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A meta-analysis pooling survival curves in randomized controlled trials and propensity-score matched studies of endovascular versus open abdominal aortic aneurysm repair ☆,☆☆,★

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Regarding mid-to-long-term survival following elective endovascular aneurysm repair (EVAR) versus open surgical repair (OSR) for non-ruptured abdominal aortic aneurysm (AAA), authors of recent meta-analyses combined odds (ORs) [1] or risk ratios (RRs) [2,3] 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) [4]. 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. In studies of EVAR versus OSR for AAA, however, survival curves often cross, i.e. EVAR may yield better survival in the beginning of the study, but this effect may be reversed after some time. Under the proportional hazards assumption, crossing of the survival curves is impossible [5]. If the proportional hazards assumption fails to hold for the treatment, the HR cannot be interpreted as a relative risk. According to the method by Pereira et al. [6], we performed a meta-analysis pooling survival curves themselves (not ORs, RRs, and HRs for mortality) of EVAR and OSR for AAA in randomized controlled trials (RCTs) and propensity-score matched studies.

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

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

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

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 the Eqs. (1) and (2) gives

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

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

Monthly hazard rates from single series of EVAR or OSR were combined in random-effects modeling to yield a pooled estimate of survival for each repair and each month of follow-up [6]. The product of successive monthly pooled estimates of survival then yielded a pooled measure of cumulative survival for each type of repair. We constructed a strategy to combine survival curve because different grids of time intervals had been used in the reviewed studies [6].

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 greater than 1 month $[t_i, t_j]$.

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

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

The variance of $s_{k-1,k}$, $var(s_{k-1,k})$, was obtained as the following approximation:

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

Third, to obtain a pooled interval survival rate, $S_{k-1,k}$, and its variance, $var(S_{k-1,k})$; study specific interval survival rates ($s_{k-1,k}$) were combined using inverse variance-weighted averages in the

Table 1
Trial characteristics and patient profiles.

Study	Design	Follow-up (year)	Patient (n)	Age (year)	Men (%)	Diabetes (%)	Tobacco use (%)	Hypertension (%)	Hyperlipidemia (%)	Carotid disease (%)	Cardiac disease (%)	Renal disease (%)	Pulmonary disease (%)
Included study													
ACE 2011 [E1]	RCT	4	299	69.4	99.0	13.0	49.2	64.9	67.2	8.0	38.1[a]	12.0[b]	23.7
DREAM 2010 [E2]	RCT	7	351	70.1	91.7	10.0	59.6	56.4	49.8	14.9	43.8	8.0	23.0
EVAR 1 2010 [E3]	RCT	8	1252	74.1	90.7	10.4	21.6[c]	N/A	N/A	N/A	42.3	N/A	N/A
OVER 2009 [E4]	RCT	2	881	70.0	99.4	22.7	41.2[c]	76.8	N/A	N/A	40.7[a]	N/A	29.4[d]
Egorova 2011 [E5]	PSM	6	84,640	75.2[e]	77.6[e]	12.4[e]	N/A	64.9[e]	27.9[e]	N/A	48.5[ae]	4.7[be]	37.5[e]
Lee 2013 [E6]	PSM	11	440	72.58	82.5	11.1	23.0[c]	55.2	63.2	10.0[f]	30.2[g]	1.4[h]	18.4
Mark 2013 [E7]	PSM	5	8966	75–84, 42.5%	84.5	14.5	N/A	N/A	N/A	N/A	43[a]	5[b]	30[d]

Study	Design	Follow-up (year)	Patient (n)	Publication	Remark
Major excluded study					
Schermerhorn 2011	PSM	1	45,660	J Am Coll Surg 2011;212:349–55	All patients (Medicare 2001–2004) included in Egorova 2011 (Medicare 1995–2006)
Giles 2011	PSM	6	45,652	J Vasc Surg 2011;53:6–12,13.e1	All patients (Medicare 2001–2004) included in Egorova 2011 (Medicare 1995–2006)
Schermerhorn 2008	PSM	5	45,660	N Engl J Med 2008;358:464–74	All patients (Medicare 2001–2004) included in Egorova 2011 (Medicare 1995–2006)

ACE: Anevrysme de l'aorte abdominale: Chirurgie versus Endoprothese; DREAM: Dutch Randomized Endovascular Aneurysm Repair; EVAR: United Kingdom Endovascular Aneurysm Repair; OVER: N/A: not available; Open Versus Endovascular Repair; PSM: propensity-score matching; RCT: randomized controlled trial.

[a] Coronary disease.
[b] Renal insufficiency.
[c] Current smoker.
[d] Chronic obstructive pulmonary disease.
[e] Data in original 322,892 patients before propensity-score matching.
[f] Surgery on carotid arteries.
[g] Myocardial infarction.
[h] Dialysis.

random-effects model using Comprehensive Meta-Analysis version 2 (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:

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

The variance of S_k, $\mathrm{var}(S_k)$, was calculated as the following formula:

$$\mathrm{var}(S_k) = \mathrm{var}(S_{k-1})\mathrm{var}\left(S_{k-1,k}\right) + \mathrm{var}(S_{k-1})\left[S_{k-1,k}\right]^2 + \mathrm{var}\left(S_{k-1,k}\right)[S_{k-1}]^2.$$

The 95% confidence interval (CI) of S_k was obtained as follows:
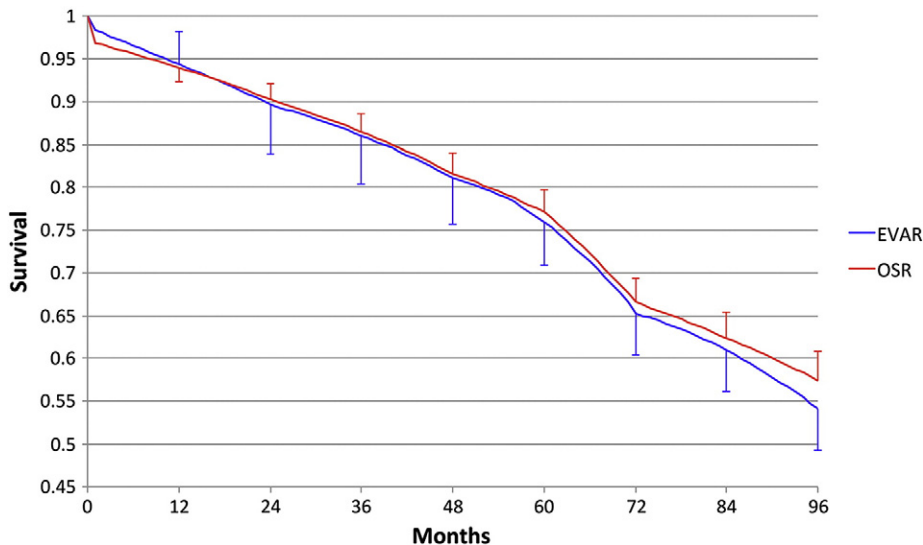

Fig. 1. Pooled survival curves of elective endovascular aneurysm repair (EVAR) (blue) and open surgical repair (OSR) (red) for non-ruptured abdominal aortic aneurysm.