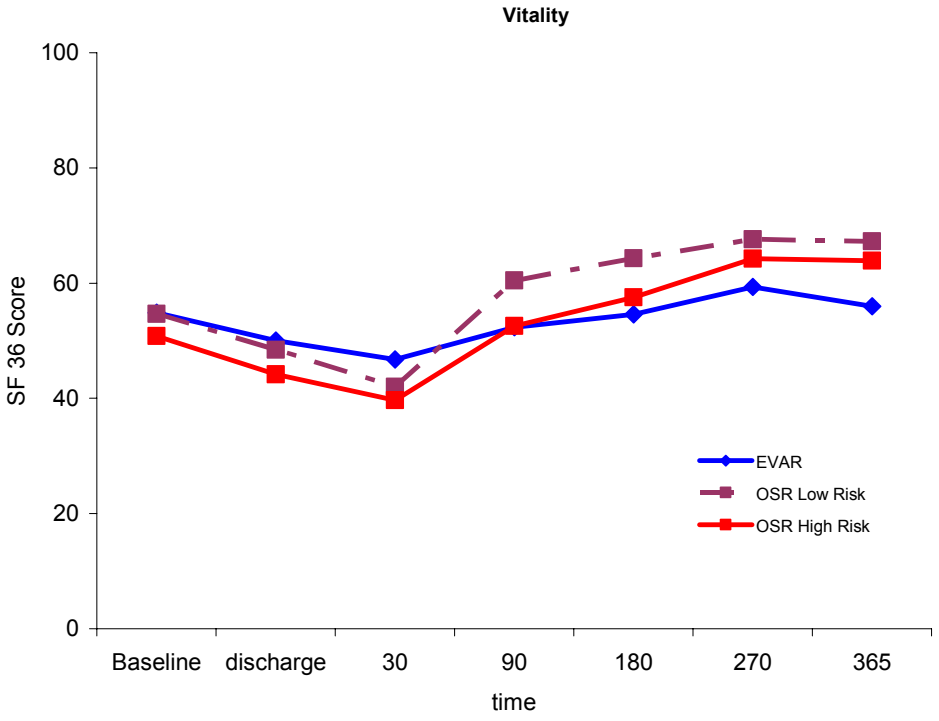


Figure 8d: SF-36 Dimension: General Health

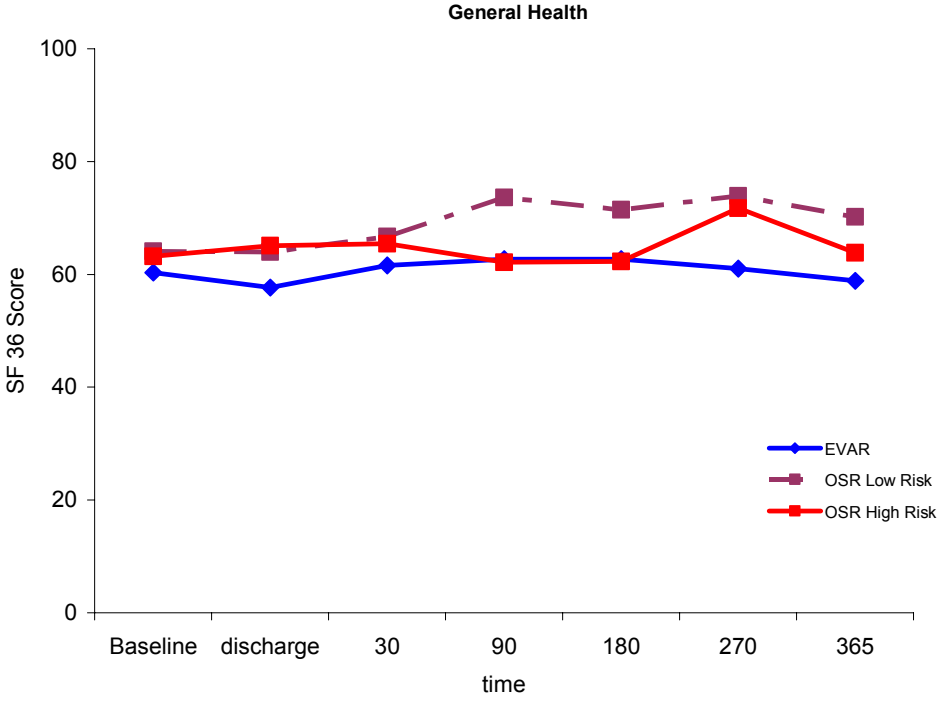


Figure 8e: SF-36 Dimension: Role Physical

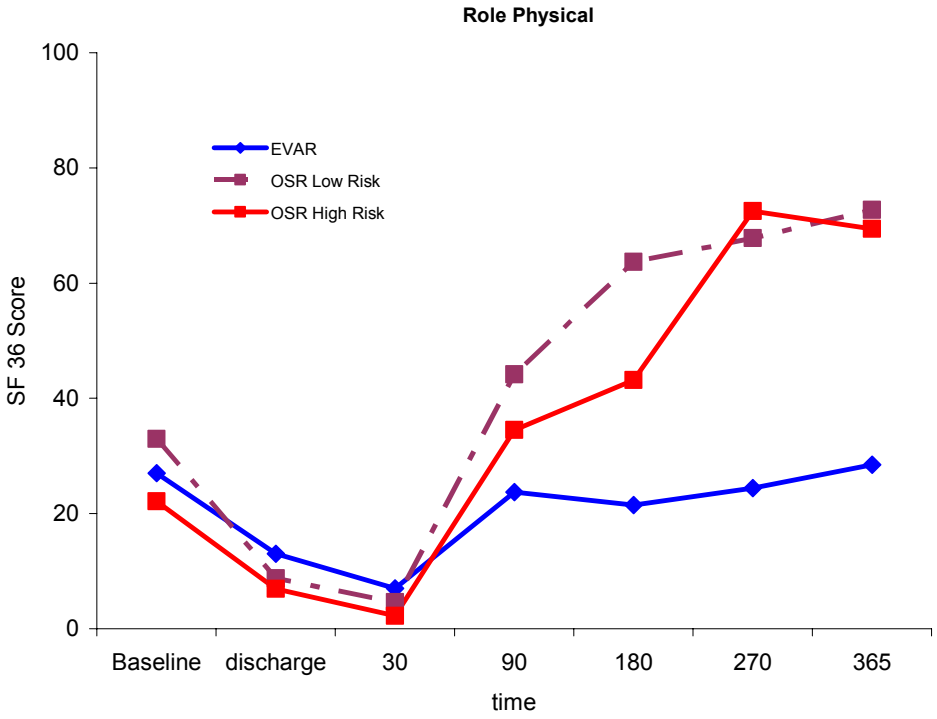


Figure 8f: SF-36 Dimension: Mental Health

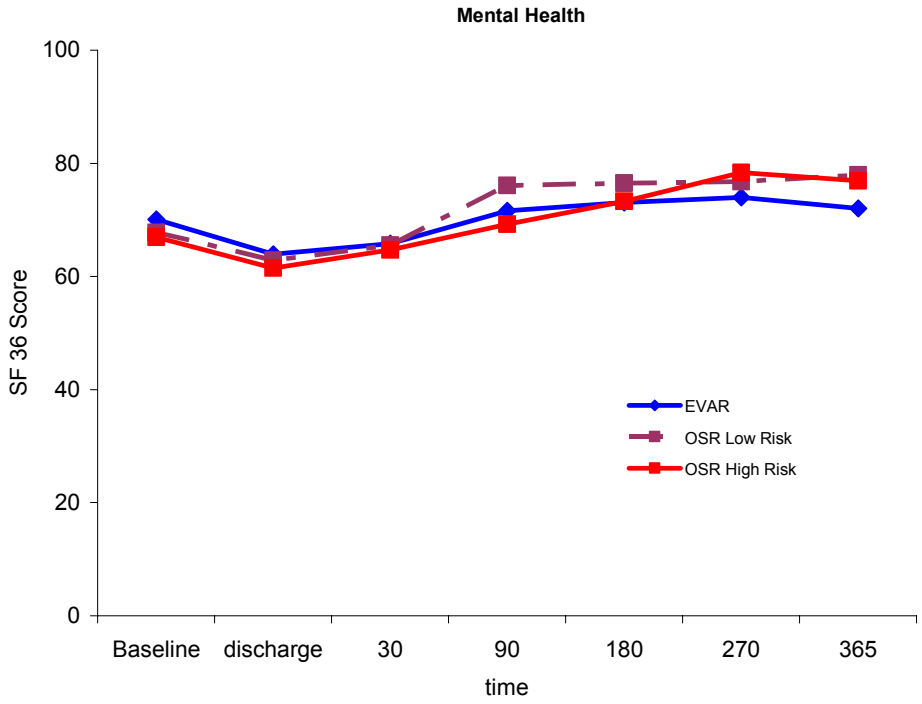


Figure 8g: SF-36 Dimension: Role Emotional

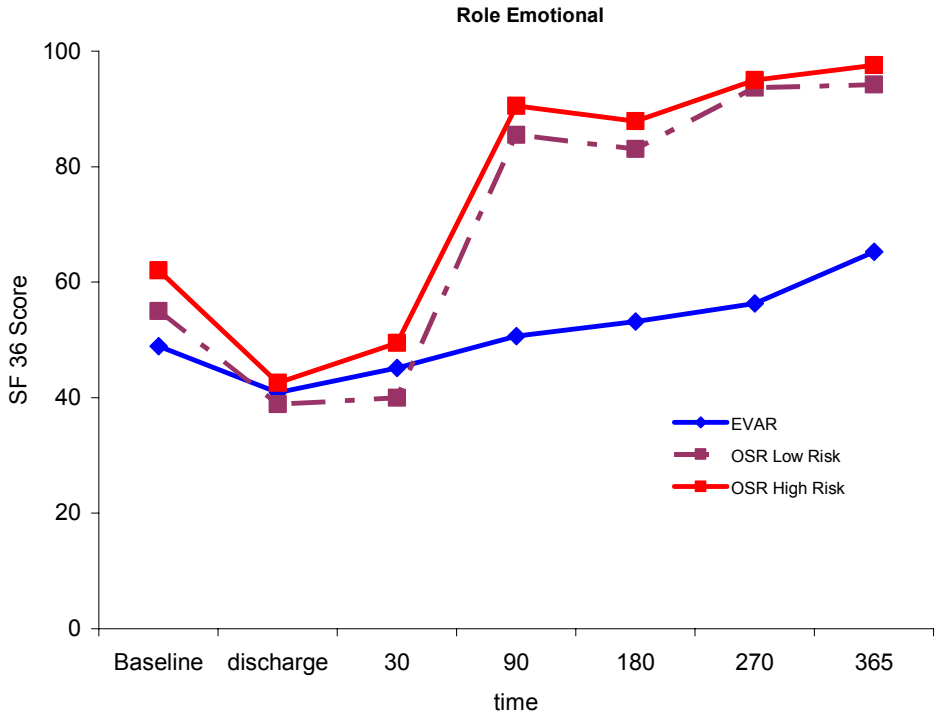
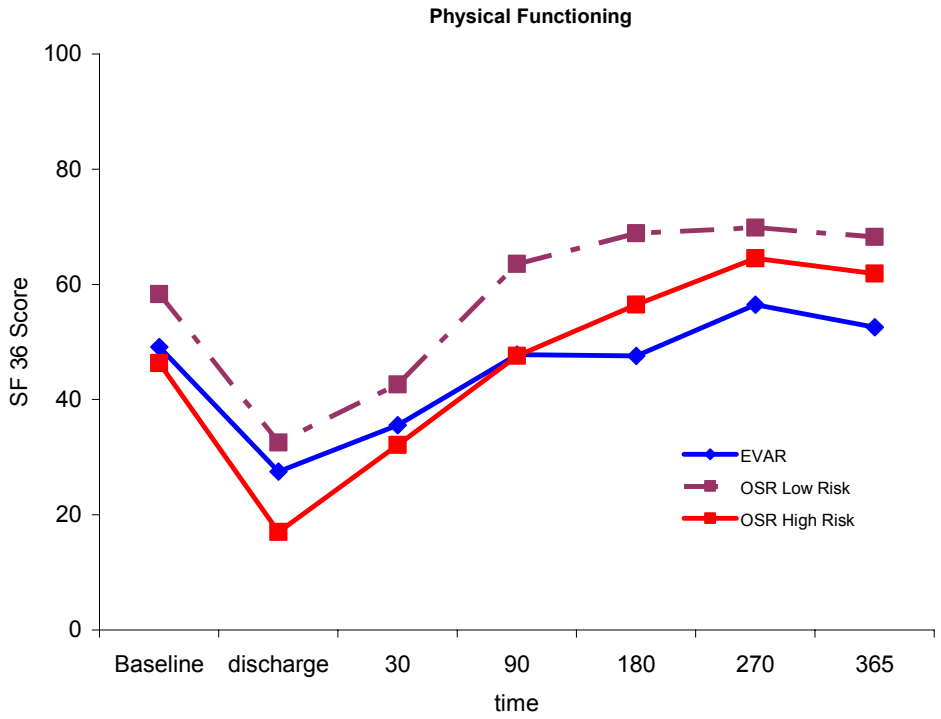


Figure 8h: SF-36 Dimension: Physical Functioning



3.4.4.2 EQ-5D

The second quality of life questionnaire used in this evaluation was the EQ-5D. The EQ-5D is a generic health status instrument with 5 questions representing 5 health state dimensions. Health utility summary scores for the EQ5D were estimated using the weighting system based on the general U.K. population.[107] These utility scores are also used in the economic evaluation (section 4.5) to derive QALYs to assess EVAR and OSR.

Figure 9 presents the observed EQ-5D utility summary scores for EVAR and OSR treatment groups over time. The patients' utility is lower at discharge compared to baseline utilities and then increases over time for the three treatment groups. However, the utility scores of EVAR patients increased over time to a level similar to their baseline values. For OSR patients, the utilities after one year were higher than the baseline values. The mean utility scores at 12 months for EVAR and OSR patients were 0.76 and 0.91, respectively.

Figure 10a to 10e outline the results of the 5 individual questions of the EQ-5D instrument. For each of these 5 questions, three degrees of impairment are possible: no impairment (1), some impairment (2) and extreme impairment (3). As shown in Figures 11a to 11e, EVAR patients reported a lesser improvement at one year relative to baseline values as compared than OSR patients. This is more apparent for the questions regarding usual activities and mobility.

Figure 9: Observed EQ-5D Utility measurements over time

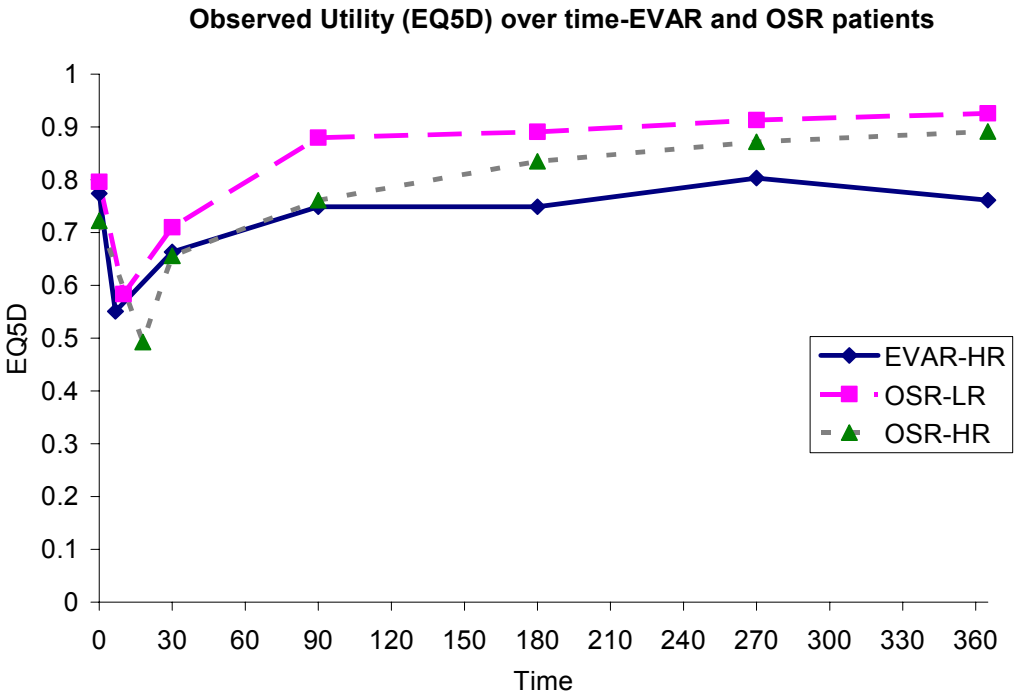


Figure 10a: Mean responses to individual EQ5D questions: Self Care

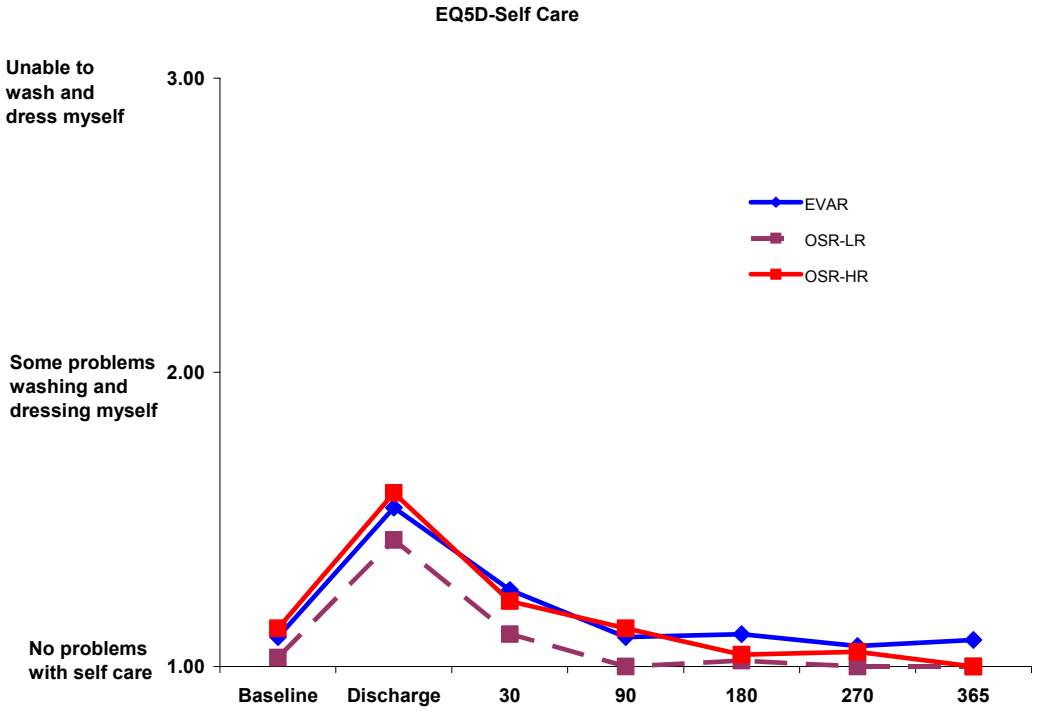


Figure 10b: Mean responses to individual EQ5D questions: Usual activities

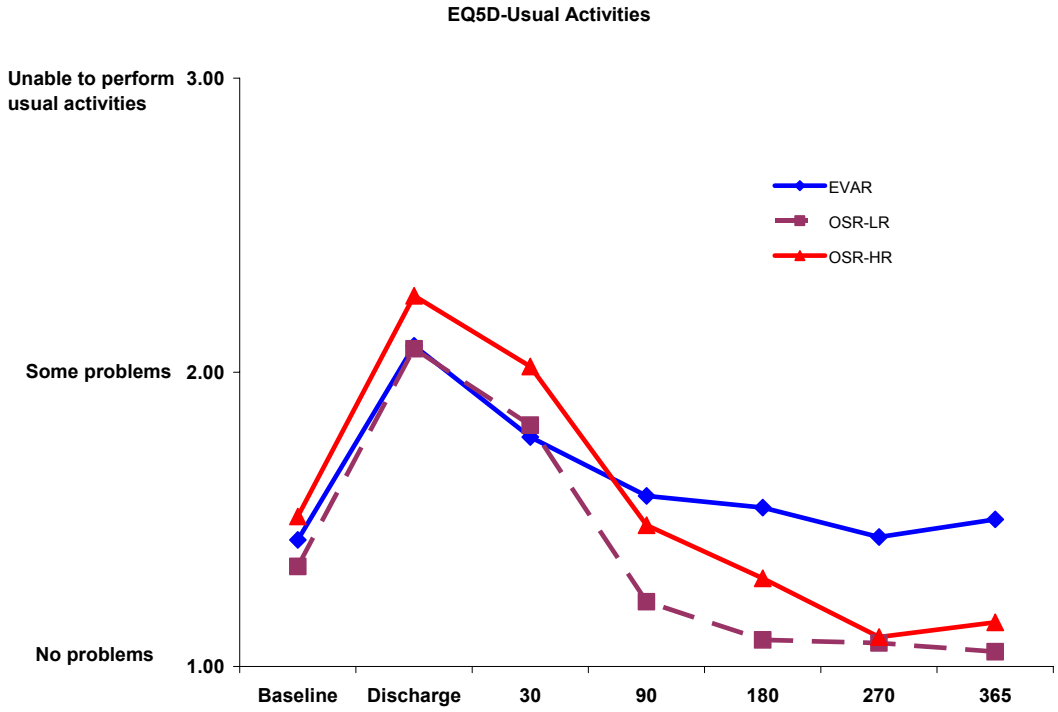


Figure 10c: Mean responses to individual EQ5D questions: Depression and Anxiety

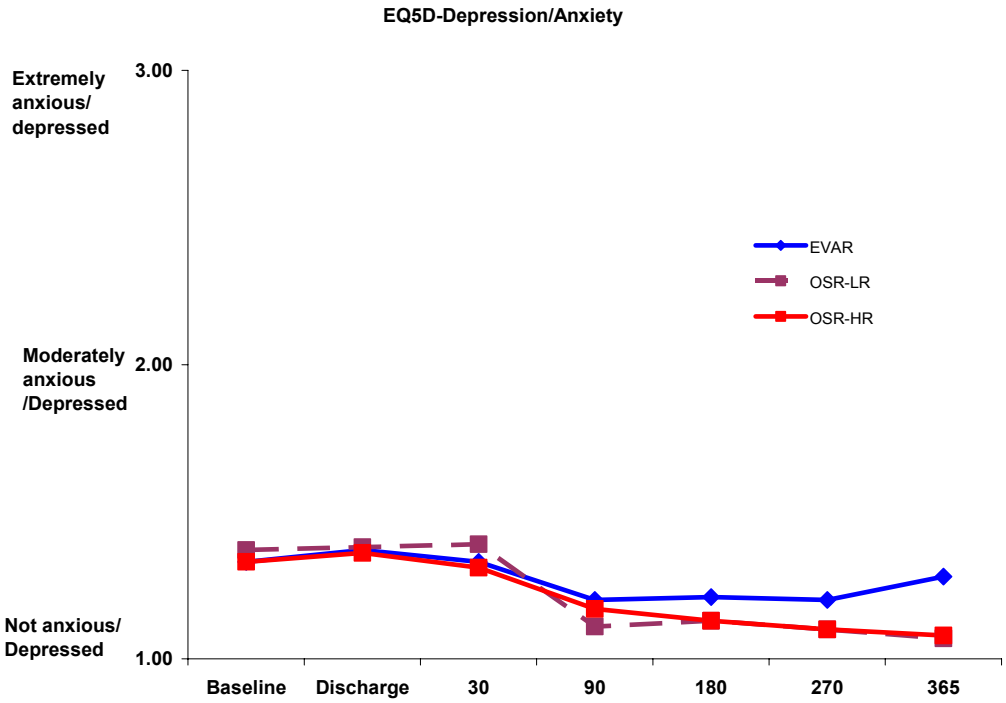


Figure 10d: Mean responses to individual EQ5D questions: Pain

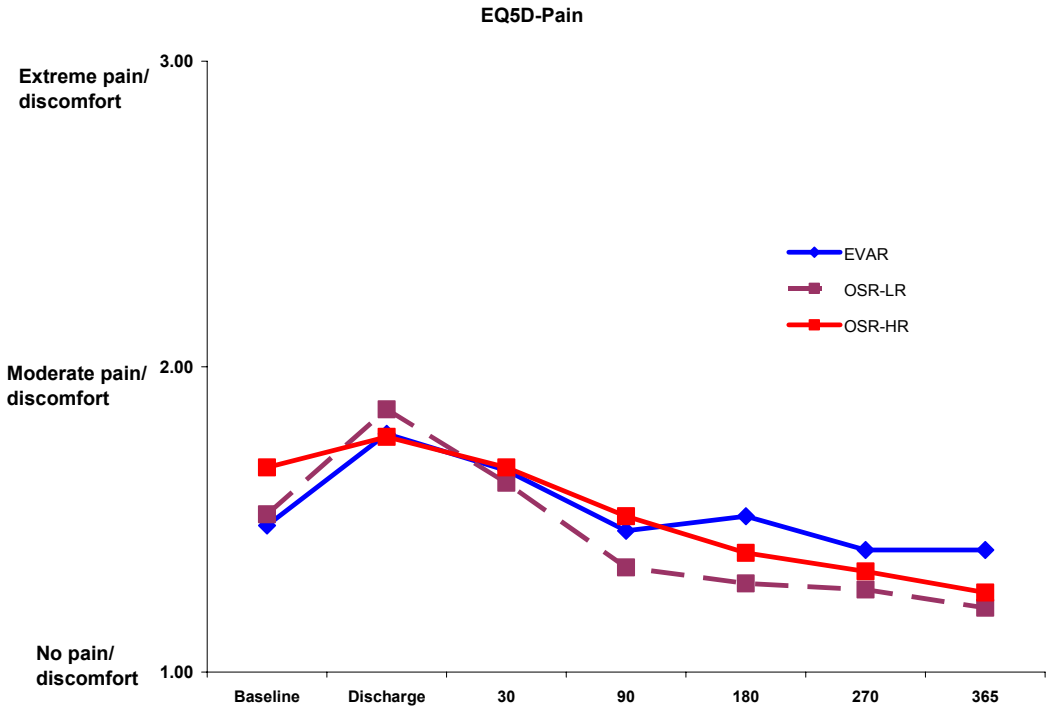
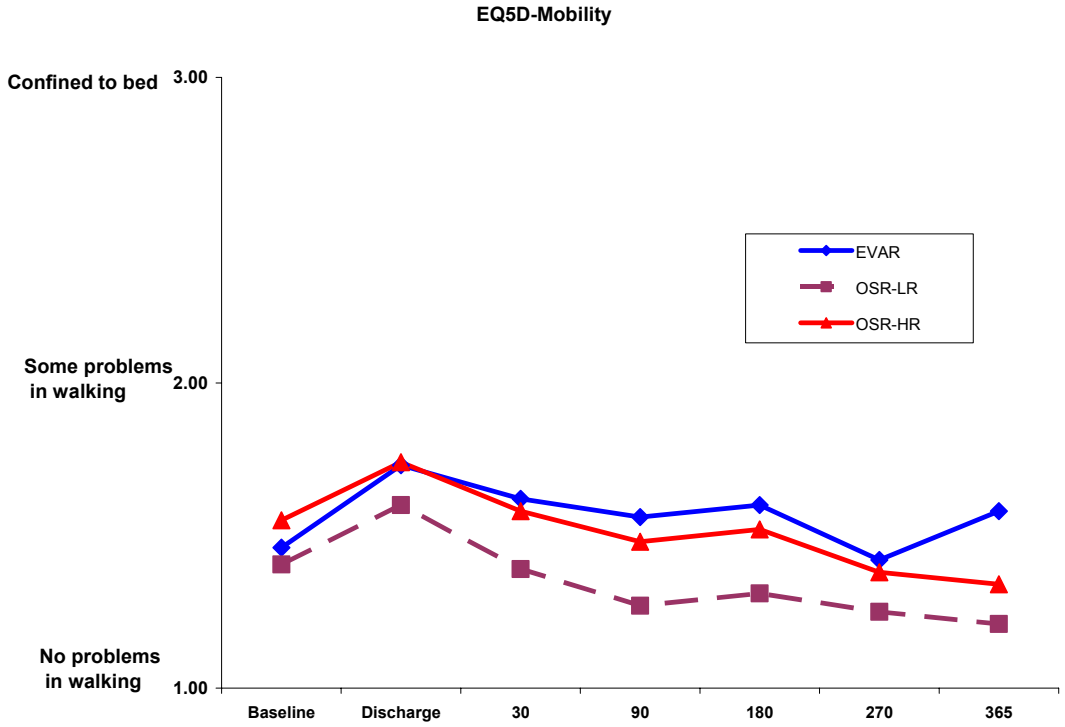


Figure 10e: Mean responses to individual EQ5D questions: Mobility



3.5 Field Evaluation Cost-Effectiveness Analysis

A cost-effectiveness analysis was conducted based upon the field evaluation results to compare costs and outcomes for EVAR and OSR for high risk patients. The OSR high risk group was deemed to be the appropriate comparator group since all EVAR patients were at a high risk of operative complications. Two cost effectiveness outcomes were evaluated and expressed as incremental cost-effectiveness ratios (ICER's) as appropriate. The first cost-effectiveness outcome was the incremental cost per LYG gained (EVAR versus OSR high risk) and the secondary cost-effectiveness outcome was the incremental cost per QALY gained. Incremental cost-effectiveness ratios (ICERs) were not calculated if one treatment strategy dominated the other (i.e. lower costs and better outcomes). The analysis was taken from the perspective of the Ontario Ministry of Health and the time horizon was 1 year.

3.5.1 Methods

3.5.1.1 Costs

The methods to derive the costs used in this 1-year economic evaluation are described in section 3.3 and are summarized in Tables 20 & 21.

3.5.1.2 Life Year Gained

The mean number of life years over the 1 year study period was estimated using Kaplan-Meier survival curves. For EVAR and OSR high risk strategies, the expected life years was calculated as the area under each survival curve as shown in Figure 11.

3.5.1.3 QALYs

Quality adjusted survival for EVAR and OSR-HR groups were estimated by combining Kaplan-Meier survival curves with utility estimates over time. As shown in Figure 12, the mean baseline utility was lower for the OSR-HR group

compared to EVAR and therefore due to these differences, utility curves were re-estimated in order to control for baseline utility values as described below.

At each assessment point (discharge, 1, 3, 6, 9 and 12 months), ordinary least squares regression was used to estimate the mean change in utility from baseline for the two treatment groups. In each regression model (e.g. 1, 3 months), patient specific utility values were used as the dependant variable. Patient baseline utility value and a treatment indicator were used as independent variables, allowing at each assessment point the calculation of an estimate of the mean change from baseline. Utility values were then calculated at each time period assuming a common baseline utility value of 0.77 for each group. This baseline utility value of 0.77 was chosen because it was the mean baseline utility value for all patients enrolled in the field evaluation.

Utilities were then multiplied by the probability of being alive at each day following treatment assignment producing quality adjusted survival curve for each group. QALYs were calculated as the area under the 2 quality adjusted survival curves.

3.5.1.4 Uncertainty and time horizon sensitivity analysis

To measure uncertainty on observed 1 year costs and effects, non-parametric bootstrap techniques were applied. Uncertainty results were expressed using cost-effectiveness acceptability curves, showing the probability that EVAR is cost-effective compared to OSR for high risk patients, at various willingness-to-pay values.

The long term impact of EVAR's lower operative mortality on costs and outcomes may be underestimated due to the 1 year time horizon of the study. Therefore using modeling techniques, the time horizon was extended 10 years in sensitivity analysis. Age specific mortality rates were based on Canadian life tables. It was assumed that all patients entering the study were males 75 years of age, the average age of all high risk patients at study entry. Patients in the study may be

at increased risk of death compared to the general population. Therefore, the 1 year within trial mortality for subjects alive after 30 days was compared to the life tables 75 year old male mortality rate. Based on this analysis, the risk of death in study patients was found to be 30% higher compared to the general population of 75 year old males. Therefore a relative risk of 1.30 was applied to the life table data to estimate age specific mortality rates.

Routine follow-up costs for EVAR patients were assigned in the time horizon sensitivity analyses. Based on clinical experts, it was assumed that EVAR patients would have 2 CT-cans and specialist consults performed annually for the first two years after initial treatment and 1 CT scan and specialist consults per year thereafter. No routine follow-up cost was assumed for OSR patients.

The same utility rate was applied to both treatment groups in the sensitivity analysis. The utility rate was set equal to the lowest average observed 12 month utility rate between EVAR and OSR patients. A discount rate of 5% was applied to all costs and outcomes.

The time horizon analysis was run under a number of assumptions regarding convergence of cumulative mortality rates for EVAR and OSR groups:

a) No convergence specified
b) Cumulative mortality converges after 10 years
c) Cumulative mortality converges after 5 years
d) Cumulative mortality converges after 3 years

3.5.2 Incremental Cost-Effectiveness Results

The 1-year costs associated with EVAR and OSR high risk patients were $34,146 and $34,169, respectively, resulting in an incremental cost of -$24.

The estimated number of life years gained as determined from the Kaplan Meier survival curves for EVAR and OSR high risk patients were 0.959 and 0.848, respectively, as shown in Figure 11. The EQ-5D utility scores over time over the course of 1 year, adjusted for baseline values, are outlined in Figure 12. Figure 13 presents the resulting Quality Adjusted Survival curves and the QALYs for EVAR and OSR were calculated to be 0.713 and 0.688, respectively.

Figure 11: Kaplan Meier Survival curves

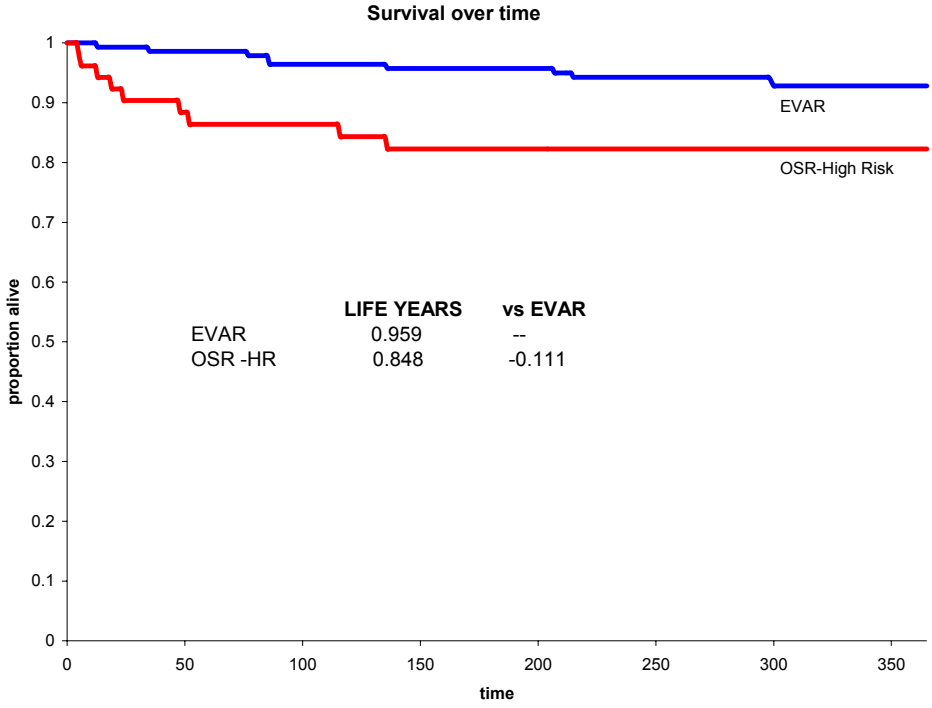


Figure 12: Mean EQ-5D utility scores over time (adjusted)

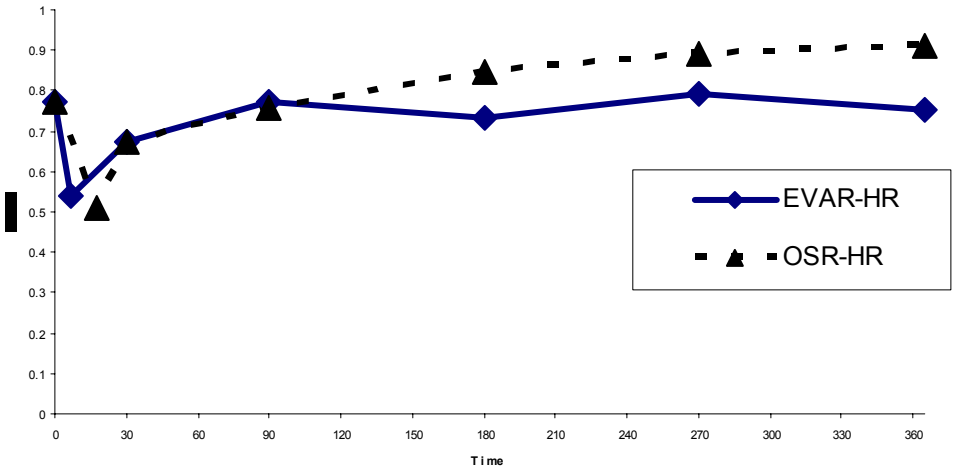


Figure 13: Estimated QALYs over a year for EVAR and OSR HR patients

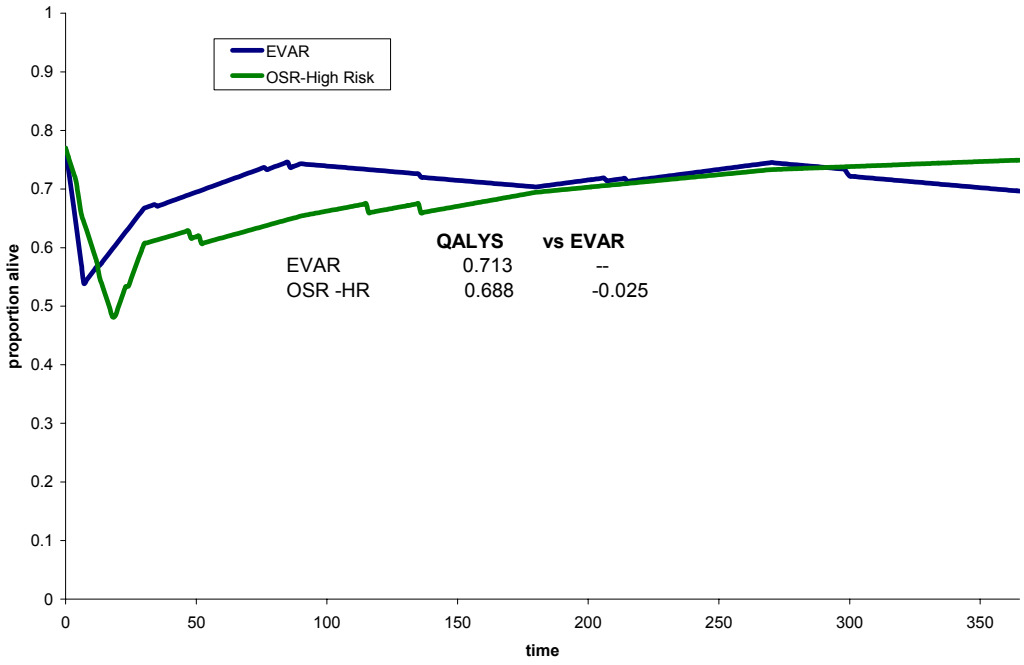


Table 22 summarizes the cost-effectiveness results. EVAR has slightly lower 1-year cost (-$24) compared to OSR for high risk patients. However, the 95% confidence intervals associated with the costs ranged from -$11,582 to $9,165. EVAR had 0.111 more life years compared to OSR for high risk patients (95% CI 0.022 to 0.213). More QALYs (0.025) were also associated with EVAR (95% CI: -0.075; 0.128).

Table 22: Cost-Effectiveness Results

	Costs	LY's	QALY's	$/LYG	$/QALY
EVAR	$34,146	0.959	0.713		
OSR HR	$34,170	0.848	0.688		
Difference	-$24	0.111	0.025	dominates	dominates
Lower 95%CI	-$11,582	0.022	-0.075	dominates	dominates
Upper 95%CI	$9,165	0.213	0.128	$190,000	dominated

Based on these point estimates, EVAR dominates OSR for high risk patients in terms of incremental cost per LYG and incremental cost per QALYs. However, as indicated by the CIs, the differences in the costs and QALYs are not significant at the 5% level.

Figures 14 & 15 present the bootstrap estimates of uncertainty for the 2 cost-effectiveness measures. As shown by this cost-effectiveness plane there is a lot of uncertainty regarding the costs and the QALYs and less uncertainty regarding LYGs.

Figure 16 presents the cost-effectiveness acceptability curves for cost per LYG and the cost per QALYs. Not suggesting any particular threshold, but it may be worthwhile to consider two commonly quoted thresholds of $50,000 and $100,000 per QALY gained.[108] The way to interpret these curves is to consider a threshold that decision makers might be willing to pay for a unit of effect (i.e. willingness to pay per QALY gained) along with the horizontal axis and read along the vertical axis the probability that the treatment is cost-effective after accounting for uncertainty. If society is willing to pay $50,000 per life year gained, the probability of EVAR of being cost-effective is 0.76. The probability of being cost-effective increases to 0.9 if society is willing to pay $100,000 per LYG.

In terms of cost per QALY, the probability of EVAR being cost-effective is lower with probabilities of 0.55 and 0.58 when using thresholds of $50,000 and $100,000, respectively.

Figure 14: Incremental cost and effect pairs for cost per life year gained (LYG) comparing EVAR to OSR HR

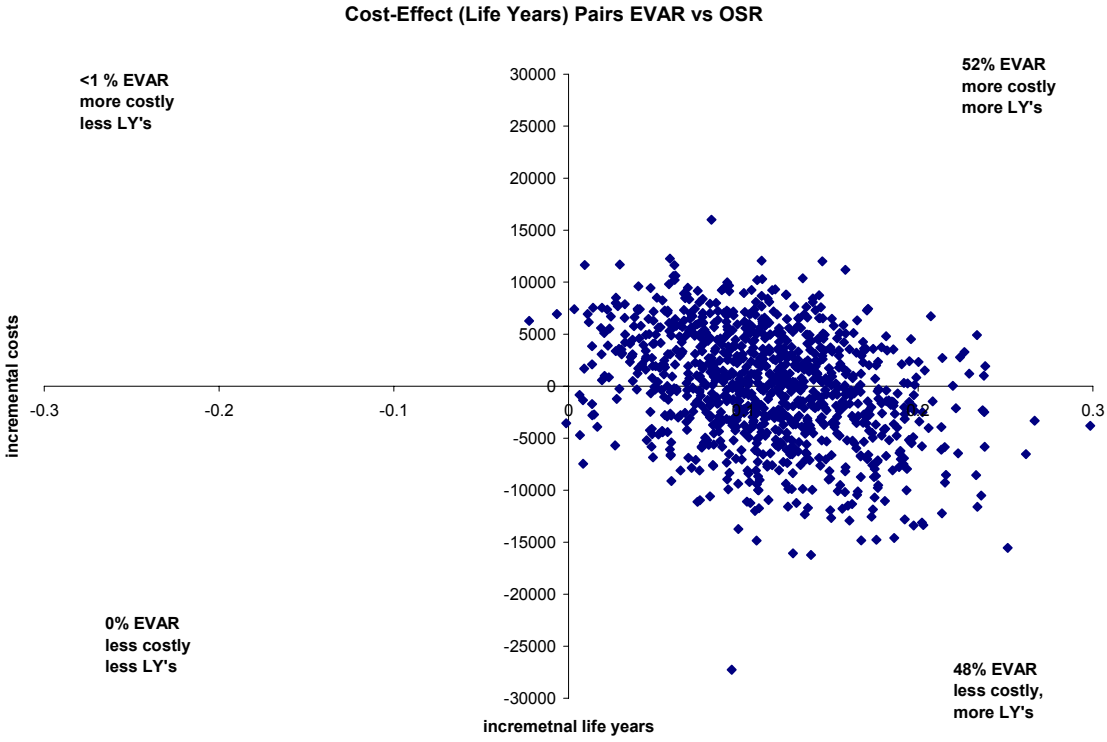
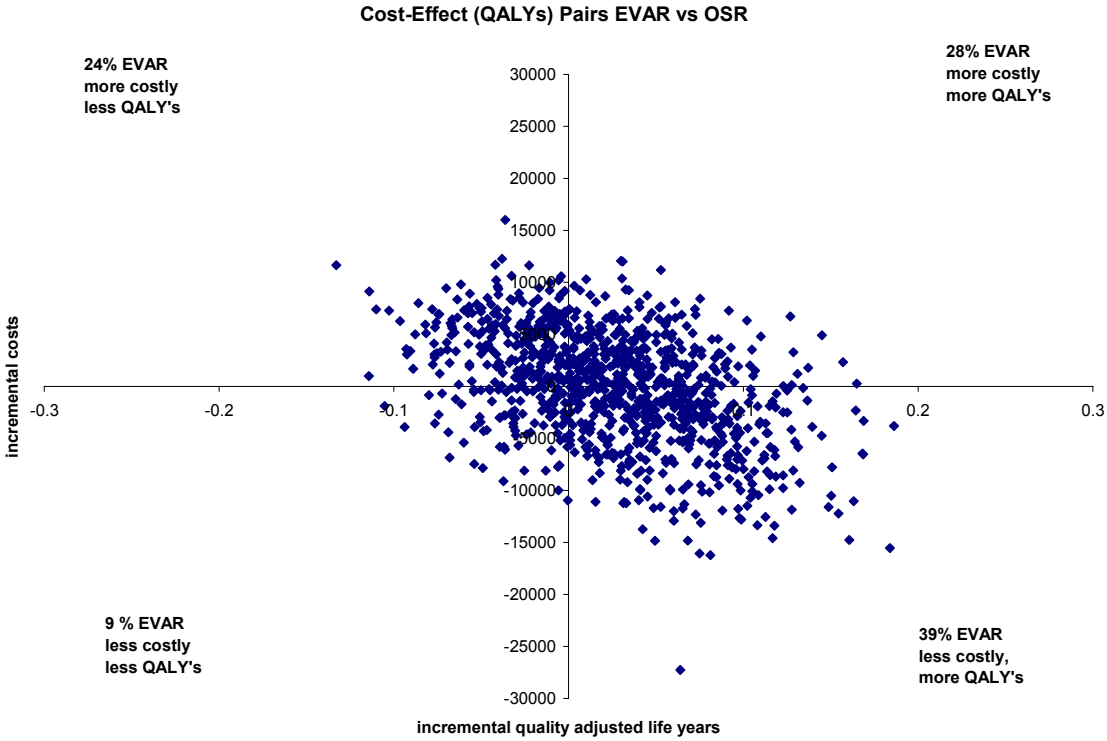
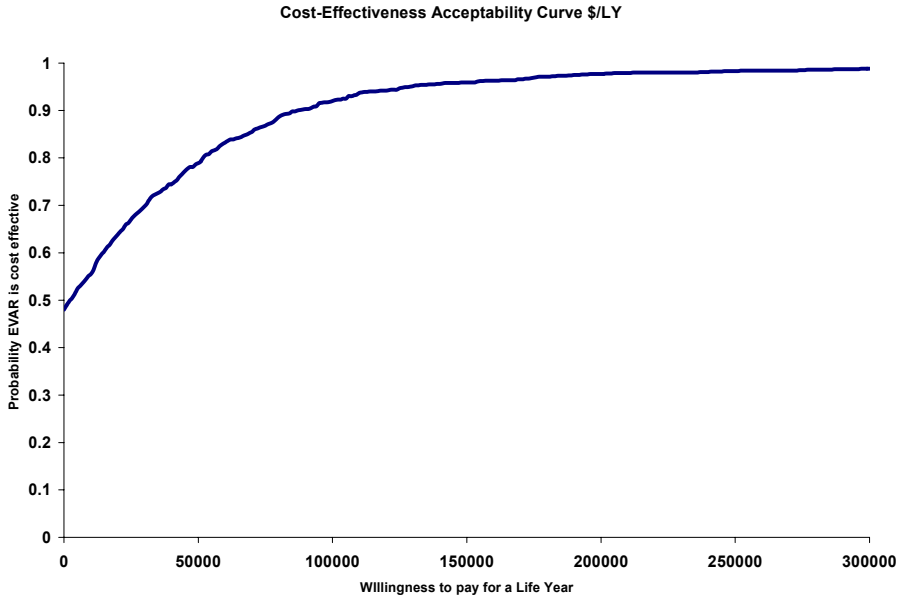
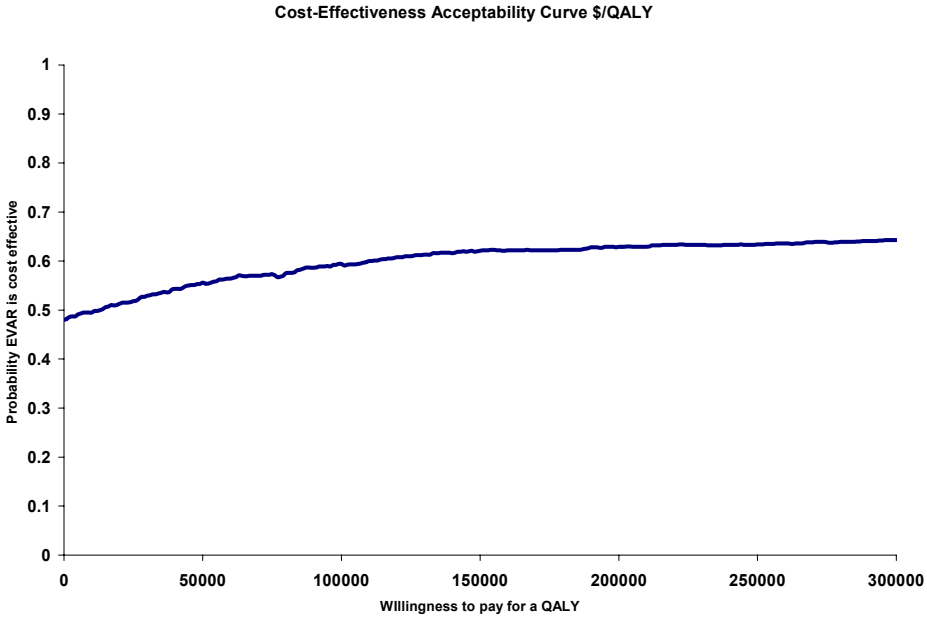


Figure 15: Incremental cost and effect pairs for cost per quality adjusted life year gained (QALYs) comparing EVAR to OSR HR



Figures 16: Cost-effectiveness Acceptability Curves for life years gained and quality adjusted life years gained





3.5.2.1 Time horizon sensitivity analyses

Table 23 presents incremental cost-effectiveness results after extending the time horizon of the analysis to 10 years. As shown, in all sensitivity analyses the incremental costs of EVAR compared to OSR are positive. Therefore, when the time horizon is modeled to 10 years a trade off between higher costs and better outcomes EVAR compared to OSR exists. Incremental cost-effectiveness differs depending on the assumption used for cumulative survival. If no convergence of cumulative survival is specified, the proportion of patients alive after 1 year in both group are assigned the same mortality rates. Under this assumption the incremental cost per life year for EVAR is estimated to be $2,983 while the cost per QALY is estimated to be $4,507. The assumption least favorable to EVAR is convergence of cumulative survival between the two groups after 3 years. This assumed the mortality benefit observed for EVAR after 1 year disappears 3 years later. Under this assumption the incremental cost per life year and cost per QALY are $8,710 and $18,616 respectively.

Table 23: Incremental costs, life years, QALYS and Cost-effectiveness Ratios Modeling the Time Horizon of the Study to 10 years

				ICER	
	Costs	**Life Years**	**QALYs**	**$/Life Year**	**$/QALY**
Basecase (1 year observed)	-$24	0.111	0.025	dominates	dominates
No specified convergence	$1,968	0.660	0.437	$2,983	$4,507
Convergence after 10 years	$1,909	0.500	0.317	$3,819	$6,029
Convergence after 5 years	$1,832	0.290	0.159	$6,313	$11,493
Convergence after 3 years	$1,798	0.206	0.097	$8,710	$18,616

3.6 DISCUSSION

Endovascular repair of the aneurysm can be done safely and effectively. In this observational study conducted at LHSC, all EVAR and OSR procedures were were completed successfully. More importantly, in high risk patients, significant reductions in mortality and major cardiopulmonary complications were associated with EVAR. This led to shorter length of stay and number ICU days in EVAR patients compared to OSR patients This finding is similar to other evaluations of elective AAA repair in high risk patients.[38,72,84] The use of hospital resources are decreased with EVAR with shorter hospital length of stays.

Mid-term problems with endograft integrity and the occurrence of type I or III endoleaks did not occur in the EVAR treated patients. In addition, there has not been a need to re-intervene in any of the patients treated by the LHSC program as a part of this study with follow-up information available for some individuals for up to 3.5 years.

Patients were found to return to pre-intervention levels of activity more rapidly with EVAR than OSR. This may be reflected through improved quality of life measures after surgery. The high risk OSR patients, had slightly more impairment at the time of discharge as demonstrated by lower quality of life indices (SF36, EQ5D) This patient group however, was found to have better quality of life measurements at 1 year as compared to the EVAR treated patients. This pattern of quality of life over time has been previously seen by others evaluating EVAR to OSR.[77,109]

The 1 year health related costs for EVAR patients were found to be nearly identical ($24 less) to the costs for high risk OSR patients despite the additional cost of the endograft. This finding can be largely attributed to the lower rate of major complications observed in the EVAR group. In the absence of post-operative complications, the mean cost of EVAR index hospitalization was found to be $9000 higher than hospitalizations for OSR high risk patients. Over 1 year,

EVAR patients were found to have more life years and slightly more QALYs compared to OSR high risk patients. Based on these results, the EVAR treatment group was found to be 'dominant' in terms of cost-effectiveness. However, uncertainty regarding cost-effectiveness was found when bootstrap techniques were used. When the field evaluation results were modeled to 10 years the cost-effectiveness of EVAR compared to OSR, remained favourable.

This prospective, non-randomized study evaluated consecutive patients and compared outcomes in patients with a high surgical risk of mortality and post-operative complications. As with all non-randomized studies, there may be concern over the comparability of treatment groups (i.e. selection bias). This concern was partially addressed through the stratification of patients according to surgical risk. The baseline demographics and co-morbidities were found to be very similar for EVAR and OSR high risk patients. The potential impact of anatomical suitability for EVAR on outcomes was not examined within this study as all patients treated with EVAR were anatomically suitable for the procedure while nearly all OSR patients were not. In addition, we may not have collected all relevant baseline characteristics, which may have introduced bias in the results.

The comparative analyses focused on patients at high risk of surgical complications. Therefore the results may not be generalisable to lower risk patients or studies evaluating mixed patient risk populations as commonly found in published studies comparing EVAR to OSR. Additionally, the results of the study are based upon a single centre in Ontario, and this should be considered if results are to be applied to other jurisdictions.

Despite some limitations, this field evaluation provides valuable insights into both the effectiveness and cost-effectiveness of EVAR in Ontario. The assessment is based on an Ontario specific EVAR program, making the results particularly relevant for health policy decision makers in the province.

4.0 CONCLUSIONS

For patients at a high risk of surgical mortality and complications, EVAR is a safe effective and cost-effective procedure with fewer complications and mortality occurring in EVAR patients compared to OSR patients with similar baseline risk. Reintervention for the management of endoleaks or endograft failure was not required. The total initial hospitalization costs associated with EVAR compared to OSR HR were lower and differences in the mean total annual 1 year costs were negligible.

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6.0 APPENDICES

APPENDIX I: CLINICAL CRITERIA FOR ENDOVASCULAR ANEURYSM SURGERY

LHSC Clinical Criteria for Endovascular Aneurysm Surgery

Endovascular repair is considered to be the most suitable treatment for patients falling into one or more of the 'high-risk' categories outlined below:

I: High-Risk/comorbid diseases*

- **Cardiac:**
  - Class II-III angina
  - Significant myocardium at risk
  - Left Ventricular Ejection Fraction (LVEF) < 30%
  - Recent Congestive Heart Failure (CHF)

- **Pulmonary:**
  - Chronic Obstructive Pulmonary Disease (COPD) or emphysema
  - Severe pulmonary dysfunction
  - Home O2 or Forced Expiratory Flow (FEF) 25-75 of < 20% predicted

- **Renal:**
  - Creatinine > 250 umol/L
  - Dialysis dependent

*** (ASA III or IV) or (SVS/ISCVS Category II or III) (see References – Hollier)**

II: Hostile Abdomen

III: Technical Challenges

- Inflammatory aneurysm
- Renal anomalies eg: horseshoe kidney
  renal allograft
- Anastomotic aneurysm

IV: Thoracic Aortic Pathology

- Aneurysm
- Dissection
- Penetrating thoracic ulcer
- trauma

London Health Sciences Centre Endovascular Aortic Repair Program

PATIENT SELECTION CRITERIA

"Patients with aortic pathology, known to be at higher risk for perioperative morbidity (e.g. paraplegia) and mortality with standard open surgical therapy, either because of the nature of the aortic pathology and/or patients' associated co-morbid conditions."

"Patients with an otherwise estimated life expectancy of at least 24 months."

A. Thoracic Aorta (irrespective of age and co-morbid conditions).

- traumatic rupture of thoracic aorta
- ruptured (symptomatic) thoracic aortic aneurysm/aortic ulcer.
- asymptomatic thoracic aortic aneurysm >6.0 cm in diameter.
- adjunct to treatment of thoracic aortic dissection (i.e. failure of medical therapy).
- recurrent thoracic aortic aneurysm (i.e. pseudoaneurysms, anastomotic

B. Abdominal Aorta and Iliac Arteries

- Ruptured (symptomatic) infrarenal aortic and/or iliac artery aneurysm. (Irrespective of age and co-morbid conditions).
- anastomotic or para-anastomotic aortic and/or iliac artery aneurysm following previous open surgical repair
- asymptomatic infrarenal aortic aneurysm > 5.5 cm in diameter (with high risk anatomical and/or physiological criteria).
- asymptomatic iliac artery aneurysm > 4.0 cm in diameter (with high risk anatomical and/or physiological criteria).

  "HIGH-RISK" Anatomical Criteria

  - "inflammatory" abdominal aortic aneurysm.
  - patient with "hostile abdomen" (i.e. numerous previous laparotomies, known retroperitoneal fibrosis, abdominal wall stomas).
  - special anatomical situations (e.g. horseshoe kidney, renal transplant graft).
  - aborted attempt at open surgical repair.
  - patient refuses to accept blood transfusion (e.g. Jehovah Witness).

"HIGH-RISK" Physiological Criteria

Endovascular repair to be considered in patients with any of the following high-risk co-morbid conditions (SVS/ISCVS Category II or III). J Vasc Surg 1992;15: 1046-1056.

Age >80 years

Cardiac

- stable angina or prior myocardial infarction, but moderate coronary lesions, or abnormal myocardial perfusion scan without major areas of reperfusion.
- Class II - III angina or significant myocardium at risk on basis of coronary angiography or myocardial perfusion scan with large areas of reperfusion.
- left ventricular ejection fraction (LVEF) <30%.
- recent congestive heart failure.
- recent myocardial infarction.
- moderate-to-severe aortic valvular stenosis.

Pulmonary

- chronic obstructive pulmonary disease (COPD), emphysema or previous pulmonary resection with moderate-to-severe pulmonary dysfunction (documented with pulmonary function studies).
- pulmonary dysfunction requiring home oxygen or with forced expiratory flow (FEF) of <20% predicted.

Renal

- serum creatinine >250 umol/L.
- dialysis dependent.

Such "high risk" patients are classified as ASA III, IV, or V.

American Society of Anaesthesiologists (ASA) grade:

III - severe systemic disease that limits activity but is not incapacitating.
IV - incapacitating systemic disease which is constantly life threatening.
V - moribund, not expected to survive 24 hours without surgery.

C. Anatomical Suitability (for infrarenal AAA)

1) Proximal Neck

   a) 10 mm. in length.
   b) 32 mm. in diameter.
   c) infrarenal neck/AAA angulation 80 degrees.
   d) free of circumferential aortic calcification and/or significant thrombus.

2) at least one common iliac artery must be patent and 6 mm. in diameter.

3) iliac artery angulation <90 degrees or <60 degrees in presence of severe calcification.

4) dispensable inferior mesenteric artery.

D. Exclusion Criteria

1. unsuitable anatomy.
2. serious systemic or groin infection.
3. anaphylactic reaction to contrast material (true anaphylaxis).
4. allergy to stainless steel or polyester.
5. serious (uncorrectable) coagulopathy.
6. unwillingness or inability to comply with follow-up surveillance protocol.
7. patient's life expectancy estimated at <2 years.

APPENDIX II: LITERATURE SEARCH STRATEGY

Appendix II: Literature Search Strategy

Guide to Search Syntax (OVID)

exp	Explode the search term. Retrieve the search concept plus all narrower terms.
?	Optional wildcard, single character. Used within or at the end of a search term to substitute for one or no characters.
#	Mandated wildcard, single character. Retrieves all possible variations of a word in which the wildcard is present in the specified place.
$	Truncation symbol, unlimited. Retrieves all possible suffix variations of the root word indicated.
ADJ	Proximity operator. Words must be adjacent.
ab	Search in article abstract.
/	Descriptor i.e., subject heading (a controlled, thesaurus term).
mp	Search in variety of fields, depending on database searched.
pt	Publication type.
sh	Descriptor i.e., subject heading (a controlled, thesaurus term).
ti	Search in titles.

DATABASES	DATES/ LIMITS	SUBJECT HEADINGS/KEYWORDS
OVID MEDLINE®, MEDLINE® In-Process & Other Non-Indexed Citations, EMBASE®, CINAHL, CDSR, ACP Journal Club, DARE, CCTR	Original search run Nov. 2004 limited to: Human, English, 1990 - 2004 Update search run Dec. 2005 limited to: Human, English, 1990 - 2005	1. exp Aortic Aneurysm/ *[Subject Heading]* or (aort$ or aneurysm$).mp. 2. Aorta Abdominal/ or Abdominal Aortic Aneurysm/ or exp Aorta, Abdominal/ OR exp Aortic Aneurysm, Abdominal/ or aaa.mp. or abdom$.mp. 3. 1 and 2 4. Blood Vessel Prosthesis/ or Vascular Surgical Procedures/ or Blood Vessel Prosthesis Implantation/ or exp Stents/ or exp Blood Vessel Prosthesis/ or Vascular Surgery/ or Endovascular Surgery/ or Aorta Surgery/ or Aorta Graft/ or Aorta Prosthesis/ or Stent/ or exp Blood Vessel Prosthesis/ or exp Vascular Surgery/ or exp Stents/ or exp Grafts/ or endograft.mp. or (EVAR or EVR).mp. or endovascular repair.mp.

		or endoluminal.mp. or stent$.mp. or (ancure or vanguard or trivascular or aneurx or talent or challenger or quantum lp or lifepath or excluder or zenith or powerlink or anaconda).mp. or Prosthesis Failure/ or exp Prosthesis Failure/ or endoleak.mp. or graft migration.mp. 5. 3 and 4 6. exp Clinical Trials/ or exp Clinical Trial/ OR exp Clinical Study/ or exp Comparative Study/ or exp Comparative Studies/ or clinical trial$.mp. or compar$.mp. or study.mp. or registr$.mp. or (prosp$ or retrosp$).mp. 7. 5 and 6
OVID Health and Psychosocial Instruments	Original search run Nov. 2004 limited to: 1990 - 2004 Update search run Dec. 2005 limited to: 1990 - 2005	1. aortic aneurysm.mp. *[Textwords searched in title, abstract, acronym or descriptors]* or (aort$ or aneurysm).mp. 2. abdominal aortic aneurysm.mp. or aaa.mp. or abdom$.mp. 3. 1 and 2
OVID	Update	1. exp Aortic Aneurysm/

MEDLINE®, MEDLINE® In-Process & Other Non-Indexed Citations, EMBASE®	search run Nov. 2006 limited to: Human, 2005 - 2006	*[Subject Heading]* or (aort$ or aneur#sm$).mp. *[Textwords searched in title, abstract, name of substance word or subject heading word]* 2. Aorta Abdominal/ or Aortic Aneurysm, Abdominal/ aaa.mp. or abdom$.mp. 3. 1 and 2 4. Blood Vessel Prosthesis/ or Vascular Surgical Procedures/ or Blood Vessel Prosthesis Implantation/ or exp Stents/ or exp Blood Vessel Prosthesis/ or Vascular Surgery/ or Endovascular Surgery/ or Aorta Surgery/ or Aorta Graft/ or Aorta Prosthesis/ or Stent/ or endograft?.mp. or (EVAR or EVR).mp. or endovascular repair.mp. or endoluminal.mp. or stent$.mp. or (ancure or vanguard or trivascular or aneurx or talent or challenger or quantum lp or lifepath or excluder or zenith or powerlink or anaconda).mp. or Prosthesis Failure/ or exp Prosthesis Failure/ or endoleak.mp. or graft migration.mp. 5. 3 and 4 6. exp Controlled Clinical Trials/ or Multicenter Studies.sh. *[MeSH heading for MEDLINE®]* or (Multicenter Study or Randomized Controlled Trial or Controlled Clinical Trial).pt. *[Publication types for MEDLINE®]* or (random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.

		[Textwords searched in title, abstract] or ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab. or ((control$ adj (study or studies or trial$)) or rct$).ti,ab. or ((multicent$ or multi cent$) adj (study or studies or trial$)).ti,ab. or (Major Clinical Study or Multicenter Study or Randomized Controlled Trial).sh. *[EMTREE terms for EMBASE®]* 7. exp Epidemiologic Studies/ or exp Comparative Study/ or Registries.sh. *[MeSH heading for MEDLINE®]* or Comparative Study.pt. *[Publication types for MEDLINE®]* or (case adj control$ adj (study or studies or trial or trials)).ti,ab. or (compar$ adj (study or studies)).ti,ab. or (case adj series).ti,ab. or (retrospective adj (study or studies or trial or trials)).ti,ab. or (cohort adj (analysis or analyses or study or studies or trial or trials)).ti,ab. or (prospective adj (study or studies or trial or trials)).ti,ab. or (observational adj (study or studies or trial or trials)).ti,ab. or (follow adj up adj (study or studies or trial or trials)).ti,ab. or (followup adj (study or studies or trial or trials)).ti,ab. or (open adj label adj (study or studies or trial or trials)).ti,ab. or (registry or registries or register).ti,ab. or exp Controlled Study/ or (Comparative Study or Intermethod Comparison or Case Control Study or Prospective Study or Retrospective Study or Cohort Analysis or Implant Registry or Register).sh. *[EMTREE terms for EMBASE®]*

		8. 5 and (6 or 7)
The Cochrane Library (Wiley) Issue 4, 2006	2005 - 2006	Same MeSH and keywords as per MEDLINE® search, excluding study design filter. Appropriate syntax used.

APPENDIX III: LITERATURE SCREENING & DATA ABSTRACTION FORMS

EVAR Study Data Abstraction Form

Reviewer Initials: _____ RefMan no: _____
Study Rating: + / 0 / - Date: _____
Citation: _____

Inclusion criteria for Literature Review:

Study examined Abdominal Aortic Aneurysm (AAA)	Yes	No
Study examined non-ruptured AAA	Yes	No
Mean AAA size > 5 cm	Yes	No
Publication date is 1991 onwards	Yes	No

Study Information:
First Author: _____ Country: _____
Year of Publication: _____ Randomization: _____
Study Time: _____
Duration of outcomes: Perioperative (Yes/No). Long-term follow-up: __ months.
Study Type: RCT, Case Control, Observational, Lit. Review, Other _____
Prospective or Retrospective: _____

EVAR suitability in OSR group	Yes	No
Risk Level: High / Low / Unspecified		
Kaplan Meier Estimates	Yes	No

Study Objectives:
_____

_____

_____

	Study Arm	
Characteristics	**EVAR**	**OSR**
# of patients		
% Males		
Mean age		
Mean AAA size ± s.d.		
Median AAA size (range)		
SVS risk levels		
ASA risk levels		
Risk Factors (# patients)		
Tobacco use		

Hypertension		
Diabetes		
Hyperlipidemia		
Cardiac disease		
Cerebral vascular disease		
Pulmonary disease		
Peripheral vascular disease		
Renal problems		
Strokes		
Procedural information		
Length of procedure (hrs)		
Mean blood loss (ml)		
Time in ICU (days)		
Length of hospital stay (days)		
Recovery Time (days)		
Devices Used		
Outcomes		
Deaths < 30 days		
Deaths > 30 days		
Endoleaks (< 30 days)		
Type 1 (distal attachment)		
Type 1 (proximal attachment)		
Type 1 (unspecified)		
Type 2 (retrograde flow to branches)		
Type 3 (graft degeneration)		
Type 4 (porosity)		
Endoleaks (> 30 days)		
Type 1 (distal attachment)		
Type 1 (proximal attachment)		
Type 1 (unspecified)		
Type 2 (retrograde flow to branches)		
Type 3 (graft degeneration)		
Type 4 (porosity)		
Secondary Procedures (< 30 days)		
Amputation		
Endograft extension/cuff		
Conversion to open repair		
Eendograft/artery stent		

Endograft/artery PTCA		
AAA embolization		
Artery bypass		
Femofemoral endograft		
Aortoiliac endografting		
Total graft removal		
Rupture		
Amputation		
Endograft extension/cuff		
Conversion to open repair		
Endograft/artery stent		
Secondary Procedures (> 30 days)		
Endograft extension/cuff		
Conversion to open repair		
Endograft/artery stent		
Endograft/artery PTCA		
AAA embolization		
Artery bypass		
Femofemoral endograft		
Aortoiliac endografting		
Total graft removal		
Rupture		
Amputation		
Cardiac Complications (< 30 days)		
Cardiac (MI)		
Cardiac (CHF)		
Cardiac (arryth)		
Cardiac (angina)		
Cardiac - unspecified/other		
Cardiac - major		
Cardiac - moderate		
Cardiac Complications (> 30 days)		
Cardiac (MI)		
Cardiac (CHF)		
Cardiac (arryth)		
Cardiac (angina)		
Cardiac - unspecified/other		
Cardiac - major		
Cardiac - moderate		
Pulmonary Complications (< 30 days)		

Pulmonary (failure)		
Pulmonary (edema)		
Pulmonary (pneumonia)		
Pulmonary (pneumothorax)		
Pulmonary (embolism)		
Pulmonary - unspecified		
Pulmonary - major (if not specified)		
Pulmonary - moderate (if not specified)		
Pulmonary Complications (> 30 days)		
Pulmonary (failure)		
Pulmonary (edema)		
Pulmonary (pneumonia)		
Pulmonary (pneumothorax)		
Pulmonary (embolism)		
Pulmonary - unspecified		
Pulmonary - major (if not specified)		
Pulmonary - moderate (if not specified)		
Renal Complications (< 30 days)		
Renal (permanent failure)		
Renal (temp failure)		
Renal - unspecified		
Renal - major		
Renal - moderate		
Renal Complications (> 30 days)		
Renal (permanent failure)		
Renal (temp failure)		
Renal - unspecified		
Renal - major		
Renal - moderate		
Neural Complications (< 30 days)		
Stroke		
TIA		
Bowel/colon ischemia		
Limb ischemia		
Other ischemia		
Neural Complications (> 30 days)		
Stroke		

TIA		
Bowel/colon ischemia		
Limb ischemia		
Other ischemia		
Other Graft Problems (< 30 days)		
Graft obstruction		
Graft infection		
Graft kinks or folds		
Graft migration		
Graft thrombosis		
Arterial or graft obstruction		
Other Graft Problems (> 30 days)		
Graft obstruction		
Graft infection		
Graft kinks or folds		
Graft migration		
Graft thrombosis		
Arterial or graft obstruction		
Surgical Complications (< 30 days)		
Hemorrhage - major		
Hemorrhage - moderate		
Thromboembolism - major		
Thromboembolism - moderate		
Groin hemotoma / seroma / lymphocoele - minor		
Obstruction of main renal artery		
Iatrogenic perforation - severe		
Surgical Complications (> 30 days)		
Hemorrhage - major		
Hemorrhage - moderate		
Thromboembolism - major		
Thromboembolism - moderate		
Groin hemotoma / seroma / lymphocoele - minor		
Obstruction of main renal artery		
Iatrogenic perforation - severe		
Surgical Complications (< 30 days)		
Groin/wound infection		
Peudoaneurysm - abdominal		

Pseudoaneurysm - groin		
Aortenteric fistula		
Groin - major problem		
Wound - major problem (hernia,etc)		
Iatrogenic perforation - severe		
Surgical Complications (> 30 days)		
Groin/wound infection		
Peudoaneurysm - abdominal		
Pseudoaneurysm - groin		
Aortenteric fistula		
Groin - major problem		
Wound - major problem (hernia,etc)		
Iatrogenic perforation - severe		
Other		
Dehiscence		
Parapalegia (Tefera)		
Prolonged ileus		
Delerium tremors		
Sciatic nerve palsy		
Erectile/orgasmic function		

EVAR Full Text Screening
Identification of Unique Patient Populations

Refman #: _____
Author: _____
Publication Year: _____

Time period of patient enrollment: _____ to _____

In what country(ies) was the study conducted
(also specify States/Provinces if provided)

Is this study a single centre report or from multiple centres?

Single Multiple

If from a single centre please provide the name of the centre.

Centre name: _____

Is this study a subanalysis of a multiple centre trial?

Yes No Can't Tell

What was (were) the primary device(s) used in the study?

Comparing this study to the other trials, is this study a unique or primary publication of patient data.

Yes No Can't tell

If No, then is this study the most recent publication from the centre with greatest sample size.

Yes No Can't tell

Reviewed by (initials): _____ Date: _____

APPENDIX IV: ARTICLES INCLUDED IN SYSTEMATIC REVIEW

Comparative Clinical Studies (n = 84) excluding studies with duplicate patient information (listed alphabetically)

Aarts F, van Sterkenburg S, Blankensteijn JD. Endovascular aneurysm repair versus open aneurysm repair: comparison of treatment outcome and procedure-related reintervention rate. Annals of Vascular Surgery 2005;19(5):699-704.

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Carpenter JP, Baum RA, Barker CF, Golden MA, Velazquez OC, Mitchell ME, et al. Durability of benefits of endovascular versus conventional abdominal aortic aneurysm repair. Journal of Vascular Surgery 2002;35(2):222-8.

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APPENDIX V: ARTICLES CONTAINING DUPLICATE PATIENT DATA FROM SYSTEMATIC REVIEW

Comparative Clinical Studies (n = 40) excluded studies with duplicate patient information (listed alphabetically)

Anonymous. Cost-effectiveness of endovascular abdominal aortic aneurysm repair. Journal of Vascular Surgery 2005: 42(4), 820.

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APPENDIX VI: REPORTING OF BASELINE CHARACTERISTICS IN COMPARATIVE CLINICAL STUDIES, EVAR VS. OSR

	RCT (n=4 studies)		all nRCT (n=27 studies)		Multi-centre (n=16 studies)		Single centre (n=59 studies)		Low volume (n=31 studies)		High volume (n=28 studies)		Suitable (n=5 studies)		High risk (n=8 studies)	
	EVAR	OSR	EVAR	OSR	EVAR	OSR	EVAR	OSR	EVAR	OSR	EVAR	OSR	EVAR	OSR	EVAR	OSR
N	791	752	16,407	41,238	12,036	36,443	4,371	4,795	1,496	1,752	2,875	3,043	260	235	332	352
Male	791	752	12,199	11,619	8,183	7,435	4,016	4,184	1,455	1,659	2,561	2,525	253	204	306	303
ASA I	171	174	566	692	0	0	566	692	250	300	316	392	127	67	46	28
ASA II	228	193	554	702	0	0	554	702	250	300	304	402	127	67	34	38
ASA III	228	193	1,015	1,175	190	60	825	1,115	303	330	522	785	180	97	46	38
ASA IV	171	174	2,201	2,782	907	1,247	1,294	1,535	250	300	1,044	1,235	127	67	34	38
Smoking history	791	752	4,871	4,787	3,138	2,982	1,733	1,805	668	744	1,065	1,061	136	153	68	81
Hypertension	248	213	9,349	7,095	5,802	3,316	3,547	3,779	1,211	1,374	2,336	2,405	253	204	242	244
Diabetes	791	752	11,750	10,847	8,185	7,083	3,565	3,764	1,273	1,416	2,292	2,348	253	204	68	81
Hyperlipidemia	734	733	3,413	3,598	1,823	2,069	1,590	1,529	558	543	1,032	986	126	137	0	0
Cardiac Disease	791	752	9,200	7,703	5,758	3,659	3,442	4,044	1,254	1,413	2,188	2,631	253	204	276	272
CVD	0	0	2,171	2,675	1,109	1,267	1,062	1,408	315	271	747	1,137	10	16	0	0
Pulmonary	248	213	11,216	10,573	8,023	6,995	3,193	3,578	1,005	1,186	2,188	2,392	253	204	208	191
PVD	0	0	3,057	2,410	2,153	1,697	904	713	340	367	564	346	0	0	52	46
Renal disease	191	194	10,821	10,392	7,738	7,239	3,083	3,153	875	1,045	2,208	2,108	253	204	208	191
Stroke	0	0	3,161	3,017	1,328	917	1,833	2,100	406	397	1,427	1,703	190	158	223	212
AAA diameter	791	752	6,472	3,384	3,615	622	2,857	2,762	1,109	1,307	1,748	1,455	250	219	89	118
Age	791	752	11,781	12,390	7,745	8,248	4,036	4,142	1,283	1,386	2,753	2,756	260	235	267	306

Appendix VII: Reporting of post-operative complications in studies comparing EVAR to OSR

	RCT (n=4 studies)		nRCT (n=27 studies)		Multicentre (n=16 studies)		Single centre (n=59 studies)		Low Volume (n=31 studies)		High Volume (n=28 studies)		Suitable (n=5 studies)		High Risk (n=8 studies)	
	EVAR N	OSR N	EVAR N	OSR N	EVAR N	OSR N	EVAR N	OSR N	EVAR N	OSR N	EVAR N	OSR N	EVAR N	OSR N	EVAR N	OSR N
Peri-operative Mortality	791	752	16391	41222	12036	36443	4355	4779	1496	1752	2859	3027	260	235	332	352
amputation	771	732	6864	3151	3989	469	2875	2682	1008	537	1867	2145	260	235	262	247
rupture	600	539	6901	3150	3989	469	2912	2681	973	529	1939	2152	260	235	53	76
artery_bypass	0	0	2098	2167	435	179	1663	1988	561	509	1102	1479	207	205	53	69
Cardiac																
Myocardial Infarction	57	19	3546	3635	860	739	2686	2896	467	505	2219	2391	73	107	242	257
Congestive Heart Failure	228	19	2434	2549	382	126	2052	2423	405	394	1647	2029	73	107	224	226
Arrhythmia	0	0	2453	2546	400	157	2053	2389	389	378	1664	2011	73	107	242	257
Angina	0	0	1642	1724	192	66	1450	1658	383	372	1067	1286	73	107	224	226
Unspecified	228	193	5090	5398	2905	2903	2185	2495	674	692	1511	1803	190	158	243	234
Pulmonary																
Failure	0	0	2844	3085	842	708	2002	2377	423	400	1579	1977	73	107	174	163
Edema	0	0	1569	1769	208	91	1361	1678	335	296	1026	1382	73	107	18	31
Pneumonia	0	0	2507	2905	668	673	1839	2232	484	462	1355	1770	73	107	18	31
Pneumothorax	0	0	1840	1955	190	60	1650	1895	484	397	1166	1498	73	107	0	0
Embolism	0	0	2292	2651	650	642	1642	2009	483	412	1159	1597	73	107	0	0
Unspecified	0	0	3864	4084	2063	2195	1801	1889	612	599	1189	1290	190	158	35	71
Pulmonary major	171	174	675	956	460	582	215	374	81	59	134	315	0	0	0	0
Pulmonary moderate	171	174	81	166	0	0	81	166	81	59	0	107	0	0	0	0
Renal																
Permanent failure	171	174	5717	6550	3693	4653	2024	1897	327	361	1697	1536	0	0	174	163
Temporary failure	171	174	2422	2364	850	722	1572	1642	177	217	1395	1425	0	0	16	35
Renal unspecified	0	0	5172	6646	4233	5417	939	1229	335	337	604	892	190	158	53	36
Stroke & Ischemia																
Stroke	0	0	3161	3017	1328	917	1833	2100	406	397	1427	1703	190	158	223	212
TIA	57	19	2003	1956	400	157	1603	1799	383	372	1220	1427	73	107	242	257
bowel/colon ischemia	171	174	2529	2565	476	189	2053	2376	603	701	1450	1675	190	158	49	49
limb ischemia	0	0	2062	1818	476	189	1586	1629	231	308	1355	1321	73	107	30	41

other ischemia	0	0	1685	1723	476	189	1209	1534	191	207	1018	1327	73	107	46	76
spinal ischemia	171	174	1440	1551	190	60	1250	1491	268	305	982	1186	190	158	12	10
Local/vascular complications																
graft infection	171	174	2024	1877	625	239	1399	1638	218	188	1181	1450	83	123	12	10
graft thrombosis	0	0	2026	1779	643	239	1383	1540	196	188	1187	1352	83	123	30	10
aortenteric fistula	0	0	640	428	425	159	215	269	196	188	19	81	83	123	12	10
arterial or graft obstruction	0	0	1748	1749	240	126	1508	1623	382	371	1126	1252	200	174	0	0
groin - major	0	0	821	624	432	192	389	432	196	188	193	244	83	123	186	173
groin - minor	0	0	2134	2545	240	126	1894	2419	727	762	1167	1657	83	123	12	10
groin or wound infection	57	19	3651	4221	890	768	2761	3453	747	908	2014	2545	200	174	221	208
hemorrhage - major	171	174	3702	3510	1996	1650	1706	1860	707	770	999	1090	200	174	0	0
hemorrhage - moderate	171	174	1221	1294	0	0	1221	1294	477	435	744	859	83	123	50	63
iatrogenic perforation	771	732	3240	2648	1961	1213	1279	1435	413	413	866	1022	187	128	212	204
obstructed renal artery	171	174	1283	1342	253	130	1030	1212	188	173	842	1039	83	123	18	31
pseudoaneurysm abdomin	0	0	1084	990	425	159	659	831	506	542	153	289	83	123	12	10
pseudoaneurysm groin	0	0	774	636	425	159	349	477	196	188	153	289	83	123	12	10
thromboembolism major	171	174	1739	1881	190	60	1549	1821	491	514	1058	1307	83	123	0	0
thromboembolism moderate	171	174	1494	1546	190	60	1304	1486	543	579	761	907	83	123	12	10
wound major	171	174	1820	1620	667	291	1153	1329	215	239	938	1090	200	174	205	173
Procedural outcomes																
Operating room time	791	752	3320	2935	1057	431	2263	2504	886	1031	1377	1473	253	204	64	56
blood loss	191	194	3552	2864	1057	431	2495	2433	723	962	1772	1471	253	204	28	45
Intensive care stay	248	213	2849	3074	1325	1716	1524	1358	636	723	888	635	63	46	50	63
Total length of hospital stay	791	752	5108	7390	1963	4116	3145	3274	1259	1536	1886	1738	143	184	69	104
EVAR outcomes																
Type 1 endoleaks	20	0	2330	0	1075	0	1255	0	496	0	759	0	260	0	90	0
Type 2 endoleaks	20	0	2536	0	1075	0	1461	0	496	0	965	0	260	0	90	0
Type 3	20	0	2598	0	1343	0	1255	0	496	0	759	0	260	0	90	0
Type 4	20	0	2155	0	1075	0	1080	0	496	0	584	0	260	0	90	0
Conversion	771	0	7584	31	4007	31	3577	0	1008	0	2569	0	260	0	280	31
graft kinks or folds	0	0	1506	0	625	0	881	0	297	0	584	0	83	0	12	0
graft migration	0	0	1795	0	865	0	930	0	346	0	584	0	83	0	12	0
graft obstruction	0	0	1207	1060	390	140	817	920	233	225	584	695	83	123	12	10

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