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Worse late-phase survival after elective endovascular than open surgical repair for intact abdominal aortic aneurysm

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ABSTRACT

Objectives: To determine whether follow-up survival is better after elective endovascular aneurysm repair (EVAR) than open surgical repair (OSR) for intact abdominal aortic aneurysm (AAA), we combined 5-year survival curves themselves of EVAR and OSR in randomized controlled trials (RCTs) and propensity-score matched (PSM) studies.
Methods: Eligible studies were RCTs or PSM studies of elective EVAR versus OSR enrolling patients with intact AAA and reporting 5-year (at least) survival curves. Data regarding detailed inclusion criteria, duration of follow-up, and survival curves were abstracted from each individual study. In case of crossing of the combined survival curves, a pooled late-phase (between the crossing time and 5 years) hazard ratio (HR) for all-cause mortality was calculated.
Results: Our search identified 7 eligible studies (including 2 RCTs and 5 PSM studies) enrolling a total of 92,333 patients with AAA assigned to EVAR or OSR. Pooled survival rates after EVAR and OSR were 98.1% and 96.1 at 1 month, 94.2% and 93.1% at 1 year, 85.1% and 86.8% at 3 years, and 75.8% and 78.8% at 5 years, respectively. The survival curves crossed at 1.8 years with the survival rate of 90.5%. A pooled late-phase (between 1.8 years and 5 years) HR for calculated from data of the combined survival curves significantly favored OSR (1.29, 95% confidence interval, 1.24 to 1.35; $p < 0.00001$).
Conclusions: For intact AAA, although survival was better immediately after elective EVAR than OSR, the survival curves crossed at 1.8 years. Thereafter until 5 years, survival was worse after EVAR than OSR.

1. Introduction

In elective treatment for intact (non-ruptured) abdominal aortic aneurysm (AAA), endovascular aneurysm repair (EVAR) is associated with lower short-term all-cause mortality than open surgical repair (OSR) [1,2]. This benefit from EVAR, however, does not persist at long-term follow-up [2–5]. Authors of previous meta-analyses of follow-up outcomes combined odds ratios (ORs) [2,4] or risk ratios (RRs) [3,5] for mortality. The most appropriate way of summarizing time-to-event (survival) data, however, is to use methods of survival analysis and express the intervention effect as a hazard ratio (HR) [6]. When comparing interventions in a study or meta-analysis a simplifying assumption is often made that the HR is constant across the follow-up period, even though hazards themselves may vary continuously, which is known as the proportional hazards assumption [6]. Our preliminary meta-analysis [7] pooling survival curves themselves of elective EVAR versus OSR for intact AAA, however, suggests that survival curves may cross; i.e. although EVAR yields better survival in the beginning of the study, this effect is reversed after some time. Under the proportional hazards assumption, crossing of the survival curves is impossible [8]. If the proportional hazards assumption fails to hold for the treatment, the HR cannot be interpreted as a relative risk [8]. In the present article updating our preliminary meta-analysis [7], to determine whether follow-up survival is better after elective EVAR than OSR for intact AAA, we combined 5-year survival curves themselves of EVAR and OSR in randomized controlled trials (RCTs) and propensity-score matched (PSM) studies. In case of crossing of the combined survival curves, a pooled late-phase (between the crossing time and 5 years) HR for all-cause mortality was calculated.

Abbreviations: AAA, abdominal aortic aneurysm; DREAM, Dutch Randomized Endovascular Aneurysm Repair; EVAR, endovascular aneurysm repair; HR, hazard ratio; IPD, individual patient data; OR, odds risk; OSR, open surgical repair; PSM, propensity-score matched; RCT, randomized controlled trial; RR, risk ratio.

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2. Methods

2.1. Search strategy

All RCTs and PSM studies of elective EVAR versus OSR enrolling patients with intact AAA were identified using 2-level strategy. First, databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through August 2016 using Web-based search engines (PubMed and OVID). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. Search terms included *abdominal aortic aneurysm/aneurysms*; *endovascular*; and *randomized*, *randomized*, *randomly*, *randomization*, or (*propensity* and [*match*, *matching*, or *matched*]).

2.2. Study selection and data abstraction

Studies considered for inclusion met the following criteria: the design was a RCT or PSM study: the study population was patients with intact AAA; patients were assigned to elective EVAR versus OSR; and outcomes included 5-year (at least) survival curves. Data regarding detailed inclusion criteria, duration of follow-up, and survival curves were abstracted (as available) from each individual study.

2.3. Statistical analysis

2.3.1. Combined survival curve

Suppose the numbers at risk, $n_1, n_2, \ldots, n_p$ are given on the survival curve at each of p time-points $t_1, t_2, \ldots, t_p$. Survival rates were read off the curves at $t_1, t_2, \ldots, t_p$ and denoted by $s_1, s_2, \ldots, s_p$. Let $t_0 = 0$, $s_0 = 1$, $n_0 =$ randomized or PSM number. Following the actuarial approach, in which censoring is assumed to be constant within each time interval, but not necessarily across intervals

$$s_j = s_i\left(1-d_{i,j}/\left[n_i-c_{i,j}/2\right]\right) \quad (1)$$

$$n_j = n_i-d_{i,j}-c_{i,j} \quad (2)$$

where $d_{i,j}$ = number of deaths during the interval $[t_i, t_j]$ and $c_{i,j}$ = censored number during the interval $[t_i, t_j]$. Rearranging Eqs. (1) and (2) gives

$$d_{i,j} = \left(n_i + n_j\right)\left(s_i-s_j\right)/\left(s_i + s_j\right)$$

$$c_{i,j} = 2\left(n_i s_j-n_j s_i\right)/\left(s_i + s_j\right).$$

We constructed a strategy to combine survival curves according to the method by Pereira et al. [9], because different grids of time intervals had been used in the reviewed studies. First, for each month k of follow-up, we redistributed, in equal quantities ($d_{k-1,k}$ and $c_{k-1,k}$) at 1-month intervals $[t_{k-1}, t_k]$, the numbers of deaths ($d_{i,j}$) and censored ($c_{i,j}$) at intervals >1 month $[t_i, t_j]$.

Second, an interval survival rate, $s_{k-1,k}$, was determined as follows:

$$s_{k-1,k} = 1-d_{k-1,k}/\left(n_{k-1}-c_{k-1,k}/2\right).$$

Third, to obtain a pooled interval survival rate, $S_{k-1,k}$, study specific interval survival rates ($s_{k-1,k}$) were combined with the use of inverse variance-weighted averages in the random-effects model by means of Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ).

Finally, the product of pooled interval survival rates ($S_{k-1,k}$) yielded the pooled cumulative survival rate at month k, S_k, as follows:

$$S_k = S_{0,1}S_{1,2}\ldots S_{k-1,k}.$$

2.3.2. Late-phase survival

In case of crossing of the combined survival curves, a pooled late-phase (between the crossing time and 5 years) HR for all-cause mortality was calculated.

2.3.2.1. Pooled late-phase HR from combined survival curves. A pooled late-phase (between the crossing time and 5 years) HR was calculated from data of the combined survival curves (pooled numbers at risk and pooled survival rates at each month) with the use of a HR calculations spreadsheet provided by Tierney et al. [10] based on statistical methods reported by Parmar et al. [11] and Williamson et al. [12].

2.3.2.2. Pooled late-phase HR from study-specific late-phase HRs. Study-specific late-phase (between the crossing time and 5 years) HRs were calculated from data of the study-specific survival curves (numbers at risk and survival rates at each month) by means of the HR calculations spreadsheet [10] and then combined with the use of inverse variance-weighted averages in the random-effects model by means of Review Manager version 5.3 (available from http://tech.cochrane.org/revman).

3. Results

3.1. Search results

Our search identified 7 eligible studies (including 2 RCTs [13,14] and 5 PSM studies [15–19]) enrolling a total of 92,333 patients with AAA assigned to EVAR ($n = 46.164$) or OSR ($n = 46.169$) (Table 1). Major excluded studies [20–26] were also summarized in Table 1.

3.2. Combined survival curve

Combined 5-year survival curves were illustrated in Fig. 1, and their details were summarized in Table 2. Pooled survival rates after EVAR and OSR were 98.1% and 96.1 at 1 month, 94.2% and 93.1% at 12 months (1 year), 85.1% and 86.8% at 36 months (3 years), and 75.8% and 78.8% at 60 months (5 years), respectively. The survival curves crossed at 22 months (1.8 years) with the survival rate of 90.5%.

3.3. Late-phase survival

Late-phase survival between 22 months (1.8 years) and 60 months (5 years) was significantly worse after EVAR than OSR. A pooled late-phase HR for all-cause mortality calculated from data of the combined survival curves (q.v. *2.3.2.1.*) significantly favored OSR (1.29, 95% confidence interval [CI], 1.24 to 1.35; $p < 0.00001$). An alternative pooled late-phase HR combining study specific late-phase HRs (q.v. *2.3.2.2.*) also significantly favored OSR (1.23, 95% CI, 1.03 to 1.47; $p = 0.02$; Fig. 2).

4. Discussion

4.1. Main findings

For intact AAA, although survival was better immediately after elective EVAR than OSR, the survival curves crossed at 22 months (1.8 years) with the survival rate of 90.5%. Thereafter, survival was worse in EVAR than OSR (pooled HR for all-cause mortality between 22 months [1.8 years] and 60 months [5 years], 1.29, 95% CI, 1.24 to 1.35; $p < 0.00001$) with the survival rate of 75.8% versus78.8% at 60 months (5 years).

4.2. Early mortality

Early (30-day or in-hospital) all-cause mortality is lower after EVAR than OSR. A meta-analysis by Thomas et al. [1] of 42 studies (including 4 RCTs) favored EVAR with respect to 30-day mortality with a pooled odds ratio (OR) of 0.34 (95% CI, 0.31 to 0.38; $p < 0.001$). A Cochrane systematic review by Paravastu et al. [2] of 4 high-quality RCTs found short-term (30-day or in-hospital) mortality with EVAR to be significantly lower than with OSR (1.4% versus 4.2%; pooled OR, 0.33, 95% CI; 0.20 to 0.55; $p < 0.0001$).

4.3. Follow-up mortality

Previous meta-analyses [2–5] demonstrated similar follow-up mortality after elective EVAR and OSR. In the Cochrane systematic review by Paravastu et al. [2] of 3 RCTs, there was no significant difference in long-term (beyond 4 years) mortality, with a mortality rate of 37.3% after EVAR and 37.8%s after OSR (pooled OR, 0.98; 95% CI, 0.83 to 1.15; $p = 0.78$). Also in a meta-analysis by Qadura et al. [3] of 4 RCTs, there is no statistical difference in long-term (beyond the 2-year mark) mortality between both groups (pooled RR, 0.97; 95% CI, 0.86–1.10; $p = 0.65$). Furthermore, in a meta-analysis by Stather et al. [4] of 4 RCTs and information from the US Medicare and Swedish National Registry for Vascular Surgery database, there was no difference in mortality (34.7% after EVAR versus 33.8% after OSR; pooled OR 1.11; 95% CI, 0.91 to 1.35;

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