Review

A clinical and ethical review on late results and benefits after EVAR

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HIGHLIGHTS

- The long-term results after endovascular repair (EVAR) for abdominal aortic aneurysms (AAA) are still considered one of the main limitations of this treatment option.
- This paper is a comprehensive review of the current literature on long-term mortality after EVAR procedures.
- An analysis on informed consent for EVAR from a non-surgical point of view is reported for the very first time.

ARTICLE INFO

ABSTRACT

Introduction: The aim of this review is to assess if late mortality after endovascular repair (EVAR) of abdominal aortic aneurysms (AAA) is a real problem, and whether it could be an issue in the case of medical litigation.
Material and methods: A review of all English language literature was performed on PubMed web-site, looking for all papers reporting EVAR long-term mortality rate. EVAR performances were reviewed also from an ethical and medico-legal point of view, based on current Italian laws.
Results: Mono-centric studies, and international registers suggest that today EVAR offers similar (if not better) results than open repair (OR) in the treatment of AAAs with standard and complex anatomies, even if performed outside the devices-specific instructions for use. In contrast, large randomized trials, and consequently current guidelines, suggest that EVAR still has an ancillary role compared to OR, only to be used for highly selected patients.
Recently, specific litigation cases on surgical options related to the treatment of aortic aneurysms has developed. The informed consent process needs to include not only mortality and major complications related to the procedure but also the chance of patients' outcomes. For those reasons, the generic nature of informed consent has been criticized.
Conclusions: No conclusive data is currently available to assess the initial question of late mortality after EVAR but results are still improving. In the meantime, widespread use of EVAR as first choice for treating AAA may only be acceptable in high-volume centres validating their results by a strict follow up protocol.

Contents

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1. Introduction

Since the introduction of endovascular aortic repair (EVAR) [1] for abdominal aortic aneurysms (AAAs) treatment in the early 1990s, progressive improvements have been achieved in stent-graft technology, and surgeons' experience has considerably increased.

Reports from individual centres document that up to 60—70% of infrarenal AAAs can be treated with commercially available endovascular devices [2,3]. The aspiration of offering a less invasive procedure to patients with larger aneurysms and multiple comorbidities is reflected in the changing trends in aneurysms repair, with EVAR constituting an ever-increasing proportion of elective and emergency surgery for AAAs [4].

Despite these considerations and the diffusion of EVAR, evidences and guidelines (as well as judges' decisions in case of medical litigation [5—7]), are based on the conclusions of randomized clinical trials (RCTs), which only report an initial partial benefit for EVAR when compared to open repair (OR), and indicate EVAR only for highly compromised patients with suitable anatomies [8—10].

As a result, certain authors believe that EVAR is not the preferred approach in patients fit for OR and with long life expectancy, due to concerns about durability, reinterventions, surveillance requirements, and lack of late survival advantage [11]. Moreover, Brown et al. also suggested that although EVAR offers a clear 30-day mortality benefit over OR, this early benefit is not translated into a long-term survival advantage [12].

Nevertheless, improvements in EVAR have ensued from general developments in surgical techniques and peri-operative procedures [13,14], the advent of endovascular surgery, improvements in critical care and vascular anaesthesia, and the centralization of aortic surgery with specialist teams having high operative caseloads [10,15]. These findings are confirmed by the experience of high volume centres, sustaining the feasibility of the endovascular approach and suggesting that EVAR is the preferred treatment for AAA patients with standard and challenging anatomies [16—18].

The aim of this review was to assess whether late mortality after EVAR is a real problem, and whether it could be an issue in the case of medical litigations.

2. Review of the literature

In 2004 the results of the first two RCTs were published [8,9]. The EVAR-1 trial described a clear advantage of EVAR with respect to OR at 30 days. These results were obtained in patients judged fit for both procedures, aged at least 60 years with aneurysms of 5.5 cm or more in diameter. Greenhalgh and collaborators reported that 30-day mortality in the EVAR group was 1.7% (9/531) versus 4.7% (24/516) in the OR group (p = 0.009); the patients enrolled were treated between 1999 and 2003. Their results were interpreted as a licence to continue scientific evaluation of EVAR, but not to change clinical practice [8]. More enthusiastic conclusions came from the analysis of the DREAM trial. This trial reported an operative mortality rate of 4.6% in the OR group (8/174 patients) and 1.2% in the EVAR group (2/171 patients), in a series of patients treated between 2000 and 2003, resulting in a risk ratio of 3.9 (95% CI 0.9—32.9). The combined rate of operative mortality and severe complications was 9.8% in the OR group (17/174 patients) and 4.7% in the EVAR group (8/171 patients), resulting in a risk ratio of 2.1 (95% CI, 0.9—5.4). The authors concluded that EVAR was preferable to OR in patients who have AAA at least 5 cm in diameter. Nonetheless, long-term follow-up was demanded to determine whether advantage persisted [9].

One year later, both trials published their mid-term results [19,20]. In the EVAR-1 trial, years after randomisation, all-cause mortality was similar in the two groups (approximately 28%; p = 0.46), but a persistent reduction in AAA-related deaths was recorded in the EVAR group (4% vs 7%; p = 0.04). On the other hand, the proportion of patients with postoperative complications was 41% in the EVAR group and 9% in the OR group (p < 0.0001) [19]. In the DREAM Trial, two years after randomization, the cumulative survival rates were 89.6% for OR and 89.7% for EVAR and the cumulative rates of AAA-related death were 5.7% for OR and 2.1% for EVAR. This advantage of EVAR over OR was entirely accounted for by events occurring in the perioperative period, with no significant difference in subsequent AAA-related mortality. The rate of survival free of moderate or severe complications was also similar in the two groups at two years (65.9% OR vs 65.6% EVAR) [20]. Consequently, both trials concluded that EVAR offered no advantage with respect to all-cause mortality and the survival advantage only persisted in the first postoperative year.

Meanwhile, the EVAR-2 trial showed a considerable 30-day operative mortality in patients unfit for OR and treated by EVAR, with respect to no intervention [21], and increasing the uncertainty about EVAR.

A systematic review on electively treated AAAs, published in 2007 by Lederle and co-workers, reported no improvement in all-cause mortality and AAA-related mortality for repair, either OR or EVAR, versus observation, or in AAA-related mortality. Comparing OR and EVAR, the endovascular approach reduced 30-day mortality (relative risk, 0.33 [CI, 0.17—0.64]) but not mid-term (up to 4 years) mortality (relative risk, 0.95 [CI, 0.76—1.19]). The authors concluded that EVAR was associated with lower operative mortality than OR, similar mid-term mortality, and unknown long-term mortality, however they admitted that the data was derived from very few trials of small or moderate size [22].

The OVER trial, which included patients treated between 2002 and 2007, was published in 2010[10]. On the basis of a mean follow-up of 1.8 years, OVER results showed that perioperative mortality was lower for EVAR (0.5% vs 3.0%; p = 0.004), without any difference at 2 years (7.0% vs 9.8%, p = 0.13). Mortality after the perioperative period was similar in the two groups (6.1% vs 6.6%), however 4 late deaths in the EVAR group were AAA-related compared with none in the OR group. No differences between the two groups in terms of major morbidity, procedure failure, secondary intervention, AAA-related hospitalizations, or health-related quality of life

were recorded. Interestingly, no increased mid-term mortality after EVAR resulting in the loss of early survival advantage as shown in previous trials (EVAR-1 [8,19], DREAM [9,20]) was observed [10].

One year later, a French RCT (ACE Trial) reported quite different results with no differences between EVAR and OR. Although only low to intermediate risk patients were enrolled, OR and EVAR offered no difference in survival (96.5% vs 95.2% at 1 year, and 86.7% vs 86.3% at 3 years, respectively) or in major and minor complications (95.9% vs 93.2% at 1 year, and 85.1% vs 82.4% at 3 years, respectively) [23]. These results led to a change in point of view: EVAR was considered as feasible as OR without any advantages, even in the short term.

The same year, a new US study, with a 6-year follow-up on 45.652 Medicare beneficiaries undergoing EVAR or OR in the period 2001 to 2004 was analysed to clarify the late results of endovascular procedures. Throughout follow-up, overall reinterventions or readmissions rates were similar with the two repair methods but slightly more common after EVAR (7.6 vs 7.0/100 person-years; p < 0.001). Overall 30-day mortality with any reintervention or readmission was 9.1%.

EVAR patients had more AAA-related reinterventions (3.7% vs 0.9%; p < 0.001; mortality, 5.6%). Conversely, EVAR patients had fewer laparotomy-related reinterventions than OR patients (1.4% vs 3.0%; p < 0.001; mortality, 8.1%) and fewer readmissions without surgery (2.0% vs 2.7%; p < 0.001; mortality 10.9%). Overall, reinterventions and readmissions accounted for 9.6% of all EVAR deaths and 7.6% of all OR deaths in the follow-up period (p < 0.001). The authors concluded that reintervention and readmission were slightly higher after EVAR. Survival was negatively affected by reintervention or readmission after EVAR and OR [24].

Analysing results from UK trials, Brown et al. reported a significantly lower operative mortality for EVAR (in patients fit either for EVAR and OR) but no differences in all-cause or AAA-related mortality in the long term late due to endograft ruptures. However, they admitted the theoretical existence of subgroups of patients in whom EVAR could perform particularly well (younger [11] and very elderly patients [25]). EVAR was also found to offer a significant long-term benefit with respect to no intervention in terms of AAA-related mortality, though all-cause mortality was apparently unaffected [12].

Otherwise, the role of EVAR in young patients (<60-year-old) is controversial. Some authors believe that EVAR is not the preferred approach in younger patients with long life expectancies because of concerns about durability, reinterventions, surveillance requirements, and lack of an early survival advantage [26]. In contrast, Lee recently reported that EVAR offers durability and long-term survival similar to those of OR in younger patients, as long as aneurysm anatomy and manufacturers' instruction for use are adhered to [11]. In an experience with 169 patients (50/169, 30% undergoing EVAR) they reported 3 in-hospital deaths (0.5%) in OR group and none in EVAR group (p = 0.6) and early reintervention rates did not differ between the two groups (p = 0.66) nor did the long-term reintervention rate (p = 0.8). Overall mean life expectancy was 11.5 years, and there was no difference between the two groups (EVAR 9.8 vs OR 11.9 years; p = 0.09). Nor was there any difference in long-term survival rate between the two groups (EVAR, 78% vs OR, 85%; p = 0.09) [11].

In 2014, a new retrospective analysis was published by Thomas et al. on 632 patients electively treated for AAA (EVAR in 497 patients, 78.6%, and OR in 135, 21.4%). The authors reported that mortality at 30 days was less common in EVAR patients (1.6% vs. 6.7%, p < 0.004), but was not sustained (16.9% vs. 17.8%, p < 0.797); mean survival free from mortality was not different between the two groups (EVAR 6.14 vs OR 6.11 years, p = 0.378). They concluded that EVAR was associated with lower 30-day mortality rates;

however, this benefit was not sustained in longer term follow-up. No significant difference in major complications was found at 30 days or with long-term follow-up [27].

To shed light on the issue, several documents were published in 2015 addressing contemporary outcomes of EVAR [28–30]. Chang and co-workers published a review on 23.670 patients (EVAR in 51.7%) followed for a mean period of 3.3 years. At 30-day, all-cause mortality was higher for OR patients, while all-cause readmission rates were similar between the 2 groups. Beyond 30-day, EVAR repair patients had lower all-cause mortality up to year 3, beyond which they had higher all-cause mortality rates. However, unlike the clinical trial results, in their experience the survival advantage of EVAR repair was maintained until 3 years after the operation. Beyond 3 years, mortality was higher for patients who underwent EVAR repair. They speculated that this was explained by the willingness of the surgeons to undertake EVAR repair in older patients knowing that the less-invasive procedure is safer than OR [28].

Schermerhorn et al. published a retrospective study on 128,598 patients over 67 years of age treated in the period 2001–2008. Perioperative mortality was 1.6% in the EVAR group versus 5.2% in the OR group (p < 0.001), and the EVAR group, as compared with the OR group, also had lower rates of perioperative medical and surgical complications (p < 0.001), was more likely to have been discharged from hospital (p < 0.001), and had a shorter hospital stay (p < 0.001) than the OR group. The early survival benefit of EVAR persisted for approximately 3 years, after which time the estimated survival curves were similar.

All these results are coherent with those published by Verzini [16]; despite the indications of RCTs, the early survival advantage with EVAR among patients of all ages is estimated to persist through 7 years, and the outcomes of EVAR have been improving over time and will presumably continue to improve [30].

Notwithstanding mortality and reintervention rates represent the most investigated and reported issues in comparing OR and EVAR treatments for AAAs, several different factors (like post-operative renal failure [31], quality of life, and treatment satisfaction [32,33]) have been considered and should be reported. That's because, as better discussed later, a deep knowledge in these factors could drive patients' decision.

Post-operative kidney failure (KF) is considered a major complication, representing a well-recognized independent predictive factor for post-operative mortality. Moreover, dependence on dialysis seriously affect survivors' quality of life [31]. Although no conclusive data is currently available, results of EVAR seem promising in reducing the rate of post-operative KF compared to OR. That is in vulnerable subjects with severe comorbidities, and ruptured aneurysm. Possibly, these results could be explained by avoidance of aortic cross-clamping, and general anaesthesia [34,35].

Another interesting and debated difference between EVAR and OR is about the impact on quality of life, and patients' satisfaction after treatment. It had been assumed for long time that patients submitted to OR experienced greater negative impact on their quality of life in the early postoperative period than those who underwent EVAR, but then recovered and surpassed their EVAR counterparts as the physical aspects of the operation become less relevant and other factors such as concerns about the need for ongoing surveillance or reintervention affected the EVAR group [36,37]. New data, recently published by Peach and co-workers, challenged those assumption [33]. In their experience impact of AAA repair on quality of life appeared to worsen progressively after OR and improve progressively after endovascular aneurysm repair (EVAR).

The different observed and reported between EVAR and OR stressed the need to compare the two different procedures also on

economic basis [38], particularly because endovascular devices are much more expensive than surgical prosthesis. Different papers have reported the cost of EVAR examining its efficacy versus OR, reporting different results. Based on DREAM trial conclusions EVAR was not cost-effective compared to OR, due to cost related to endografts, surveillance and reinterventions [12]. However, cost of materials is gradually reduced, while results of EVAR are become more and more consistent. According with a recent Dutch experience, at present time EVAR could be considered cost-effective for AAA patients if performed in selected centres. Reduction in length of hospital stay, reintervention and mortality are still essential to guarantee this result [39].

3. Ethical and medico-legal considerations

The traditional approach, based on an ethic of beneficence, is one in which the paternalistic physician unabashedly filters or manipulates information to convince the patient to adhere to a therapeutic course of action presumed to be in the latter's best interest. This approach has finally given way to a liberal ethic which encourages the patient's self-determination and gives new legitimacy to the medical act by also legitimising the patient's freedom of choice [40,41].

In daily practice, however, the information relating to surgery, whether OR or EVAR, is often judged to be of very poor quality. Special procedures for promoting the patient's understanding of options and outcomes to come to a decision have therefore been created [42,43].

As already mentioned, the patient must first understand the risks of rupture as well as those connected with the development of symptoms to monitor potential risks. It is then necessary to list therapeutic possibilities relating to OR or EVAR to offer tailored information [44]. This issue is not only of ethical importance but is also linked to professional responsibility, because as pointed out, patients undergoing such kinds of aortic surgery are sometimes completely unaware of the options, related risks and the prognosis [45]. This injunction to respect the decisional autonomy of the patient remains valid even when the life of the patient is threatened [40].

By national survey and by obtaining the opinions of surgeons and patients, some study groups have examined the characteristics of information and understanding underlying a patient's consent.

It has been demonstrated that surgeons consider that essential risk information regarding OR should include mortality, myocardial infarction, kidney failure, residual impotence and finally the need for mechanical ventilation for more than 24 h after surgery. As regards EVAR, it is believed that the patient should be informed about mortality as well as about the possibility of further surgery, contrast and radiation exposure and post-surgical rupture [46].

It is interesting to note changes in the quality of information in relation to the surgeon's experience: expert surgeons base information on experience acquired and on the percentage of adverse events that have occurred in their hospitals [46]. Considering qualitative differences between surgeons, guidelines on options, risks and prognosis should be created for informed consent and to ensure that the patient has understood. Research shows that the safety of the procedure is the most important of the various risks outlined to the patient, and this is confirmed by our study [32]. The information provided must be objective and complete, and must include an explanation of the diagnosis, therapeutic options, risks and benefits of treatments or refusals of treatment, and prognoses. It must also be presented in a manner which is compatible with the individual patient's educational level, comprehension skills, and psychological and emotional status, and must, therefore, be conducive to a full and accurate understanding [40]. According to

Winterborn, methodological tools based on information databases should be available [47].

Indeed, it has been pointed out that in the case of AAA repair, information should go beyond the classical canons and take the form of a doctor-patient exchange in which both parties express their preferred options and their understanding of the risks and subsequent quality of life, without provoking anxiety about the operation itself. Frank open communication should enable the patient to make a truly informed choice that expresses his or her real preferences regarding surgical approach [48]. The requirement for informed consent is that the level of awareness of the patient is less than in conventional practice, since the risk-benefit ratio must be completely explained when making an informed choice about the type of treatment to select. In the event of alternative treatments, the vulnerability of patients and their relatives can easily lead to hasty decisions, based on inadequate information [49].

Specific litigation cases on surgical options related to the treatment of aortic aneurysms has developed. The informed consent process needs to include not only mortality and major complications related to the procedure but also the chance of patients' outcomes that can considerably putting anxiety to the patient and his/her family [50]. When patients are well informed during the acquisition of informed consent are more satisfied with the decision they make and live better the outcome [51].

Recently, a Court in Rome criticized the generic nature of informed consent that appears to be a standard form which lists the possible complications without being packaged as a tailored suit for the patient [52]. This decision appears to be perfectly conform to the British statement that the Court will require further evidence that the practice proclaimed has a logical basis, and that the defendant practitioner has weighed up the benefits and risks of the treatment [53].

As it has been proposed, the standard for informed consent in such cases should be based on a tailored approach. Cost-effectiveness of Personalized Medicine strategies is based on the ability of earlier and appropriate treatment application to reduce costs, by improving efficacy and tolerability [54,55].

Another question is how to assess frequent conflicts of interest between authors of guidelines. These conflicts may affect the neutrality of information regarding treatment.

At this point, it is interesting to ask questions like those recently raised in an article on guidelines querying the "nomological statute on guidelines, also in relation to the process of their development, variety and provenance" [56]. This very recent study offers the view, possibly under-researched, that guidelines are often based on expert opinion and relatively low levels of evidence, which make them prone to prejudice and scientific bias.

The painful conclusion is that most guidelines lack transparency about their development, and the scientific evidence supporting the recommendations is often flimsy. Certainly, there is a need for assessment regarding: a) the method used to draw up the guideline; b) the thoroughness and quality of the consent to the recommendation. We fully subscribe to the view that scientific quality should underpin studies, the 'instructions' that emerge from them and the objective evidence that corroborates them. It is therefore to be hoped that guidelines can be classified according to their source, implementation and circulation in order to facilitate the selection of those that are authoritative and reliable. In Italy this not only regards certain health treatments but by law is also linked to an assessment of medical responsibility. Perhaps a positive feature of the recent Italian reforms is that the law seeks to ensure the soundness of guidelines and therapeutic practice through validation by the scientific community. The professional conduct of the therapist can therefore only be judged favourably if he or she abides by guidelines which are firmly established and recognized as such.

4. Conclusions

No conclusive data is currently available to assess the initial question of late mortality after EVAR. Results of RCTs and meta-analysis disagree with those of more recent clinical experience, and besides, EVAR results are still improving. A clear answer will probably become available in the next few years. In the meantime, widespread use of EVAR as first choice for treating AAA may only be acceptable in high-volume centres that control results and have strict follow-up programs.

Moreover, a strategy of EVAR as first line treatment only in selected centres could avoid the needing for reintervention or, at least, guarantee an optimal management of complication when needed. This approach seems to be crucial in reducing mortality, patients' discomfort and procedure related costs [57,58].

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Author contribution

Carlo Setacci, Study Concept, overall responsibility. Pasqualino Sirignano, Data collection and writing paper. Paola Frati, data collection and analysis. Giovanna Ricci, data collection and analysis. Vittorio Fineschi, data interpretation, overall responsability. Francesco Speziale, data interpretation, overall responsability.

Conflicts of interest

None.

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Consent

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