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Endovascularly Placed Grafts for Infrarenal Abdominal Aortic Aneurysms:

A Systematic Review of Published Studies of Effectiveness

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EXECUTIVE SUMMARY

Purpose

This report was written by the Management Decision and Research Center (MDRC) Technology Assessment (TA) Program in response to a request from the Technology Recommendations Panel for information about the effectiveness of endovascularly placed grafts for the repair of aortic and carotid artery disease. This report is confined to infrarenal abdominal aortic aneurysms (AAAs), the condition for which there was the most literature.

Background

Endovascularly placed grafts are an evolving, minimally invasive alternative to standard open surgical repair that combine intravascular stents with prosthetic graft technologies. An aortic aneurysm is an abnormal widening of the wall of the aorta, the main vessel of the arterial system that carries oxygenated blood from the heart to the rest of the body. ***Infrarenal*** AAA refers to the anatomic location of an aneurysm in the section of the aorta that descends from the heart through the thoracic cavity to the abdominal cavity situated or occurring below the kidneys. AAAs are often classified into "small" and "large" (or expanding), with the threshold between the categories at 4 to 5 cm of diameter. Most AAAs are relatively asymptomatic.

The incidence of AAA varies with the population studied. AAAs are more prevalent among the elderly than the young, and among men than women. Prevalence in male veterans between 60 and 75 years has been estimated to be 9%; in fiscal year 1997, 128 patients in VA had a primary diagnosis code indicating AAA. AAA rupture causes approximately 15,000 deaths annually and is the tenth leading cause of death in men over age 55 in the United States.

The five-year risk of rupture is 1–2% for aneurysms less than 5 cm in diameter and 20–40% for those greater than 5 cm. Elective open surgical repair of the AAA is effective in avoiding rupture and is performed in patients with symptomatic or expanding AAAs. The optimal strategy for managing small AAAs remains undefined; as most AAAs never rupture, the risks and benefits of the procedure must be weighed.

Outcomes of AAA management strategies from the literature
(sources documented and cited in full text)

Strategy	Procedure-Related Mortality	5 Yr Survival	10 Year Survival (Or Expansion And Progression To Rupture)
Elective standard surgery, large or expanding aneurysm	6.8% overall (meta-analysis of published studies); 0-16%, depending on subgroups analyzed (qualitative review)	60-84%	38-41% (less than age- and sex-matched controls)
Surgical treatment in VA	5.2%(48-hour in hospital mortality)	64%	N/A
Emergency surgical treatment of ruptured aneurysm	40-50%	–	25-75%
Unoperated aneurysm, small	Not Applicable	73%	Expansion rates have not been directly proportional to AAA size in all studies
Unoperated aneurysm, large	Not Applicable	52%	Rupture rates of 4-19% per year (overall mortality after rupture is 78%)

In this context, critical questions in assessing this technology to be addressed in this report are:

- *For patients who are eligible for standard open surgical repair of their AAAs, does endovascular repair result in lower morbidity, mortality and/or health care costs than does standard treatment?*
- *For patients who would otherwise be eligible for standard open surgical repair of their AAAs, were it not for the presence of severe comorbid medical conditions, does endovascular repair result in lower morbidity, mortality, and/or health care costs than does medical management?*
- *For patients with small, nonexpanding AAAs, (less than 5 cm diameter) who have favorable morphology for endovascular repair, does endovascular repair result in lower morbidity, mortality, and/or health care costs than medical management followed by standard open surgical repair when indicated?*

Key Findings

Cost, Reimbursement, and Regulation

Currently, all graft devices for endovascular exclusion of AAAs are being used in investigational studies under the FDA Investigation Device Exemption regulation. Medicare does not have a national coverage policy for the endovascular placement of grafts for the exclusion of AAA. Reviewed studies did not address the cost of endovascular repair of AAAs.

Evidence of Effectiveness

Published studies were predominantly case series, which is a relatively weak study design that does not provide strong evidence of effectiveness. Current evidence provides encouraging data on the feasibility of endovascular repair of AAAs. However, all studies have methodological limitations. Studies varied in the manufacture and design of the graft used. Graft devices and their method of deployment are undergoing continual refinements, and the devices reported on in the literature may differ from devices that might be approved for marketing in the United States.

There was no uniform reporting of patient severity of illness, and little uniformity in the reporting of study outcomes, which further weakens the available body of evidence and limits the conclusions that can be drawn from it. No standard criteria for patient selection for endovascular AAA repair have been developed.

- Immediate post-operative <u>technical success</u> ranged from 48-95%, but improved to 60-97% with additional endovascular interventions or spontaneous sealing of endoleaks (extravasation of contrast material into the aneurysmal sac) during or after hospitalization. By follow up, 0-30% of patients had an open surgical procedure, most often a <u>conversion to standard open surgical repair</u>.

- <u>Perioperative mortality</u> ranged from 0-36% (average of 8% across all case series). <u>Overall mortality</u> on follow-up ranged from 0.6-23% (average of 10%).

- <u>Complications</u> ranged from 10-31% of total patients across studies, whereas individual complications occurred in 0.6-20% of patients. If aneurysms were successfully excluded, there appeared to be no subsequent increase in aneurysmal size and possibly a decrease at least in the

short-term. Long-term follow-up is necessary to detect the possibility of late developing endoleaks.

- There has been little systematic study of variables related to health care costs. Expected lengths of stay ranged from 3.8 to 11.5 days.

- Comparative studies of endovascular repair to alternative interventions are very few, and with significant methodological limitations. Existing evidence reported less blood loss, shorter duration of ICU stay, and a higher incidence of local/vascular complications with endovascular repair than with standard surgery.

- Little systematic research has been conducted on factors that can affect the outcomes of endovascular repair of AAAs. Short proximal aneurysm neck length may be associated with an increased risk of endoleaks, whose presence risks aneurysmal rupture. More complex aneurysms may be associated with a higher risk of complications, as well as longer operative times and hospital stays.

Conclusions/Discussion

The currently available literature represents studies that are methodologically inadequate to definitively answer the questions addressed in this report. A critical issue in the evaluation of endovascular repair of AAA will be similar to that for other minimally invasive procedures: ***Does the availability of a minimally invasive treatment option lead to over-utilization of that procedure in patients with marginal indications for surgery?***

The VHA Office of Research and Development Cooperative Studies Program is conducting two studies on AAAs. The first study is called the Aneurysm Detection and Management (ADAM) Study, which is comparing surgery versus observation in patients with AAA 4.0-5.4 cm in diameter who are an acceptable surgical risk. The second study will determine the incidence of rupture and death from AAA rupture in patients with AAA of at least 5.5 cm in diameter.

Other Assessments

The Centre for Clinical Effectiveness, Monash Medical Centre, Southern Healthcare Network, Clayton, Victoria, Australia has published an assessment of endoluminal graft procedures for the treatment of abdominal aortic aneurysms (July 1988). This assessment used similar methods and reached similar conclusions to those of the MDRC assessment. The Australian report is available at http://www.med.monash.edu.au/psychmed/clinicaleff/evreports.htm.

The Agencia de Evaluación de Tecnologías Sanitarias, Madrid, Spain (December 1997) has also used similar methods and reached similar conclusions to those of the MDRC report. An English summary of the Spanish report is on file with the MDRC.

TABLE OF CONTENTS

I. INTRODUCTION AND BACKGROUND 1
A. Introduction 1
B. Abdominal Aortic Aneurysms 2
C. Standard Treatment 3

II. ENDOVASCULAR GRAFTS FOR ABDOMINAL AORTIC ANEURYSM EXCLUSION 4

III. REGULATION AND REIMBURSEMENT 8

IV. METHODS FOR THE SYSTEMATIC REVIEW 8

V. APPRAISAL OF THE LITERATURE 10
A. Application of the Inclusion Criteria 10
B. Data Synthesis 10

VI. PUBLISHED FINDINGS 10
A. Description of Patients, Treatment, and Outcomes 10
B. Reported Outcomes of Case Series of Endovascular Repair of Abdominal Aortic Aneurysms 14
C. Comparative Studies of Endovascular Repair of Abdominal Aortic Aneurysms 18
D. Factors Associated with Improved Treatment Outcomes 19

VII. DISCUSSION 20

VIII. CONCLUSIONS 21

IX. ONGOING TRIALS AND CLINICAL TRIAL RESOURCES 22

X. REFERENCES R-1

LIST OF TABLES AND FIGURES

Figure 1. EUROSTAR Registry Patient Inclusion and Exclusion Criteria 7
Figure 2. Inclusion Criteria for Systematic Review 9
Figure 3. Study Designs to Assess Effectiveness 9
Table 1. Eligible studies, Effectiveness of Endovascular Repair of AAAs 10
Figure 4. Description of Endovascular Grafts Noted in Table 2 11
Figure 5. American Society of Anesthesiologists Evaluation Scale for Preoperative Physical Status 12
Figure 6. Definition of Outcomes of Endovascular Repair of Infrarenal Abdominal Aortic Aneurysms 12
Figure 7. Definition of Primary Composite Study Endpoint of Endovascular Repair of Infrarenal Abdominal Aortic Aneurysm 13
Figure 8. Definition of Outcomes Presented in Table 2 13
Table 2. Summary of Evidence from Case Series: Effectiveness of Endovascular Graft Repair of Infrarenal Abdominal Aortic Aneurysms 16

I. INTRODUCTION AND BACKGROUND

A. Introduction

VA's Technology Recommendations Panel (TRP) received requests from several Veteran Integrated Service Networks (VISNs) to review endovascularly placed grafts for the repair of aortic and carotid artery disease. These VISNs were considering the purchase of operating room equipment (International Surgical Systems, Phoenix, Arizona, Model 2000) for graft placement or the establishment of referral centers for these minimally invasive vascular surgery procedures.

The VISNs were particularly interested in carotid and aortic surgery. Since the vast majority of the literature that the MDRC was able to identify addressed the use of grafts to repair infrarenal abdominal aortic aneurysms (AAAs), this assessment is confined to that indication. Only four articles could be identified that addressed the endovascular placement of grafts or stent-grafts to treat carotid artery disease, while 16 studies of endovascular technologies for the treatment of AAA met inclusion criteria for this review.

Technology advocates at the VISNs felt that endovascularly placed grafts would avoid much of the mortality and morbidity associated with standard, open surgical repair of AAAs, and lower hospital costs. Advocates also cited the potential for decreased use of blood products and length of post-operative hospitalization.

The available literature echoes these beliefs in potential benefits, and also indicates that patients with smaller AAAs (i.e., those less than 4 or 5 cm in diameter), which are not always repaired (but rather are sometimes monitored and repaired only when their size and/or risk of rupture increases) may more frequently be considered candidates for elective repair, as would patients who are poor surgical risks. Endovascular repair may become an option for high-risk patients who might not tolerate a major abdominal operation and aortic cross-clamping. According to Parodi (1995), vascular surgeons are increasingly encountering older patients with severe comorbid medical conditions which can increase operative morbidity rates and may significantly elevate mortality rates for aortic surgery. Thus, the technology questions to be addressed include:

- For patients who are eligible for standard open surgical repair of their AAAs, does endovascular repair result in lower morbidity, mortality, and/or health care costs than standard treatment?

- For patients who would otherwise be eligible for standard open surgical repair of their AAAs, were it not for the presence of severe comorbid medical conditions, does endovascular repair result in lower morbidity, mortality, and/or health care costs than medical management?

- For patients with small, asymptomatic, nonexpanding AAAs (less than 5 cm) who have favorable morphology for endovascular repair, does endovascular repair result in lower morbidity, mortality, and/or health care costs than medical management followed by standard open surgical repair when indicated?

B. Abdominal Aortic Aneurysms

The aorta is the main vessel of the arterial system, and carries oxygenated blood from the heart to the rest of the body. It is a large-diameter artery, and its walls must withstand the shearing effect of each systolic thrust of blood; it is consequently under greater tension than the rest of the arterial system, and the effects of hypertension are particularly deleterious on the aorta. It is also subject to necrosis and arteriosclerosis. Four major diseases result from these stresses: aneurysm, dissection, arteriosclerotic occlusive disease, and aortitis. The number of deaths due to diseases of the aorta is uncertain because other cardiovascular diseases (including hypertension and ischemic heart disease) often coexist and take priority on death certificate data coding (Dzau and Creager, 1998).

An aortic aneurysm is an abnormal widening that involves all three layers of the vessel's wall. The basic defect is in the elastic fibers of the media, or middle layer. The increased diameter leads to stretching and thinning of the wall and to an increase in tension, and eventually to risk of rupture (Dzau and Creager, 1998). According to Rooke and Stanson (1996), an AAA exists when the abdominal aorta enlarges to a diameter of 2.5 to 3.0 cm. Colburn and Moore (1996) define an aortic aneurysm as any enlargement of the aorta equal to or greater than twice the normal vessel diameter.

Diagnosis is often made on physical examination, where a pulsating mass in the midepigastrum is found (Dzau and Creager, 1998). Morphologically aneurysms vary from small aneurysms limited to a portion of the infrarenal aorta, without involvement of the proximal and distal ends of the infrarenal aorta, to extensive aneurysms which obliterate the proximal and distal ends or extend into one or both iliac arteries (Ahn et al., 1997). The etiology of AAA is largely unknown and probably multifactorial (Boll and van der Vliet, 1998). Familial clustering indicates a genetic defect. Candidate genes may be those associated with collagen matrix defects, accelerated connective tissue turnover, or tissue proteases (Boll and van der Vliet, 1998).

The incidence of AAA varies with the population studied. Most such aneurysms occur in men over the age of 60; many have associated hypertension and atherosclerosis and are cigarette smokers (Dzau and Creager, 1998). A study of high-risk individuals (males aged 60 to 75 years of age with hypertension or coronary artery disease) reported a 9% incidence (Rooke and Stanson, 1996). The estimates of the prevalence of AAA in men ages 60 to 80 years range from 2-7.8% (Frame et al., 1993). The prevalence of AAA has been reported to have increased 300% in the past 30 years (Zarins and Harris, 1997). Risk factors for AAA include increasing age, male sex, tobacco use, family history, and possibly hypertension (Frame et al., 1993).

In fiscal year 1997 there were 128 patients of the veterans health care system (VA) with a primary diagnosis code indicating abdominal aortic aneurysm. Readily available VA data sets do not contain sufficient clinical detail to know the distribution of small and large aneurysms among these patients.

AAAs may enlarge approximately 0.2 to 0.8 cm per year, but this is very variable and the factors influencing enlargement are largely unknown. Most AAAs are relatively asymptomatic (Rooke and Stanson, 1996). Hollier et al. (1992) observe that some aneurysms will remain stable and some patients will die of other disease processes before their AAA might rupture. Standard texts (e.g., Dzau and Creager, 1998) state that symptomatic or expanding aneurysms should have prompt surgical correction; the therapeutic decision for patients with smaller or asymptomatic aneurysms is more problematic.

Reports from the 1950s and 1960s of 5-year survival for unoperated AAAs range from 17-19%, but these series included many cases with large aneurysms (Dorros et al., 1997; Szilagyi et al., 1966; Wolf and Bernstein, 1994). A more current finding is a 5-year survival rate without surgery of 52% (Wolf and Bernstein, 1994). According to Dorros et al. (1997), the generally accepted 5-year rupture rate for aneurysms <4 cm is approximately 2%, and for aneurysms >5.0 cm, 25-41%.

The overall mortality for AAA rupture is 78% (Rooke and Stanson, 1996). In the United States, AAA rupture accounts for 1.2% of male and 0.6% of female deaths of persons older than 65 years of age (Frame et al., 1993). The number of deaths annually due to AAA rupture in the United States is approximately 15,000 and it is the tenth leading cause of death in men over age 55 (Colburn and Moore, 1996). Other less common complications of unoperated AAA include embolization, fistulization, and thrombosis, but there are no firm estimates on the risk for these complications (Hollier et al., 1992).

C. Standard Treatment

The standard treatment of AAA is an open surgical procedure with placement of a synthetic graft in the involved segment (Blum et al., 1997a; Zarins and Harris, 1997). Most AAAs involve the aortic bifurcation and the common iliac arteries which necessitates a bifurcated graft so as to completely exclude the AAA (Allen et al., 1997; Chuter et al., 1996). Approximately 40,000 operations per year in the United States are surgical repairs of AAA (Moore and Vescera, 1994). The purpose is to prevent rupture, relieve symptoms, and restore arterial circulation.

According to Dorros et al. (1997), indications for emergent surgery include known or suspected rupture, symptomatic aneurysm without evidence of rupture, or suspected expanding aneurysm. Indications for elective surgery are a fusiform aneurysm ($\geq$ 5.0 cm in diameter), a saccular aneurysm (may be < 5.0 cm or more than twice the diameter of the infrarenal aorta), uncontrolled hypertension, living in a remote area without appropriate medical care, or serial imaging showing progressive aneurysm enlargement (4.0 to 5.0 cm) (Dorros et al.,1997).

The overall mortality rate for standard surgical treatment of AAA is estimated as 4% (reported range from 1.4-7.6% and up to 10% in patients with symptomatic aneurysms) (Blum et al., 1997a). An analysis of published studies by Zarins and Harris (1997) provides the following estimates of operative mortality for repair of nonruptured AAA: approximately 2.1% (range 0-3.7%) for centers with experienced surgeons with a

particular interest in aneurysm repair, approximately 4.2% (range, 3.6-4.9%) for multicenter reports which likely represents a broader cross-section of surgeons performing aneurysm repair, and approximately 7.3% (range, 6-7.3%) for population-based studies. Studies have reported 5-year survival rates ranging from 60-84%, and 38-41% 10-year survival rates (Hollier et al., 1992). Whereas many patients with ruptured aneurysms die before treatment, among those who are treated surgically survival rate has been reported to range from 25-75% (D'Angelo et al., 1993).

The reported early complications of elective AAA repair, and approximate rate of occurrence, include myocardial ischemia, arrhythmia, or congestive heart failure in up to 15% of patients, pulmonary insufficiency (8%), renal damage (6%), bleeding complications (4%), distal thromboembolism (3%), and wound infection (2%) (Zarins and Harris, 1997). Late graft-related complications leading to morbidity or death are infrequent. Findings reported in a study of 1087 patients followed for 6 to 12 years after successful AAA repair included aortoenteric fistula (0.9%), pseudoaneurysms (1.3%), bowel ischemia (not necessarily related to AAA repair) (0.4%), and graft infection (0.3%) (Hollier et al., 1992).

Colburn and Moore (1996) point out that standard surgical repair of AAA requires several hours of operating time, frequent transfusions, prolonged hospital stays, and months of recovery during which time patients are rarely able to return to work or resume previous levels of activity. It is with the hope of lowering post-operative morbidity and mortality, the possibility of treating patients who otherwise have contraindications to standard surgery, and potential lower costs that drives interest in endovascular repair of AAAs.

Surgery is warranted when the risk of rupture is greater than the risk of operation. Patients with AAAs often have coexisting morbid conditions which increase the risk of the standard open surgical procedure (Blum et al., 1997a). Patients at high surgical risk are those with cardiac, renal, or pulmonary comorbidity or those whose predicted life span would be shortened by a malignant neoplasm (Steyerberg et al., 1995).

Steyerberg et al. (1995) used patient and literature data to generate a clinical prediction rule in which the strongest factors arguing against surgery were congestive heart failure and cardiac ischemia on the electrocardiogram; renal impairment, history of myocardial infarction, pulmonary impairment, and female gender were also risks for surgical mortality. The Society for Vascular Surgery and the International Society for Cardiovascular Surgery Joint Council Subcommittee have developed medical risk categories for elective AAA repair based on patient age, cardiac function, pulmonary function, and renal function. Aneurysm morphology may also influence perioperative morbidity and mortality, but the nature of this relationship is not clear (Zarins and Harris, 1997).

II. ENDOVASCULAR GRAFTS FOR ABDOMINAL AORTIC ANEURYSM EXCLUSION

Endovascular grafts evolved from intravascular stent and prosthetic graft technologies. They are inserted through remote arterial access sites which obviates the need to directly expose the diseased artery through extensive incisions or dissections. Typically, after a guide wire is inserted through the access vessel and interpretation of preinsertion computerized tomography (CT) scans

and angiograms, endovascular grafts contained in delivery catheters are advanced to the desired location, the delivery catheter is withdrawn, and the graft-to-artery attachment system deployed under fluoroscopic control (Marin et al., 1995; Myers and Devine, 1997). Many devices use stents to anchor the grafts, whereas others use alternative fixation systems.

Deployment requires a combination of vascular surgical skills and expertise in catheter and guidewire techniques and radiological imaging (Harris, 1996). The procedure may often be complex and difficult. According to Marin et al. (1995), surgical and endovascular rescue techniques are often required. They argue that these devices should be used initially by a health care team that combines the highest levels of skill in vascular surgery and interventional radiology.

Endovascular graft devices and their method of deployment are undergoing continual refinements, and the devices reported on in the literature will not necessarily be identical to the devices which might be approved for marketing in the United States (Harris et al., 1997). There are many features of endovascular grafts which potentially can affect the success of deployment, complications, and short- and long-term patient outcomes. Device size affects the type of incision for remote arterial access (groin incisions of the common femoral arteries for smaller devices and for larger devices the inclusion of incision of the inguinal ligament or a retroperitoneal approach to expose the iliac vessels). Device length has to be such that it excludes the entire AAA.

Modular designs consist of multiple sections which can be overlapped and thereby accommodate unexpected length variation requirements at the time of implantation (Allen et al., 1997). Graft configurations include straight or tubular for aortoaortic placement, tapered aortoiliac or aortofemoral (proximal end placed in the aorta with the tapered distal end placed in a common iliac artery or femoral artery and also includes occlusion of the contralateral iliac artery with femorofemoral bypass), and bifurcated or Y-shaped (proximal end placed in the aorta and the Y branches in the common iliac arteries).

Material flexibility will affect ability to navigate tortuous and angulated arteries. Radiopacity of stent material (such as radiopaque markers) facilitates fluoroscopic visualization during implantation, but it should not interfere with CT or magnetic resonance evaluation. Stents require strength and rigidity for proper anchoring and conformance flexibility for proper sealing and prevention of endoleaks (extravasation of contrast material into the aneurysmal sac). Stents are anchored and sealed with hooks or by relying on friction. Stents can be self-expanding or expanded with the use of a balloon. Stents may extend the entire length of a stent-graft or be placed only at the proximal and distal ends. The stent support frame may be on the inside or outside (exoskeleton) of the graft material.

There are various types of graft material, such as Dacron which can be knitted or woven and of variable thickness and polytetrafluoroethylene (PTFE) which can be of varying porosity. Endovascular graft devices may be maneuvered into place by pulling or pushing into the delivery catheter, and deployed by retracting a capsule cover or extruding the device with a pusher system (Allen et al., 1997).

Veith et al. (1995), writing privately (in the form of suggested guidelines for research, rather than in a regulatory document) for the Food and Drug Administration's (FDA's) Endovascular Graft Committee, divide transluminally placed endovascular grafts into several categories, based on:

- the type of device (covered single stent or end fixation), the delivery system (with or without a sheath, over a wire or without a wire);
- nature of the attachment or fixation system and method (balloon-expandable, spring-expandable, or mechanically-expandable stent or other device, with or without hooks for fixation to the vessel wall), and;
- the nature of the graft or covering material component (knitted polyester [Dacron], woven polyester [Dacron], PTFE, or other developmental prosthetic material).

These authors also believe that both device and usage categories (lesion location and lesion pathology) are critical to the evaluation of the devices and that safety, efficacy, and use should be considered separately for each device and each use. Ahn et al. (1997) recommend that investigators report device-related factors including configuration, graft material, type of fixation system, manufacturer, and the diameter of the proximal and distal fixation sites.

Myers and Devine (1997) provide the names of eight endovascular grafts and whether their fixation devices are rigid stents or Nitinol (a nickel-titanium alloy), and whether the grafts are of Dacron or polyurethane. According to Myers and Devine (1997), rigid stents with Dacron grafts include Parodi, White-Yu, Endovascular Technology, Chuter, and Lawrence-Browne. Nitinol stents with Dacron grafts include Mintec Mialhe Stentor and Talent Taheri-Leonhardt. Corvita is a Nitinol stent with polyurethane graft.

Since endovascular repair requires navigable arteries and accurately sized devices, preoperative evaluation, including measurements of diameter and length of involved arteries and the lesions, is required to assess patient suitability for stent-graft placement (Parodi, 1995). Inaccurate graft sizing can result in endoleaks, which can result in aneurysm expansion and rupture (Chuter et al., 1996). Preoperative information is needed about the caliber or diameter of arteries (common femoral, iliac), tortuosity of iliac arteries, angularity of the aorta, renal ostial position, presence of calcified stenosis or atherosclerotic disease, presence of collateral mesenteric flow pattern or aberrant renal artery anatomy, and diameter and length of arterial implantation sites (Allen et al., 1997; Fox et al., 1996; Mialhe et al., 1997; Moore and Rutherford, 1996; Parodi, 1995).

The EUROSTAR (EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair) registry provides typical example dimensions defining patients with AAAs without symptoms of rupture or expansion who are suitable for elective endovascular repair (Harris et al., 1997) (Figure 1).

Figure 1: EUROSTAR Registry Patient Inclusion and Exclusion Criteria

Inclusion criteria:

AAA measuring ≥ 45 mm in diameter.

Anatomic configuration suitable for a stented tube or bifurcated prosthesis:

- Infrarenal neck length ≥ 15 mm and diameter < 25 mm.
- Iliac artery angulation < 90° (or correctable angulation).

Common iliac artery < 12 mm in diameter and nonstenotic (> 6 mm diameter after balloon dilation, if necessary).

Distal extension categories A to C (A, normally sized aortic segment of 1.5 to 2 cm in length above the bifurcation; B, AAA extends to the common iliac arteries, which are of normal size; C, the common iliac arteries are aneurysmal in the proximal third, but there is an adequate sealing zone that does not jeopardize the internal iliac arteries).

Exclusion criteria:

AAA measuring < 45 mm in diameter.

Ruptured or symptomatic AAA.

Juxta- or suprarenal-extension.

Occluded superior mesenteric artery or an open Riolan arch necessitating retained patency of the inferior mesenteric artery.

Stringent indications for combined reconstruction of other intra-abdominal vessels (e.g., renal arteries).

Need to sacrifice both internal iliac arteries due to aneurysmal dilatation in both common iliac arteries over their entire length.

Patient age < 21 years, connective tissue diseases, fertile female, acute infection.

Source: Harris et al., 1997

Ahn et al. (1997) indicate that a combination of aortographic and CT or MRI scans, preferentially with three-dimensional reconstruction when available, is necessary to properly document anatomical characteristics, and to allow for precise measurement. According to Fox et al. (1996), angiography, ultrasonography, and conventional CT cannot be relied upon to provide these parameters and argue for the use of magnetic resonance imaging as providing the most comprehensive anatomic picture for patient selection for endovascular grafting.

Chuter et al. (1996) consider standard imaging modalities, such as magnetic resonance imaging, CT, or angiography as inadequate for endovascular repair. Chuter et al. (1996) rely primarily on spiral CT (which provides three-dimensional reconstruction of the image) for graft sizing and assessment of the aortic neck, and angiograms are used mainly to study the dimensions of the iliac arteries.

Myers and Devine (1997) use digital subtractive angiography and CT with appropriate measurements to select the appropriate size of an endovascular device, but also indicate that spiral CT may make measurements even more accurate. According to May et al. (1994a), CT scanning with intravenous contrast medium at 0.5 cm intervals is necessary to confirm that the aortic distal neck of the aneurysm seen in an aortogram is formed by the aortic wall and not a thrombus within an aneurysmal sac. A tortuous lumen within the mural thrombus of a larger aneurysm may lead to underestimation of the length of graft required.

Ahn et al. (1997) indicate that technical success requires documentation by operative aortographic scan and follow-up CT scan, color Duplex scan, or angiogram. Intravascular ultrasonography may be helpful but according to Ahn et al. (1997) is not required. Marin et al. (1995) conducted

intraoperative completion arteriograms and sometimes intravascular ultrasound to evaluate technical procedural adequacy. Soon after the procedure they used contrast-enhanced CT scan and color duplex ultrasound and thereafter, to follow patients, periodically at 3 to 6 month intervals. These studies are used to look for events such as perigraft channels or endoleaks, altered geometric configuration (e.g., kinks, compression), device migration, and change in aneurysm size (Broeders et al., 1997; Marin et al., 1995).

In sum, investigators are learning what may be the most cost-effective preprocedure insertion patient work-up, as well as for postoperative imaging. Extensive imaging is a hallmark of research studies and may not be the protocols eventually recommended for more generalized practice (Chuter et al., 1996).

Patients undergoing endovascular AAA repair may require additional surgical or endovascular procedures in order to properly place endovascular grafts. For example, they may required balloon angioplasty procedures for iliac artery stenosis, endarterectomies of the common femoral artery, ipsilateral iliac grafting procedures, and cross-over femorofemoral bypass procedures to restore flow to the limb excluded by a unilateral aortoiliac endovascular graft (Mialhe et al., 1997). Femoral artery or isolated common iliac aneurysms requiring repair may be encountered. A graft may be sutured to the common iliac artery via a retroperitoneal approach in patients with tortuous or stenotic common femoral or iliac arteries and used as a temporary conduit to permit access to the aorta (Nasim et al., 1996; Parodi 1995).

III. REGULATION AND REIMBURSEMENT

As of this writing (May, 1998), according to a spokesperson for the FDA, all endovascular graft devices for endovascular exclusion of AAAs are being used in investigational studies under the FDA Investigation Device Exemption regulation. Thus, none of these devices has been approved for marketing in the United States. The FDA has designated these investigational devices as B-3. The Health Care Financing Administration, in its Medicare Coverage Issues Manual, does not have a national policy on coverage for the endovascular placement of grafts for the exclusion of AAA.

IV. METHODS FOR THE SYSTEMATIC REVIEW

Information about the effectiveness of endovascular repair of AAAs was obtained by conducting a ***systematic review*** of the published literature. A systematic review uses a scientific approach to limit bias and to improve the accuracy of conclusions based on the available data. A search of the English-language literature was performed using MEDLINE®, HealthSTAR®, and Current Contents® for the years 1993 through April, 1998. Terms for the search included: aortic aneurysm, carotid stenosis, stent, and minimally invasive (text words). The search yielded 555 citations and abstracts which were reviewed. An additional English language literature search was conducted May 10, 1998 of Current Contents® (weeks 1-18, 1998) using the terms *aortic aneurysm* and *abdominal* (89 titles were screened), and of MEDLINE (January-April, 1998) using the term *aortic aneurysm, abdominal* (8 titles were screened).

From the computerized literature searches, a total of 99 references were determined to be potentially relevant. However, many concerned the detection and management (by means other than endovascularly placed stents or stent-grafts) carotid artery aneurysms which were requested before the technology assessment question was refined to AAAs. Potentially relevant references were of studies evaluating the effectiveness of endovascular repair as well as references which could provide useful background information about aneurysms and endovascular repair. In addition, review of citations in reviewed articles resulted in an additional 22 potentially relevant references and 3 references were obtained from a web site (http://www.ccohta.ca/english/ews/jan-98-i2.htm). Of the total of 124 references, the full text articles could be retrieved for 118. Articles were reviewed and were included in the systematic review if they met the criteria in Figure 2.

Figure 2: Inclusion Criteria for Systematic Review

- Studies evaluating the effectiveness of endovascular repair of AAAs.
- English language journal articles reporting primary data obtained in a clinical setting, or analyses of primary data maintained in registries or institutional databases.
- Study design and methods clearly described.
- Case series including $\geq$ 10 patients, or studies with a more powerful design.
- Study not superseded by a later publication, with the same purpose, by the same group or a later publication which included the data from multiple centers involved in the same multicenter study.
- Published 1990 or later, to reflect the current status of endovascular repair for AAAs.

Studies were selected for inclusion if they provided the strongest available evidence of effectiveness. The strength of the evidence is based on how well bias and confounding factors are controlled in the design and conduct of a study. Attributes that strengthen the validity of findings include: randomized (vs. nonrandomized), controlled (vs. uncontrolled), blinded (vs. unblinded), prospective (vs. retrospective), large (vs. small), multi-site (vs. single-site), and contemporaneous (vs. historical) controls. Based on these attributes, common study designs are listed in order, from the most to the least rigorous, for internal validity and strength of evidence in Figure 3.

Figure 3: Study Designs to Assess Effectiveness
Ranked according to decreasing strength of evidence provided

- Large randomized controlled trial, systematic reviews of RCTs
- Small randomized controlled trial
- Nonrandomized trial with contemporaneous controls
- Nonrandomized trial with historical controls
- Surveillance (database or register)
- Case series, multi-site
- Case series, single site
- Case report, anecdote

Sources: Adapted from Ibrahim (1985), and Goodman (1993)

V. APPRAISAL OF THE LITERATURE

A. Application of the Inclusion Criteria

Table 1 summarizes the findings from the review of the 118 potentially eligible articles.

Table 1: Eligible Studies, Effectiveness of Endovascular Repair of AAAs

STUDY DESIGN	# ELIGIBLE STUDIES
Large randomized controlled trial, systematic reviews of RCTs	0
Nonrandomized trial with contemporaneous controls	1
Nonrandomized trial with historical controls	1
Surveillance (database or register)	0
Case series, multi-site	7* (prospective) 1 (retrospective)
Case series, single site	6 (prospective)
Case report, anecdote	Excluded
TOTAL	**16**

* Includes one study which provided follow-up data to another counted study.

Study characteristics and outcomes were extracted by the authors, with the case series summarized in Table 2, and discussed below. Studies were predominantly case series. A case series is a relatively weak study design that does not provide strong evidence of effectiveness. Case series contain useful information about the clinical course and prognosis of patients, can suggest relationships between interventions and outcomes, and can help generate ideas for further research. The dominant weakness is that without a comparison group, case series cannot provide definitive evidence on whether or not the intervention evaluated is more effective than an alternative or no treatment.

B. Data Synthesis

This report presents a qualitative review to synthesize the best available evidence. A quantitative synthesis (meta-analysis) was not attempted. The methodological weakness of case series, combined with substantial differences in design and analysis among the eligible studies, and patient selection and the type of endovascular grafts evaluated, argued against the validity and usefulness of pooling study results.

VI. PUBLISHED FINDINGS

A. Description of Patients, Treatments, and Outcomes

Studies varied in the type of endovascular graft inserted, both in terms of manufacturer and in design. Figure 4 is presented as an aid to Table 2 which summarizes the evidence from case series reports. Figure 4 provides brief descriptions of the types of endovascular grafts and the symbols used in Table 2.

Figure 4: Description of Endovascular Grafts Noted in Table 2

S	Stentor; also known as Mialhe-Stentor (MinTec, Freeport, Bahamas) and more recently as Vanguard (Boston Scientific, Oakland, NJ). Nitinol (nickel tantalum alloy) stent and woven polyester graft, self-expanding.
Pa	Passager (Boston Scientific, Oakland, NJ). A covered stent-graft used as an extension.
EVT	Endovascular Graft System (Endovascular Technologies, Menlo Park, CA). Dacron graft, self-expanding fixation system (metallic pins) in proximal and distal fixation devices.
Pz-C	Palmaz stents (Johnson & Johnson International, Inc., Warwick, NJ) and Cooley-VeriSoft (Meadox Medical, Inc., Oakland, NJ) graft.
G-C	Self-expanding Gianturco Z-stents (Cook, Critical Care, Inc., Ellettsville, IN) and Cooley-VeriSoft (Meadox Medical, Inc., Oakland, NJ) graft.
G-D	Self-expanding Gianturco Z-stents (Cook, Critical Care, Inc., Ellettsville, IN) and Dacron graft.
Par	Modified Palmaz stent capable of expanding to 35mm and crimped Dacron graft (Barone, Inc., Buenos Aires, Argentina). Follows design developed by Parodi (1995). Balloon expandable. The procedure for the aortoiliac stent-graft also includes occlusion of the contralateral iliac artery and femorofemoral bypass.
Pz-PTFE	Palmaz stents (Johnson & Johnson International, Inc., Warwick, NJ) and tapered polytetrafluoroethylene graft (Impra, Droitwich, UK). Procedure performed with occlusion of the contralateral iliac artery and femorofemoral bypass. Balloon expanded stent.
W-Y	White-Yu (also known as Sydney). Woven polyester graft with Elgiloy wire interwoven. Balloon expanded. Does not use a stent. Developed by White et al. (1994; 1997).

Endovascular graft designs included straight (tubular), tapered aortoiliac or aortofemoral, and bifurcated. The relative proportions of each varied by study, and this is an approximate indication of the variability across studies of type of aneurysm treated: limited to the aorta without iliac involvement, involvement of the aortic bifurcation, involvement of the iliac artery(ies), and involvement of the iliac bifurcation. Moreover, in some studies endovascular grafts underwent technical refinement during the duration of the study. Although proposed reporting standards have been published, these were published after many of the studies summarized in Table 2 and the individual study reports did not present enough information to apply these standards retroactively (Ahn et al., 1997; Dorros et al., 1997; Veith et al., 1995).

Reflecting the population incidence of AAA, case series study patients (Table 2) were predominantly male: proportions ranged from 81 to 97% (mean, 90%). Mean or median patient age ranged from 68 to 76 years, and individual ages from 41 to 90 years.

There was no standard reporting of patient severity of illness. Some studies used the American Society of Anesthesiologists classes I - IV (see Figure 5; Blum et al., 1997a; Coppi et al., 1997; Mialhe et al., 1997). Proportions in each class varied by study, but overall most were Class III. Other studies indicated they included mostly high-risk cases, initially included patients considered inoperable, or, as the study progressed, increasingly included more complex cases (Chuter et al., 1996; Marin et al., 1995; Parodi 1995; White et al., 1996a). Marin et al. (1995) stated their case series patients (non-EVT cases) were treated on a compassionate basis, that is, no other corrective treatment was considered feasible or the risk of such other treatment was deemed as excessive. It was not uncommon for studies to select patients who could be converted to standard open surgical repair if that became necessary. On the other hand, some studies also indicated they

included some patients who might not be eligible for standard treatment (Blum et al., 1997a).

Figure 5: American Society of Anesthesiologists Evaluation Scale for Preoperative Physical Status.

Class 1. Patient is healthy with no systemic disease. The pathological process for which operation is to be performed is localized.
Class 2. Mild to moderate systemic disturbance caused either by the condition to be treated surgically or by pathophysiologic processes.
Class 3. Patient either has multiple-system disease or well-controlled major system disease.
Class 4. Patient with severe systemic disorder that is life threatening and may not be correctable by operation.
Class 5. Patient is moribund, with little chance of survival, but is submitted to operation in desperation.
Emergency operation. Any patient in one of the above classes who undergoes operation in an emergency situation is considered to be in poorer physical condition, and the operation confers an additional degree of risk.

Source: Dentz et al. (1997)

No standard criteria for patient selection for endovascular AAA repair have been developed. According to Marin et al. (1995), early studies emphasized patients facing immediate loss of life or limb and were treated compassionately, and as these types of patients often had high medical risks this contributed to the relatively high mortality and complication rates of published case series. Indicative of their focus on investigating feasibility, case series were concerned with selecting patients suitable for the design and configuration of the particular stent-graft being evaluated.

Ahn et al. (1997), reporting for the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of The Society for Vascular Surgery/International Society for Cardiovascular Surgery, provide criteria for reporting the outcomes of infrarenal endovascular AAA repair. Their definitions are summarized in Figure 6.

Figure 6: Definition of Outcomes of Endovascular Repair of Infrarenal Abdominal Aortic Aneurysms

Technical (procedural) success: successful access to the arterial system using a remote site, successful deployment with secure proximal and distal fixation without persistent (≥ 48 hours) endoleaks, and patent endovascular graft without significant twist, kinks, or obstruction (< 20%). To be considered a technical success, success must be maintained for 30 days without death or conversion to standard aortic reconstruction.

Clinical success: successful access and deployment with secure proximal and distal fixation, and patent endovascular graft without significant twists, kinks, or obstruction. With regard to endoleaks, only graft endoleaks persisting longer than 6 months or aneurysms that expand are clinical failures.

Continuing success: Technical and clinical success without graft thrombosis, migration, infection, dilatation >20% by diameter, aneurysmal degeneration proximal or distal to the graft, fixation device failure, aneurysmal expansion ≥ 0.5 cm, requirement for open conversion, or graft replacement using open techniques.

Secondary success: Late graft complications successfully treated with another endovascular or other less invasive procedure that does not replace the original graft.

Source: Ahn et al. (1997)

An international multidisciplinary team of investigators through consensus arrived at a detailed methodology for the evaluation of endovascular repair of AAA (Dorros et al., 1997). Figure 7 summarizes their recommended primary composite study endpoint measure. Dorros et al. (1997) also provided the data collection forms to document all the necessary patient and treatment data elements.

Figure 7: Definition of Primary Composite Study Endpoint of Endovascular Repair of Infrarenal Abdominal Aortic Aneurysms

Primary composite study endpoint of early (30-day) and late endovascular AAA repair: successful aneurysmal exclusion (as documented by contrast-enhanced CT (when appropriate) or (less desirable) angiography and/or duplex ultrasonography) without perioperative death (all vascular, cardiological, neurological, "miscellaneous," or unexplained deaths are attributed to the vascular (aneurysmal) category), myocardial infarction, stroke, limb loss, or surgical crossover. In complete aneurysmal exclusion, the graft is intact, no holes are present, and the fluid (blood) seal at the proximal and distal ends has no evidence of reflux; both ends of the graft are in contact with the arterial wall without thrombus interposition; anastomotic sealing is "water tight"; and the patent graft is not compromised by any kinks or twists.

Source: Dorros et al. (1997)

Additional guidelines for evaluating endovascular grafts for the repair of AAAs can be found in Veith et al. (1995). However, existing studies do not report their results consistent with the recommendations and definitions provided by Ahn et al. (1997), Dorros et al. (1997), and Veith et al. (1995). Hence, Figure 8 provides the outcome measures used in this assessment which appeared most applicable to most studies. No studies employed quality of life outcome measures.

Figure 8: Definition of Outcomes Presented in Table 2

Technical (procedural) success: Successful deployment (e.g., no conversion) with complete exclusion (no leaks) of the AAA and restoration of normal blood flow. Does not consider perioperative deaths (it was not always possible to determine if a patient who died did not have an endoleak; if they had a leak they would have been counted as a technical failure due to the leak).

Perioperative mortality: Death from any cause within 30 days of the procedure.

Complications: As reported in studies, excluding counts of deaths or conversions

Conversion: Conversion to an open surgical procedure at any time from the initial procedure through follow-up (e.g., to correct aneurysmal leakage, rupture, or any directly related vascular surgical procedure).

Overall mortality: Mortality from time of procedure through follow-up, irrespective of attribution to procedure. Possible limitation is that investigators frequently did not specify if any late deaths were in patients who were converted to open procedures.

Late expansion and rupture: As reported in studies during follow-up.

B. Reported Outcomes of Case Series of Endovascular Repair of Abdominal Aortic Aneurysms

Table 2 summarizes the outcomes from case series studies of endovascular graft repair of infrarenal AAAs. The case series were feasibility studies, and even ever lengthening case series included their initial cases. Although studies varied in how they reported technical success, which hinders comparisons, Table 2 shows that immediately post-operatively it varied from 48-95%, and among the larger studies ($\geq$ 50 cases) from 83.5-87%. Technical success improved to 60-97% after additional endovascular interventions (predominantly insertion of additional stents or stent-grafts to seal endoleaks) and with spontaneous sealing of endoleaks during or after hospitalization. By follow-up, 0-30% of patients had an open surgical procedure, most often a conversion to a standard open surgical repair. In the largest case series (Blum et al., 1997a), technical success achieved 97% and conversions were limited to 1.9% during follow-up which ranged from 8 days to 26 months.

Perioperative mortality ranged from 0-36% (average of 8% across all studies), and although the highest mortalities occurred in the smallest case series, some moderately sized case series had mortalities comparable to the larger case series. Overall mortality on follow-up, which varied by study from a mean or median of 153 days to 23 months, ranged from 0.6-23% (average of 10%) for studies reporting this outcome.

The case series did not share a standard format for reporting complications. Case series which reported the total percentage of patients who experienced complications had results ranging from 10-31%. The incidence of individual complications that occurred ranged from 0.6-20% (excluding transient fever). Examples of major complications that may be more directly related to the procedure include rupture of iliac artery, embolization resulting in multi-organ failure and death, and embolization resulting in amputation (e.g., foot).

Microembolization is of particular serious concern, because it may cause multiorgan failure in the early postoperative period and is often fatal. Marin et al. (1995) reported that diffuse aneurysmal thrombus embolization during device insertion resulted in 3 (21%) deaths among 14 patients who had received either an aortoaortic device or an aortoiliac device with femorofemoral bypass. Parodi (1995) reported that microembolization occurred in 4 (8%) patients with death in 3 (6%), out of 50 treated.

The mechanism of microembolization is not known. It may be caused by guidewire or endovascular graft manipulation within the aneurysm sac. Chronic thrombus is common in AAAs of suitable size considered for repair, and the aorta proximal to the aneurysm often contains atherosclerotic plaque. The mural thrombus often present within aneurysms may be a source or increase the risk of microembolization (May et al., 1994). According to Parodi (1995), large, tortuous aneurysms with a substantial amount of intraluminal thrombus may pose an increased potential for embolization. According to Nasim et al. (1996), it is possible that balloon encroachment over renal artery ostia may cause atheromatous debris to embolize into the kidney, and the amount of contrast medium administered during these procedures may also contribute.

Thompson et al. (1997) conducted a concurrent cohort study comparing traditional surgery with endovascular repair of AAAs. The purpose of the study was to compare microembolizations between the two types of procedures. The study did not compare effectiveness. The number of cases was small in each study group (11 and 18 cases in the endovascular and standard treatment groups respectively), limited patient data were presented, and the two groups cannot be considered equivalent. Study findings suggested that microembolization may be greater with endovascular than standard open surgery. Thompson et al. (1997) speculated that microembolization may be related to the extent of manipulation of intraluminal devices; they also noted that since microembolization has not been reported in some series of endovascular repair, this complication may in part be technique-related.

Case series generally provided minimal information on late expansion and rupture (see last column, Table 2). Studies need to show that this technology will effectively and permanently exclude the aneurysm from the arterial circulation, and prevent aneurysm expansion and rupture (Marin et al., 1995). If aneurysms were successfully excluded, there appeared to be no increase in aneurysmal size and possibly a decrease, at least in the short-term.

Broeders et al. (1997), in a follow-up study of Balm et al. (1996), reported that a persistent endoleak was associated with further increases in maximal aneurysm diameter indicating failure of aneurysm exclusion, and the rate of expansion might be similar to untreated aneurysms indicating no beneficial effect. Broeders et al. (1997) also identified the possibility of ongoing dilatation of the aorta at the level of the proximal and distal attachment systems which could become sources of subsequent endoleaks. Patent lumbar and inferior mesenteric arteries also can reperfuse aneurysms. These may undergo spontaneous thrombosis, or they can be treated such as with percutaneous catheter embolization (Chuter et al., 1996).

There has been little systematic study of variables related to health care costs. Blum et al. (1997a) did not compare cases with less and more complex aneurysms directly, but the average length of stay was longer in the more complex cases (11.5 versus 6.75 days). Some studies provided hospital stay data for their successfully treated cases (e.g., without conversion or death) and reported mean or median lengths of stay of 3.8 (Moore et al., 1996), 6 (White et al., 1996a), 7 (Balm et al., 1996), and 8 days (Coppi et al., 1997). Nasim et al. (1996) reported a median of 9 days and Parodi (1995) stated that patients with a successful procedure were usually discharged within 3 or 4 days.

Table 2: Summary of Evidence from Case Series: Effectiveness of Endovascular Graft Repair of Infrarenal Abdominal Aortic Aneurysms

Study	Number Of Centers	Graft	N*	Technical Success	Perioperative Mortality	Complications**	Follow-Up†	Conversion+	Overall Mortality††	Late Expansion And Rupture
Blum, 1997a	3	S	154 (21 t, 131 bi)	87% immediately post-op 97% after spontaneous seals and interventions	0.6%	10% (8% minor 2% major)	12.5m (8d-26m)	1.9%	0.6%	No expansion in excluded AAA; no rupture
Mialhe,‡ 1997	>1, not specified	S	79 (4 t, 4 ta, 71 bi)	83.5% before discharge 94% at 1 month after spontaneous seals and interventions	5.1%	31%	5.7m (1-18m)	0%	7.6%	Mean diameter decreased No rupture
Dorffner, 1997	1	S, Pa	28 (11 t, 17 bi)	50% intraoperatively 89% immediately post-op, after stent-graft extensions added 68% 1 week post-op 93% latest follow-up (1 week-15 months) after spontaneous seals and with interventions	0%	3.6-19%	8.2m (1w-15 m)	3.7%	7.1%	No expansion, no rupture
Moore, 1996	13	EVT	46 (t)	48% immediately post-op 67% on follow-up (up to 27 months) after spontaneous seals and interventions	0%	2-20%	14m (up to 27m)	19.6%	2%	Cases with persistent leaks no increased size
Balm, 1996	5	EVT	31 (t)	77% one day post-op 87% in 3 weeks after spontaneous seals	3.2%	3.2-19%	153d (2-432d)	3.2%	13%	—
Broeders, 1997 (follow-up to Balm)	5	EVT	26 (t)	81% by 30 days post-op	3.2%	—	12m (6-24m)	15%	23%	Size increased in cases with leaks; no size increase if AAA excluded
Coppi, 1997	11	Par	27 (t, ta)	78% intraoperatively 85% immediately post-op with intraoperative intervention	11.1%	3.7-3.7%	23m (18-30m)	30%	11.1%	No expansion in surviving endografts
Parodi, 1995	1	Par	50 (36 t, 15 ta)	86% immediately post-op 94% with interventions	8%	2-12%	17m (1-43m)	2%	18%	1 late rupture
Marin, 1995	1	Par	11 (3t, 8ai)	—	36%	18% “minor” 36% “major”	13.3m (4-25m)	—	—	—
White, 1996a	2	Pz-C	11 (3 t, 8 b)	54.5% immediately post-op	18%	—	9m (6-15m)	18%	18%	No increase in size in excluded aneurysms

Table 2 (continued)

Study	Number Of Centers	Graft	N*	Technical Success	Perioperative Mortality	Complications**	Follow-Up†	Conversion+	Overall Mortality††	Late Expansion And Rupture
Chuter, 1996	7	G-C	41 (t, bi)	73% within 1 week post-op	7.5%	2.5-12.5%	15m	22.5%	7.5%	—
Nasim, 1996 (may overlap with Balm)	1	EVT, Pz-PTFE	10 (7 t, EVT; 3 ta)	50% before discharge 60% at 6 weeks post-op after spontaneous seal	10%	30%	up to 1y	20%	10%	—
May, 1997a (may overlap with Balm)	1	W-Y Par EVT S G-C	121 (54 t. 26 ai/af, 41 bi)	83% (counting "early" leaks)	5.0%	0.8-3.3% (36 total), local-vascular 1.6-4.1% (18 total) systemic-remote	up to 4.5y	16%	12.4%	—
Lawrence-Brown, 1996	1	G-D	21 (bi)	95% immediately post-op 81% including leaks detected by 6 week follow-up	4.8%	4.8-14.3%; in 85% stent across renal artery ostia	30w (4-60w)	0%	4.8%	No size increase

* t, tubular or straight graft; ta, tapered; bi, bifurcated; ai, aortoiliac; af, aortofemoral.
** Does not count leaks. When no overall rate was presented, the range for individual complications is provided.
† Mean or median; d, days; w, weeks; m, months; y, years.
†† Mortality from procedure to follow-up, irrespective of whether or not death due to procedure.
+ Conversion to an open procedure from time of initial procedure to follow-up.
‡ Retrospective case series.

C. Comparative Studies of Endovascular Repair of Abdominal Aortic Aneurysms

May et al. (1997b) conducted a nonrandomized trial comparing 43 patients with endovascular repair to a contemporaneous control group of 67 patients who were managed conservatively. Data were obtained from a register and were limited to patients with AAAs 5 cm or less in diameter. The purpose of the trial was to determine whether a randomized controlled trial comparing endovascular repair versus no treatment could be justified for small aneurysms. The endovascular group cases are also included in May et al. (1997a); outcomes from this case series are summarized in Table 2.

The comparative trial had methodological limitations. No primary outcome variable was defined and no statistical tests were used in comparing the study groups. The trial did not control for the range of different early prototype grafts (Parodi, EVT, White-Yu, Stentor, and Chuter) used, or various configurations. The trial did not take into account any technical modifications in graft design or procedural techniques which occurred during the 4 year span covered by the study. Although patient characteristics (age, sex) and comorbidities appeared to be somewhat similar between the endovascular and no treatment groups, they were not subjected to statistical testing.

Total mortality (perioperative and late mortality) in the endovascular group was 7.0%, and in the no treatment group 3.0%. In the endovascular group, 23% of patients had systemic/remote complications, compared to 4.5% in the no treatment group. In the endovascular group, 14.0% were converted to an open operation, whereas in the no treatment group 16.4% had their AAA repaired (10.4% endovascularly and 6.0% with an open procedure). Methodological limitations preclude definitive conclusions from this study. Although mortality and complications appeared to be higher in the endovascularly treated group, and after the endovascular procedure a significant proportion had to undergo an open surgical procedure. In the opinion of the investigators, the results did not support conducting a randomized controlled trial until the complication rate with endovascular repair could be lowered.

Investigators from the same center also conducted a nonrandomized trial with historic controls (White et al., 1996b). The study compared endovascular repair cases with standard open surgery cases including only cases which could have been treated with either procedure. Data on endovascular procedures had been collected prospectively, but data from cases with open surgical procedures were collected retrospectively for the year preceding the center's initiation of endovascular procedures.

Methodological limitations of the study include the retrospective data collection, small numbers of cases (27 in the endovascular group and 28 in the historical control group), no controlling for the different grafts and various configurations used or alterations in endovascular devices and procedural techniques during the two and a half years represented in the data, and a range of early prototype graphs represented.

No statistically significant differences were found between the two compared groups on demographics (age, sex) and a relatively few (7) risk factors, dimensions, and morphologic condition. Likewise, there were no statistically significant differences for most

comparisons between the two groups on various outcome measures, including perioperative and late deaths. Blood loss was less after endovascular repair as was the duration of ICU admission. With an intent-to-treat analysis (which included cases converted to open repair), the only statistically significant difference noted was a higher incidence of local/vascular complications in the endovascularly treated group. However, given the small sample sizes, the lack of more statistically significant differences might be attributable to lack of statistical power rather than the absence of clinically significant differences.

D. Factors Associated with Improved Treatment Outcomes

Little systematic research has been conducted on factors which can affect the outcomes of endovascular repair of AAAs. Wain et al. (1998) report on the occurrence of endoleaks in a case series of 46 patients who underwent 47 endovascular procedures (no other outcomes were studied, hence this study is not included in Table 2). Patients with persistent endoleaks risk aneurysm rupture (Lumsden et al., 1995; Wain et al., 1998). Wain et al. (1998) found that endoleaks occurred more often in cases where the aneurysm had proximal neck lengths of 2 cm or less compared to longer neck lengths (50% versus 16% respectively; $P < 0.05$). Although not statistically significant, there was an indication that endoleaks were more likely in cases with patent aneurysm side branches and in cases with severe aneurysm neck calcification, and less likely in cases with iliac occlusive disease.

May et al. (1996) compared the outcomes of cases (n=19) with AAA characteristics deemed ideal for endovascular repair to cases (n=21) without these characteristics. Ideal characteristics included a proximal neck of 2 cm or longer, a distal neck of 1.5 cm or longer between the aneurysm and the aortic bifurcation, and a minimum iliac artery diameter on either side of 8 mm. Cases without these characteristics had associated aneurysms of the iliac arteries, lack of a distal neck, or a narrow iliac artery. The number of complications were statistically significantly higher in the second, more complex group as were operative time and hospital stay. The second group also had a higher incidence of conversion to open procedure and deaths, but these did not achieve statistical significance.

The Wain et al. (1998) and May et al. (1996) studies suggest that aneurysm morphology can affect procedural outcomes, but in accordance with the opinion of Zarins and Harris (1997), the nature of this relationship is not clear. Methodological limitations of the Wain et al. (1998) and May et al. (1996) studies included small numbers of cases, the inclusion of a range of early prototype devices, and no adjustment for differences between compared groups which could have affected outcomes, such as severity of comorbid conditions.

The case series by Blum et al. (1997a) presented data separately for cases with morphologically different aneurysms: (a) aneurysm with proximal and distal aortic necks more than 10 mm in length and less than 25 mm in diameter without involvement of the iliac arteries, and (b) aneurysm involving the aortic bifurcation with proximal neck more than 10 mm in length and less than 25 mm in diameter, with a common iliac artery less than 12 mm in diameter, and aneurysm with a proximal neck more than 10 mm in length

and less than 25 mm in diameter and involved the common iliac arteries and the iliac bifurcation. Blum et al. (1997a) did not directly compare these two groups, but technical success (after spontaneous seals and interventions) was comparable, 86% and 87% respectively, although in the more complex aneurysm group average operative time was longer (105 versus 88 minutes) as was average hospital stay (11.5 versus 6.75 days).

Dorffner et al. (1997) presented data separately for cases who received a bifurcated graft and patients who received a straight graft, but did not directly compare the cases. Intraoperatively, immediate post-operative technical success was 88% in the bifurcated graft group and 91% in the tube graft group, and on follow-up technical success was 88% and 100% respectively.

VII. DISCUSSION

Endovascular repair of infrarenal AAAs offers the possibilities of reduced postoperative morbidity and pain, less compromise of gastrointestinal function, earlier return to a normal diet, improved respiratory function, earlier mobilization, earlier return to normal activity, less ICU use, shorter hospital stays, and potentially lower costs (White et al., 1996b). Some case series, in particular the largest by Blum et al. (1997a), provide encouraging findings that some of these possibilities are achievable. However, given the methodological limitations, the existing literature cannot definitively answer the basic question of whether endovascular repair is preferable to alternative interventions for patients eligible or ineligible for standard open surgical procedure, or patients with small aneurysms.

Studies were predominantly case series which is a relatively weak study design that does not provide strong evidence of effectiveness. Studies varied in patient selection and the type of endovascular graft used, both in terms of manufacturer and in design. There was no uniform reporting of patient severity of illness, which varied by study, and little uniformity in the reporting of study outcomes. No standard criteria for patient selection for endovascular AAA repair have been developed.

Immediately post-operatively, technical success varied from 48-95%, but with additional endovascular interventions or spontaneous sealing of endoleaks during or after hospitalization technical success improved to 60-97%. By follow-up, the duration of which varied by study, 0-30% of patients had undergone an open surgical procedure, most often a conversion to a standard open surgical repair. The largest case series achieved 97% technical success and a 1.9% conversion rate (Blum et al., 1997a).

Perioperative mortality ranged from 0-36% (average of 8% across all case series), and overall mortality on follow-up ranged from 0.6-23% (average of 10%). In the largest case series, perioperative and overall mortality were both 0.6% (Blum et al., 1997a). Although it is inviting to compare these outcomes to standard open surgical repair, that is a hazardous comparison because of the lack of equivalence in patients treated and the initial nature of the case series.

Studies did not share a standard format for reporting complications. For studies reporting the data, from 10-31% of patients had complications, and individual complications occurred in 0.6-

20% of patients. In the largest case series, 10% had complications (8% considered minor, and 2% major complications). Of particular concern is microembolization because it may cause multiorgan failure. If aneurysms were successfully excluded, there appeared to be no subsequent increase in aneurysmal size and possibly a decrease, at least in the short-term. However, long-term follow-up is necessary to detect the possibility of late developing endoleaks and rupture.

There has been little systematic study of variables related to health care costs. Expected lengths of stay ranged from 3.8 to 11.5 days.

Comparative studies of endovascular repair to alternative interventions are very few, and with significant methodological limitations. No definitive conclusions can be drawn from the existing studies. It may be that endovascular repair is associated with less blood loss and shorter duration of ICU stay, compared to standard surgery, and with a higher incidence of local/vascular complications. Little systematic research also has been conducted on factors which can affect the outcomes of endovascular repair of AAAs. Short proximal aneurysm neck length appears associated with an increased risk of endoleaks, whose presence risks aneurysmal rupture. More complex aneurysms may be associated with a higher risk of complications, as well as longer operative time and hospital stay.

VIII. CONCLUSIONS

For patients who are eligible for standard open surgical repair of their AAAs, does endovascular repair result in lower morbidity, mortality, and/or health care costs than standard treatment?

Existing studies are methodologically inadequate for determining if endovascular repair of infrarenal AAAs results in lower morbidity, mortality, and/or health care costs compared to standard open surgical repair for patients who eligible for either procedure.

For patients who would otherwise be eligible for standard open surgical repair of their AAAs, were it not for the presence of severe comorbid medical conditions, does endovascular repair result in lower morbidity, mortality, and/or health care costs than medical management?

Existing studies are methodologically inadequate for determining if endovascular repair results in lower morbidity, mortality, and/or health care costs than medical management for patients who are ineligible for standard open surgical repair due to the presence of severe comorbid medical conditions.

For patients with small, asymptomatic, nonexpanding AAAs (less than 5 cm) who have favorable morphology for endovascular repair, does endovascular repair result in lower morbidity, mortality, and/or health care costs than medcal management followed by standard open surgical repair when indicated?

For patients who have small, asymptomatic, nonexpanding AAAs, existing studies are methodologically inadequate for determining if endovascular repair results in lower morbidity, mortality, and/or health care costs than watchful monitoring with medical management followed by standard open surgical repair when indicated.

IX. ONGOING TRIALS AND CLINICAL TRIAL RESOURCES

Device manufacturers

As of this writing (December, 1998), there are approximately 10 to 15 manufacturer sponsored clinical studies underway which have an FDA Investigation Device Exemption (IDE), and a comparable number of investigator sponsored studies with an IDE. By law, any information about these studies cannot be released by the FDA.

VA Cooperative Studies Program

VA has funded and is conducting two studies on AAAs through the Cooperative Studies Program of the Office of Research and Development. The first is a randomized, multicenter trial, called the Aneurysm Detection and Management (ADAM) Study, which is comparing immediate, elective repair of AAA to follow up and surgery if AAAs enlarge rapidly or become symptomatic (Lederle et al., 1994). The second study, entitled "The Natural History of Large Abdominal Aortic Aneurysms," will determine the incidence of rupture and rupture death by AAA size in AAA of at least 5.5 cm in diameter.

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