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Debate: Whether young, good-risk patients should be treated with endovascular abdominal aortic aneurysm repair

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As endovascular abdominal aortic aneurysm repair has become increasingly prominent in our vascular surgery practices, the discussion regarding long-term durability continues. The initial randomized trials that enrolled patients almost 10 years ago revealed a short-term survival advantage with endovascular abdominal aortic aneurysm repair at the expense of a higher reintervention rate and loss of that initial survival advantage in the longer term. Continuing and healthy debate over the practical importance of these findings has resulted in somewhat differing practice patterns on either side of the Atlantic. This debate explores the issues surrounding whether younger, good-risk patients with a long life expectancy should be treated with endovascular repair. (J Vasc Surg 2013;58:1709-16.)

PART I: YOUNG AND GOOD-RISK PATIENTS SHOULD BE TREATED WITH ENDOVASCULAR REPAIR

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Endovascular repair of infrarenal aortic aneurysms (EVAR) has significantly improved during the past 22 years since JuanParodi et al[1] first reported their historic cases. Several commercially available devices are now approved for EVAR throughout the world. Use of this technique for infrarenal abdominal aortic aneurysm (AAA) repair varies worldwide but has been shown to be up to 80% of all AAA repairs done in the United States.[2,3] Despite its widespread use in most patients, there are still subgroups in which the benefits of endovascular repair have not clearly been demonstrated. The subgroup most often debated is the young patient with good risk factors, which serves as the basis for the following debate.

Although initially thought to be a rare occurrence, this is an important controversy, because in the United States, >5000 patients a year aged between 50 and 64 years undergo aneurysm repair.[4] There are substantial reasons why young patients with good anatomic characteristics and low comorbidities are very good candidates for EVAR, and it should be offered to this subgroup.

PERIOPERATIVE OUTCOMES AND EXPERTISE

Several large randomized controlled trials have compared EVAR with open surgical repair (OSR). The Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1),[5] Dutch Randomised Endovascular Aneurysm Management (DREAM),[6] and Veterans Affairs Open vs Endovascular Repair (OVER) trials[7] showed lower 30-day mortality in patients undergoing EVAR compared with OSR. It should be noted that the first two studies began enrollment nearly a decade ago. Since that time, additional device advances, technique improvement, and understanding in management of patients has occurred.

The Anévrisme de l'aorte abdominale: Chirurgie vs Endoprothèse (ACE) trial,[8] a prospective trial of low-risk to medium-risk patients, showed equivocal perioperative mortality between OSR and EVAR. One significant criterion for involvement in the ACE trial was expertise in both EVAR and OSR. On the basis of several articles,[9-11] including the ACE trial, this is generally defined as >30 cases per year. Currently, most vascular specialists outside of major aortic centers rarely perform this volume of cases.[12] The applicability of these outcomes to low-volume centers is therefore called into question. Most

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practicing physicians will only see a few young patients a year with aneurysmal disease; therefore, their outcomes would most likely not be the same as those conducted in the ACE trial. Thus, the results of the ACE trial are only valid when comparing outcomes at large aortic centers where >30 cases per year are performed. This is further supported by the fact that none of the aforementioned EVAR trials showed a statistical difference in medium-term to long-term all-cause mortality rates between EVAR and OSR.[7,8,13,14] Thus, it is beneficial and logical for the practicing physician in a low-volume center to perform the procedure he or she is most familiar with. In almost all situations, that would be EVAR based on today's training and experience paradigm.[12]

Medical therapy has also improved outcomes for EVAR. A recent study showed an increased rate of sac regression after EVAR in patients who were receiving statin therapy.[15] Other studies have demonstrated a decrease in all-cause mortality with improved medical management, including statin therapy, during the past decade.[16] This suggests that some of the outcome and mortality data from the trials of a decade ago may need to be reinterpreted if the patients were not all receiving optimal medical therapy. Other medications, such as doxycycline, have shown promise in improving outcomes after EVAR as well.[17] As the importance of medical management of aneurysm patients becomes more widely known, durability of repair in patients with EVAR will likely further improve and become inconsequential in choosing the best method of repair.

SECONDARY INTERVENTION RATES

Although the secondary reintervention rate is higher for EVAR than for OSR, accurate data collection is difficult. Most EVAR interventions are typically managed by endovascular means. Patients who undergo OSR typically have more OSR-related complications, such as bowel obstructions and hernias, which lead to in-patient hospitalizations.[18] In addition, there seems to be a decrease in secondary interventions from EVAR as experience grows, advanced devices become available,[19] and patient selection improves. Secondary intervention rates as low as 7.4% have been achieved.[20] This is especially true for open conversion rates, which have now been reported to be anywhere from 1.6% to 2.6%.[21,22] There has also been recent data published from the United Kingdom that younger patients treated with EVAR may have similar rates of secondary interventions compared with OSR if evaluated after several years.[23]

IMPACT OF PATIENT SELECTION

The consideration of a patient's risk factors includes physiologic, anatomic, and patient-specific risk factors. Patient selection plays a critical role in determining outcomes for EVAR. Implantation of an endoprosthesis into a preaneurysmal neck or outside the instructions for use (IFU) does not convey the same protection against rupture and long-term outcome compared with the published clinical trial results. To be ideal candidates, patients should have appropriate anatomical criteria for the specific endograft.

However, a large number of endografts inserted over the past decade have been outside their defined IFU. Analysis of a large cohort of these patients has shown an alarming rate of aneurysm sac enlargement, a high percentage of type I endoleaks, and an increase in all-cause mortality.[24,25] Patients with anatomy within the IFU have lower reintervention rates.[24] Because more advanced devices in the United States have not generally been available until recently, many patients have been treated outside their IFU. Although the intraoperative angiogram reveals sufficient aneurysmal exclusion in most instances, it is not until subsequent follow-up surveillance that many problems are identified.[26]

One of the most important aspects of EVAR is the crucial importance of follow-up evaluation. Young patients who are not willing to commit to long-term follow-up are not good-risk patients for EVAR. Although the risk of postoperative migration and endoleak is small, it still exists. Patients who do follow-up on a regular basis should be less likely to experience ruptures from undiagnosed type I or type III endoleaks.

PATIENT PREFERENCE

No clinical trial to date has demonstrated a detriment to the patient when performing EVAR with respect to long-term mortality. In addition, most studies demonstrate a distinct advantage of EVAR during the initial years after repair. It is these two facts that drive most patients in their decision. Most patients, given the choice, will invariably choose EVAR over OSR. Several studies have demonstrated that patients focus on the lower perioperative morbidity and mortality and the shorter hospital stay with EVAR, even weighing the risk of higher future secondary interventions.[27-29] This also holds true for younger patients because they may still be employed and want to return to work as soon as possible to provide for their families. This increased patient productivity may help reduce the overall economic effect of EVAR compared with OSR and should be considered when comparing these different techniques.

COSTS

Cost-comparative analyses between OSR and EVAR have been attempted, but determining the economic effect is difficult unless loss of productivity and other factors are included in the analysis. Many older studies have stated that EVAR is less cost-effective than OSR, as determined from an examination of device and hospital charges.[30] However, a recent publication from the OVER trial showed that EVAR costs less in the perioperative period than OSR.[7] When the initial 2-year postoperative period was examined, there was no difference in cost. The outcome of this analysis is also constantly changing because supply and demand, as well as hospital costs, change depending on the economic situation.[7] Additional costs are incurred during the follow-up period because axial imaging studies are used to assess the effectiveness of EVAR.

There has been some concern that computed tomography (CT) scans may also increase the risk of induced malignancy; however, most patients with aneurysmal disease, even if they are young, would rarely live long enough to be exposed to this increased risk. As better knowledge of endograft behaviors and factors that impact endoleak complications are identified, alterations in follow-up have occurred. Many centers have altered the number of CT scans acquired for surveillance, because minimum benefit is added if the initial result of the postoperative CT scan is found to be normal.[26] Institutions have also begun using a combination of X-ray imaging and color duplex ultrasound imaging for postoperative evaluation, further decreasing the costs after implantation.[31,32]

LIFE EXPECTANCY OF YOUNG PATIENTS WITH ANEURYSMS

A recently published report from the Nottingham group looked at midterm survival in young patients treated with EVAR and OSR.[23] When patients treated at their institution since 1995 were analyzed, nearly 40% of patients who were treated with OSR or EVAR died ≤6 years of their surgery; however, most of these patients did not die of aneurysmal disease. In patients who were treated with commercially available endografts, there was a trend toward improved long-term survival vs earlier custom made endografts (hazard ratio, 2.9; 95% confidence interval, 0.9-10; $P = .08$) and open repair (hazard ratio, 3.1; 95% confidence interval, 0.9-10.3; $P = .07$); however, this was not statistically significant.[23] Patients with aneurysmal aortas may not have the same life expectancy as patients in the general population, and this may be a risk factor for early mortality.

CONCLUSIONS

In young, motivated patients with good anatomic and physiologic risk factors, EVAR is as good as if not better than OSR when early mortality is factored into the equation. OSR outcomes are particularly dependent on the surgeon's experience, and that has become extremely limited in recent years. There are potential risks of future secondary interventions with EVAR; however, most of these are also repaired endovascularly, and the chance of needing an open surgical revision is extremely low. The costs of EVAR and OSR are becoming comparable, especially when societal effect is considered, as hospital costs increase, graft costs decline with competition, and alternative postoperative surveillance occurs. As medical management, operator expertise, and endograft technology improve, the long-term outcomes of endovascular therapy should also continue to improve.

Young patients with aneurysms may also not have the same long-term survival as the general population and may benefit from a procedure with lower perioperative risk. The current data suggest that in young, good-risk patients, the long-term mortality in EVAR and OSR are equivocal. However, there tends to be less perioperative mortality in EVAR, especially if the center's OSR volume is limited. Therefore, only in centers of excellence, should both OSR and EVAR be offered to all young, good-risk patients to allow the patients to decide. In almost all cases, they will choose EVAR. In all low-volume practices, EVAR should be preferentially offered.

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PART II: YOUNG AND GOOD-RISK PATIENTS SHOULD NOT BE TREATED WITH ENDOVASCULAR REPAIR

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Surgical repair is indicated for large asymptomatic abdominal aortic aneurysms (AAAs) in patients with an acceptable operative risk. After the landmark report by Parodi et al,[1] early results of randomized controlled trials (RCT)[2-4] have demonstrated lower perioperative mortality after endovascular aortic aneurysm repair (EVAR) compared with open repair (OR). Next to these results, the number of patients receiving EVAR exceeded those treated by OR.[5] However, some years later, the midterm results of these RCTs have shown equivalent mortality after EVAR or OR, with a significantly higher reintervention rate after EVAR failing to support evidence favoring its use as first-line therapy, especially in young or fit patients, or both.[6-8] The goal of this debate is to compare early and late outcomes in patients aged <65 years receiving OR or EVAR.

Table I. Reasons for skepticism regarding endovascular aneurysm repair (*EVAR*) as a first-line therapy for young patients

1. Failure to improve survival during long-term follow-up
2. New devices are more likely used outside IFU with worse effects on durability
3. Longer life expectancy of young patients increases the risk of endograft-related complications after EVAR including the risk of late AAA rupture
4. Need for follow-up by CT scan with radiation exposure and increased cancer risk
5. EVAR is not cost-effective for patients fit for surgery

AAA, Abdominal aortic aneurysm; *CT,* computed tomography; *IFU,* instructions for use.

THE PROBLEM

During the last decade, EVAR has radically changed the approach for treating AAAs. In the United States, EVAR rose from 11,171 procedures in 2001 to 21,725 procedures in 2006.[5] The same paradigm shift was observed in France, regardless of the patient's age, with 777 EVAR procedures in 2006 compared with 372 in 2001.[9] Currently in the United States, 60% of AAAs are repaired by EVAR.[10] But the use of EVAR in young patients calls into question the long-term benefits and durability of this procedure. To answer these questions, analyses of the survival rate, the risk of device-related complications, including radiation exposure by computed tomography (CT) scan,[11] and cost-effectiveness with regard to devices and reinterventions are essential (Table I).

THE EVIDENCE

Comparison of EVAR with OR in patients deemed fit for surgery is available in four RCTs (Table II). The Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) trial involved 1252 patients from 1999 to 2004[8] and demonstrated an initial benefit in aneurysm-related mortality in favor of EVAR at 6 months. But this benefit vanished after 4 years, and the risk of aneurysm-related death, ∼7%, was equivalent for the two groups at 6 years. In addition, there were more reinterventions and complications in the EVAR group. At 8 years, the complication rate was 52% for EVAR vs 15% for OR ($P = .01$), and the

Table II. Randomized controlled trials (RCTs) comparing endovascular aneurysm repair (*EVAR*) with open repair (*OR*) for abdominal aortic aneurysms (AAAs)

References	*Patients, No.*	*Age,[a] years*	*Follow-up, years*	*Perioperative mortality*	*Outcomes*
EVAR-1, 2005,[3] 2010[8]	OR: 539	74 ± 6.1	6	OR: 6.2%	Overall aneurysm-related death: 1.2/100/y with OR vs 1/100/y with EVAR ($P = .73$)
	EVAR: 543	74.2 ± 6.0		EVAR: 2.1%	Overall mortality: 7.1/100/y with OR vs 7.2/100/y with EVAR ($P = .61$)
				($P = .001$)	Reintervention rate: 1.7/100/y with OR vs 5.1/100/year with EVAR ($P < .001$)
					AAA rupture: 0 after OR vs 25 after EVAR (4.6%)
DREAM, 2005,[4] 2010[7]	OR: 174	69.6 ± 6.8	6.4	OR: 4.6%	Overall mortality: 30.1% with OR vs 31.1% with EVAR (NS)
	EVAR: 171	70.7 ± 6.6		EVAR: 1.2%	AAA-related mortality: 4.49% with OR vs 1.15% with EVAR ($P < .001$)
				($P = .01$)	Reintervention rate: 18.1% after OR vs 29.6% after EVAR ($P = .003$)
OVER, 2009,[2] 2012[6]	OR: 437	70.5 ± 7.8	5.2	OR: 3% ($P = .004$)	Overall mortality: 33.4% after OR vs 32.9% after EVAR (NS)
	EVAR: 444	69.6 ± 7.8		EVAR: 0.5%	AA-related mortality: 3.7% after OR vs 2.3% after EVAR (NS)
					AAA rupture: 0 after OR vs 6 (1.4%) after EVAR ($P = .03$)
					Reintervention rate: 17.8% after OR vs 22.1% after EVAR (NS)
ACE, 2011[12]	OR: 149	70 ± 7.1	3	OR: 0.6%	Overall mortality: 8% after OR vs 11.3% after EVAR (NS)
	EVAR: 150	68.9 ± 7.7		EVAR: 1.3%	AAA-related mortality: 0.6% after OR vs 4% after EVAR (NS)
				($P > .05$, NS)	AAA rupture: 0 after OR vs 3 (2.0%) after EVAR (NS)
					Reintervention rate: 2.7% after OR vs 16% after EVAR ($P < .0001$)

ACE, Anévrisme de l'aorte abdominale: Chirurgie vs Endoprothèse; *DREAM,* Dutch Randomised Endovascular Aneurysm Management; *EVAR-1,* Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm; *NS,* not significant; *OVER,* Veterans Affairs Open vs Endovascular Repair.
[a]Data for age are presented as mean ± standard deviation.

reintervention rate was 28% for EVAR vs 10% for OR. In addition, 25 aortic ruptures, with 18 deaths, occurred in the EVAR group (4%) and none in the OR group. These late ruptures outweighed the initial benefits of EVAR.

The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial[4,7] demonstrated the same initial benefits for EVAR, with a lower rate of in-hospital mortality (1.2% vs 4.6% for OR; $P < .05$) but with a higher rate of cardiovascular-related death in the EVAR group at 1 year, which outweighed its initial benefit in survival at 2 years. There were also more reinterventions in the EVAR group (29.6% for EVAR vs 18.1% for OR; $P = .03$), with an increased rate of reinterventions after 4 years in the EVAR group, 75% being related to stent graft failure.

The Veterans Affairs Open vs Endovascular Repair (OVER) trial[2,6] also showed a significant decrease in hospital mortality in favor of EVAR (0.5%) vs OR (3%; $P = .004$), which remained significant at 3 years. In contrast to the EVAR-1 and DREAM trials, there was no difference in the rate of reinterventions between EVAR and OR during this study. Mortality in this trial was analyzed according to several risk factors, including age, and showed an advantage for EVAR in young patients (aged <70 years) compared with OR even if a higher incidence of cancer in the OR group could explain this difference and even though six AAA ruptures with three deaths occurred in the EVAR group.

The results of the Anévrysme de l'aorte abdominale, Chirurgie vs Endoprothèse (ACE) trial[12] comparing OR (n = 149) with EVAR (n = 150) in low-risk to moderate-risk patients showed no significant difference in in-hospital mortality between the two groups (0.6%

for OR vs 1.3% for EVAR; $P = 1.0$). However, rate of reinterventions was higher in the EVAR group (16% vs 2.7%; $P < .0001$), with three ruptures resulting in two deaths vs no rupture in the OR group. The absence of early benefit of EVAR in this trial was explained by the low mortality rate of the OR group.

What have we learned from these studies? These four RCTs did not investigate the performance of EVAR among different age groups, and the mean age of the patients in these RCTs did not match with the definition of young patients and call into question the applicability of their conclusions for young patients. Other studies have concentrated exclusively on the elderly population.[13,14] However, with the development of AAA screening, there will surely occur an increase of young patients eligible for AAA repair. In a recent retrospective study of data extracted from the American College of Surgeons National Surgical Quality Improvement Program data files, Gupta et al[15] compared the results of EVAR in patients aged ≥60 years vs younger patients. This study failed to show any early benefit in mortality for EVAR (1.1%) vs OR (0.4%; $P = .22$). However, major complications were significantly higher for OR (18.8%) than for EVAR (9.2%; $P = .0004$). This contemporary study demonstrates that 30-day mortality after OR was comparable to 30-day mortality after EVAR in patients aged <60 years.

In association with age, women have been reported to have a higher risk for complications after AAA repair.[16] In this study involving patients aged <60, female gender was not associated with 30-day mortality or morbidity on multivariate regression analysis. A recent study showed that women with AAAs were significantly older than men and less likely to undergo EVAR as a result of a less favorable vascular anatomy.[17] These data suggest a limited effect of female gender on outcome for young patients.

TECHNICAL IMPROVEMENTS OF EVAR

The use of first-generation stent grafts and early experience of EVAR are significant factors that have resulted in some of the complications reported in EVAR-1, DREAM, and OVER.[14] Technical improvements of EVAR securing the sealing zone more precisely and decreasing stent graft-related complications call into question the use of these results nowadays. Two pivotal studies with recent stent grafts have reported a rate of device-related complications of <3%, with only one rupture during follow-up.[18,19] Less promising in these studies is the 15% rate of type II endoleak reported in the Zenith pivotal study[19] and the 15% rate of sac enlargement without visible endoleak in 15% of the patients in the Excluder Low-Permeability Pivotal Study.[20] These recent data still call into question the efficacy of stent grafts, even with the newest-generation devices.

Moreover, a worrisome recent report by Schanzer et al[21] showed an incidence of post-EVAR aneurysmal sac enlargement of 41% at 5 years despite the use of new-generation stent grafts. The main reason for this adverse outcome was partially related to a more liberal indication of EVAR exceeding the instructions for use. More than the patient's preference, appropriate anatomic criteria are critical to decide between OR and EVAR in this young population.

Stent graft outcome in young patients remains a concern if they live long enough. The main limitation in recommending EVAR in young patients is the risk of stent graft-related complications due to their longer life expectancy. Some authors, citing the results of the Multicentre Aneurysm Screening Study (MASS) with 11% of patients dying ≤4 years of their aneurysm operation,[22] consider that the life expectancy of these young patients is already poor. Most are likely to die from coronary disease, cancer, or other cardiovascular causes. A recent study by Darwood et al[23] reported a 42% mortality at 2 years in patients with a 4- to 5-cm AAA. They speculate that even though young, these patients with AAAs have a short life expectancy and that a stent graft was all that was required. Perhaps, the main issue in these young patients with AAAs is not the choice of EVAR or OR but rather the prevention of cardiovascular complications with a better medical management, including statin therapy.

However, there is no level I evidence to support this hypothesis, and long-term RCTs have shown that the difference in morbidity between OR and EVAR in the DREAM and in the EVAR-1 trials was partially explained by a higher rate of reintervention after EVAR,[7,8] even when accounting for an underestimation of the late complications after OR.[24] These data suggest that young patients do survive long enough to face stent graft-related complications, including AAA rupture, which remains three times more frequent after EVAR than after OR.[24]

It is also clear that prior EVAR does not confer any protective effect in the setting of a ruptured AAA.[25]

The risk of ruptured aneurysm after EVAR underscores the need for regular monitoring by CT scan, with the risk of radiation exposure during many years of follow-up. A CT scan with contrast media at 1, 6, and 12 months, and annually thereafter, is tantamount to a total effective radiation dose of 145 to 205 mSv over 5 years, which translates into a lifetime cancer risk of 1% for a 50-year-old patient.[11] To limit radiation exposure, some authors recommend a "light" follow-up based on the results of an early CT scan.[26] The most promising solution consists in the use of contrast-enhanced ultrasound imaging, which has demonstrated comparable sensitivity and specificity with the CT scan in the detection of endoleak after EVAR.[27,28] Up to now, the main limitation to its widespread use remains the experience of the operator.

Finally, cost issues also play an important role when discussing the use of stent grafts in young patients. EVAR-1[8] found that the average cost of aneurysm-related procedures after 8 years of follow-up was higher for EVAR ($23,153) than for OR ($18,586). This raw analysis could be unfair, because the costs of some laparotomy-related complications were not taken into account in the cost-analysis. However, even in recent series, EVAR continues to cost more than OR,[29] and an updated report from the French Health Agency (Haute Autorité de santé) designed to evaluate the cost-effectiveness of EVAR in France concluded that EVAR was not a viable economic solution, especially in patients fit for surgery.[30]

CONCLUSIONS

There is no evidence in the recent literature to support EVAR as the first-line therapy in young patients aged <60 years. OR remains the best option for most of them.

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