**Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years**

J. T. Powell, M. J. Sweeting, P. Ulug, J. D. Blankensteijn, F. A. Lederle, J.-P. Becquemin and R. M. Greenhalgh, on behalf of the EVAR-1, DREAM, OVER and ACE trialists

**Appendix S1** Supplementary information on search and statistical methods

**Search criteria for randomized trials**

The search was for prospective RCTs comparing endovascular aneurysm repair with open repair in patients with an abdominal aortic aneurysm considered fit for open repair, which reported mid-term outcomes (from 2 to 5 years) for mortality, complications and reinterventions and were published between 1 January 2000 and 31 December 2015. Studies with inadequate data or using an inadequate randomization technique, those with fewer than 100 persons randomized and those not published in English were excluded. The search terms were the same as for the Cochrane Review1 published in 2014.

**Supplementary information on statistical methods**

*Hazard of reintervention following aneurysm repair*

Analyses of reinterventions were restricted to individuals who underwent aneurysm repair. An Anderson–Gill multiple failure time model2 was used to estimate the hazard ratio of treatment on the risk of first or subsequent reinterventions (assuming that the hazard does not increase after each reintervention) following operation. In addition, hazard ratios were estimated separately in three prespecified time periods: 0–30 days, 31 days to 3 years, and 3 years or more. For reinterventions that occurred during the primary stay, the time of the reintervention was approximated by the midpoint between operation and discharge or death.

*Hazard of total mortality following detection and/or treatment of a type II endoleak*

To investigate whether treated and untreated type II endoleaks subsequently affect hazard of survival, a three-level time-dependent categorical variable was created for each individual based on information from their first detected type II endoleak. Specifically, follow-up for each individual was split into periods in which: no type II endoleak had been detected since randomization; the first type II endoleak had been detected but was as yet untreated; and the first type II endoleak had been detected and treated. A Cox regression model was fitted with this time-dependent exposure to assess the hazard ratios of detected untreated and detected treated type II endoleaks in relation to no detected type II endoleak.

**References**

1 Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. *Cochrane Database Syst Rev* 2014; (1)CD004178.

2 Andersen PK, Gill RD. Cox’s regression model for counting processes: a large sample study. *Annals of Statistics* 1982; **10**: 1100–1120.



**Fig. S1** Aneurysm-related mortality, overall and at 0–6 months, 6 months to 4 years and more than 4 years since randomization. Unadjusted hazard ratios are shown. EVAR, endovascular aneurysm repair

 **Fig. S2** Unadjusted hazard ratios for total mortalityby subgroups of maximum abdominal aortic aneurysm (AAA) diameter, neck diameter and neck length, overall and at 0–6 months, 6 months to 4 years and more than 4 years since randomization. Interaction *P* values for maximum AAA diameter, neck diameter and neck length were calculated using continuous measures. The number of trials contributing to each analysis is shown. EVAR, endovascular aneurysm repair



**Fig. S3** Unadjusted hazard ratios for total mortalityby subgroups of history of diabetes, BMI and smoking status, overall and at 0–6 months, 6 months to 4 years and more than 4 years since randomization. Interaction *P* values for BMI were calculated using continuous measures. The number of trials contributing to each analysis is shown. EVAR, endovascular aneurysm repair



**Fig. S4** Hazard ratio for any reintervention by time period following aneurysm repair for 2718 subjects undergoing aneurysm repair (follow-up regarding reinterventions was missing for 7 subjects after aneurysm repair). The number of reinterventions reported here may differ slightly from those reported by the individual trial publications, particularly for OVER where more reinterventions after endovascular aneurysm repair (EVAR) were included in the trial report. This difference is mainly due to the different ways in which reinterventions were categorised across the trials. For instance amputations were included in reinterventions for OVER, but placed in a separate category for all the other trials and this meta-analysis. Similarly, below-knee reconstructions were included as OVER trial reinterventions, but were not included in the meta-analysis unless there was clear evidence that these procedures were aneurysm-related



**Fig. S5** Time from repair to secondary sac rupture in patients undergoing endovascular aneurysm repair

**Table S1** Derivation of a cardiovascular risk score\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | BP (mmHg) | Previous MI | Diabetes | Smoking (never/ex/current) | EVAR-1  (*n* = 1252) | DREAM  (*n* = 348) | OVER  (*n* = 880) | ACE  (*n* = 299) |
| All optimal | SBP <120 and DBP < 80 (ACE trial only: no hypertension)  AND | No  AND | No  AND | Never | 4 (0.3) | 3 (0.9) | 7 (0.8) | 31 (10.4) |
| ≥ 1 not optimal | SBP 120–139 or DBP 80–89 (ACE trial only: SBP controlled by 1 drug or DBP ≤ 90)  OR | No  AND | No  AND | Never /ex | 173 (13.8) | 40 (11.5) | 182 (20.7) | 15 (5.0) |
| ≥ 1 raised | SBP 140–159 or DBP 90–99 (ACE trial only: 1 hypertensive drug for both SBP and DBP)  OR | No  AND | No  AND | Never/ex | 232 (18.5) | 44 (12.6) | 75 (8.5) | 49 (16.4) |
| 1 major risk factor | SBP ≥ 160 or DBP ≥ 100 (ACE trial only: ≥ 2 hypertensive drugs for both SBP and DBP or uncontrollable)  OR | Yes  OR | Yes  OR | Current | 579 (46.2) | 149 (42.8) | 397 (45.1) | 109 (36.5) |
| ≥ 2 major risk factors | SBP ≥ 160 or DBP ≥ 100 (ACE trial only: ≥ 2 hypertensive drugs or uncontrollable)  AND/OR | Yes  AND/OR | Yes  AND/OR | Current | 264 (21.1) | 112 (32.2) | 219 (24.9) | 95 (31.8) |

Values in parentheses are percentages. \*Based on a modified version of that described by Wilkins *et al.* (*JAMA* 2012; **308**: 1795–1801). Of the 2783 individuals in the individual-patient data set, four did not have complete data on BP/BP-lowering drugs or history of myocardial infarction (MI), diabetes or smoking status to enable a cardiovascular risk score to be calculated. The remaining 2779 patients were distributed across the risk categories as shown. SBP, systolic BP; DBP, diastolic BP.

**Table S2** Causes of death by randomized group, trial and time since randomization

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | EVAR-1 | | DREAM | | OVER | | ACE | |
| EVAR | Open | EVAR | Open | EVAR | Open | EVAR | Open |
| Randomization to 6 months | 26 | 45 | 6 | 10 | 11 | 17 | 3 | 1 |
| AAA-related  MI/other cardiac  Stroke  Other vascular  Cancer, lung  Cancer, other  Pulmonary  Renal  Other  Unknown | 14 (54)  4 (15)  0 (0)  2 (8)  1 (4)  2 (8)  0 (0)  2 (8)  1 (4)  0 (0) | 30 (67)  4 (9)  1 (2)  2 (4)  0 (0)  0 (0)  5 (11)  0 (0)  3 (7)  0 (0) | 3 (50)  0 (0)  0 (0)  1 (17)  1 (17)  0 (0)  1 (17)  0 (0)  0 (0)  0 (0) | 10 (100)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0) | 5 (45)  2 (18)  1 (9)  3 (27)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0) | 14 (82)  0 (0)  0 (0)  0 (0)  0 (0)  3 (18)  0 (0)  0 (0)  0 (0)  0 (0) | 3 (100)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0) | 1 (100)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0) |
| 6 months to 4 years | 125 | 116 | 33 | 25 | 73 | 78 | 13 | 10 |
| AAA-related  MI/other cardiac  Stroke  Other vascular  Cancer, lung  Cancer, other  Pulmonary  Renal  Other  Unknown | 12 (9.6)  27 (21.6)  11 (8.8)  7 (5.6)  19 (15.2)  20 (16.0)  9 (7.2)  4 (3.2)  15 (12.0)  1 (0.8) | 8 (6.9)  25 (21.6)  6 (5.2)  6 (5.2)  20 (17.2)  29 (25.0)  15 (12.9)  1 (0.9)  6 (5.0)  0 (0) | 1 (3)  8 (24)  1 (3)  0 (0)  1 (3)  12 (36)  2 (6)  0 (0)  4 (12)  4 (12) | 1 (4)  6 (24)  2 (8)  0 (0)  3 (12)  7 (28)  2 (8)  0 (0)  2 (8)  2 (8) | 2 (3)  16 (22)  3 (4)  3 (4)  7 (10)  18 (25)  4 (5)  0 (0)  12 (16)  8 (11) | 0 (0)  15 (19)  1 (1)  4 (5)  12 (15)  15 (19)  8 (10)  1 (1)  9 (12)  13 (17) | 4 (31)  2 (15)  1 (8)  0 (0)  2 (15)  2 (15)  1 (8)  1 (8)  0 (0)  0 (0) | 0 (0)  4 (40)  0 (0)  0 (0)  2 (20)  1 (10)  1 (10)  1 (10)  0 (0)  1 (10) |
| > 4 years | 109 | 103 | 19 | 25 | 62 | 51 | 1 | 1 |
| AAA-related  MI/other cardiac  Stroke  Other vascular  Cancer, lung  Cancer, other  Pulmonary  Renal  Other  Unknown | 10 (9.2)  28 (25.7)  11 (10.1)  8 (7.3)  9 (8.3)  14 (12.8)  14 (12.8)  4 (3.7)  11 (10.1)  0 (0) | 2 (1.9)  26 (25.2)  11 (10.7)  6 (5.8)  9 (8.7)  20 (19.4)  17 (16.5)  2 (1.9)  10 (9.7)  0 (0) | 2 (11)  6 (32)  1 (5)  0 (0)  0 (0)  4 (21)  3 (16)  0 (0)  3 (16)  0 (0) | 0 (0)  9 (36)  2 (8)  0 (0)  0 (0)  7 (28)  2 (8)  1 (4)  1 (4)  3 (12) | 3 (5)  15 (24)  4 (6)  5 (8)  7 (11)  7 (11)  9 (15)  0 (0)  5 (8)  7 (11) | 3 (6)  10 (20)  2 (4)  2 (4)  7 (14)  11 (22)  11 (22)  0 (0)  1 (2)  4 (8) | 0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  1 (100) | 0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  0 (0)  1 (100) |

Values in parentheses are percentages. EVAR, endovascular aneurysm repair; AAA, abdominal aortic aneurysm; MI, myocardial infarction.

**Table S3** Causes of death by categorization of baseline ankle : brachial pressure index and time since randomization

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ABPI < 0.9 | | ABPI ≥ 0.9 | |
| EVAR | Open | EVAR | Open |
| Randomization to 6 months | 13 | 23 | 29 | 43 |
| AAA-related  MI/other cardiac  Stroke  Other vascular  Cancer, lung  Cancer, other  Pulmonary  Renal  Other  Unknown | 7 (54)  0 (0)  0 (0)  4 (31)  1 (8)  0 (0)  0 (0)  1 (8)  0 (0)  0 (0) | 18 (78)  1 (4)  0 (0)  2 (9)  0 (0)  0 (0)  2 (9)  0 (0)  0 (0)  0 (0) | 15 (52)  6 (21)  1 (3)  2 (7)  1 (3)  2 (7)  0 (0)  1 (3)  1 (3)  0 (0) | 30 (70)  3 (7)  1 (2)  0 (0)  0 (0)  3 (7)  3 (7)  0 (0)  3 (7)  0 (0) |
| 6 months to 4 years | 62 | 39 | 149 | 161 |
| AAA-related  MI/other cardiac  Stroke  Other vascular  Cancer, lung  Cancer, other  Pulmonary  Renal  Other  Unknown | 6 (10)  15 (24)  3 (5)  5 (8)  6 (10)  8 (13)  6 (10)  1 (2)  7 (11)  5 (8) | 3 (8)  10 (26)  1 (3)  3 (8)  5 (13)  10 (26)  3 (8)  0 (0)  2 (5)  2 (5) | 7 (4.7)  33 (22.1)  12 (8.1)  5 (3.4)  20 (13.4)  40 (26.8)  7 (4.7)  3 (2.0)  17 (11.4)  5 (3.4) | 6 (3.7)  31 (19.3)  7 (4.3)  5 (3.1)  30 (18.6)  34 (21.1)  20 (12.4)  2 (1.2)  14 (8.7)  12 (7.5) |
| > 4 years | 35 | 36 | 144 | 131 |
| AAA-related  MI/other cardiac  Stroke  Other vascular  Cancer, lung  Cancer, other  Pulmonary  Renal  Other  Unknown | 3 (9)  9 (26)  2 (6)  4 (11)  0 (0)  3 (9)  7 (20)  0 (0)  3 (9)  4 (11) | 4 (11)  14 (39)  4 (11)  3 (8)  0 (0)  3 (8)  3 (8)  2 (6)  0 (0)  3 (8) | 12 (8.3)  34 (23.6)  13 (9.0)  8 (5.6)  14 (9.7)  22 (15.3)  19 (13.2)  4 (2.8)  15 (10.4)  3 (2.1) | 1 (0.8)  25 (19.1)  10 (7.6)  4 (3.1)  16 (12.2)  35 (26.7)  23 (17.6)  1 (0.8)  12 (9.2)  4 (3.1) |

Values in parentheses are percentages. ABPI, ankle : brachial pressure index; EVAR, endovascular aneurysm repair; AAA, abdominal aortic aneurysm; MI, myocardial infarction.

**Table S4** Operative mortality by subgroup, for individuals who underwent an operation

|  |  |
| --- | --- |
|  | Operative mortality |
| Age (years)  < 72  ≥ 72 | 12 of 1311 (0.9)  44 of 1413 (3.1) |
| Sex  F  M | 6 of 150 (4.0)  50 of 2574 (1.9) |
| eGFR (ml per min per 1.73 m2)  < 68.4  68.4 | 35 of 1341 (2.6)  20 of 1360 (1.5) |
| Angina/MI  No  Yes | 35 of 1721 (2.0)  21 of 1003 (2.1) |
| ABPI  < 0.9  0.9 | 19 of 455 (4.2)  29 of 1813 (1.6) |
| Cardiovascular risk score  < 2 major  2 major | 43 of 2052 (2.1)  13 of 668 (1.9) |
| Maximum AAA diameter (cm)  < 5.9  5.9 | 18 of 1330 (1.4)  37 of 1383 (2.7) |
| Neck diameter (cm)  < 2.3  2.3 | 23 of 1191 (1.9)  33 of 1521 (2.2) |
| Neck length (cm)  < 2.5  2.5 | 29 of 1284 (2.3)  27 of 1431 (1.9) |
| History of diabetes  No  Yes | 47 of 2317 (2.0)  9 of 399 (2.3) |
| BMI (kg/m2)  < 30  30 | 44 of 2057 (2.1)  11 of 649 (1.7) |
| Smoking status  Current  Ex/never | 14 of 814 (1.7)  42 of 1906 (2.2) |

Values in parentheses are percentages. eGFR, estimated glomerular filtration rate; MI, myocardial infarction; ABPI, ankle : brachial pressure index; AAA, abdominal aortic aneurysm.

**Table S5** Complications by trial, focusing on endovascular repair-related complications

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | EVAR-1  (*n* =1252) | DREAM†  (*n* =351) | OVER  (*n* = 881) | ACE  (*n* = 299) | Total  (*n* = 2783) |
| Follow-up for complications (years)\* | 5.3(2.5) | 5.2(2.2) | 5.2(2.1) | 2.8(1.1) | 5.0(2.4) |
| No. of complications per person-years†  EVAR  Open | 315 of 3381 (9.3)  27 of 3309 (0.8) | 125 of 906 (13.8)  7 of 932 (0.8) | 209 of 2334 (9.0)  13 of 2276 (0.6) | 103 of 419 (24.6)  8 of 408 (2.0) | 752 of 7040 (10.7)  55 of 6925 (0.8) |
| Type of complication‡  Endoleak type 1  Endoleak type 2  Endoleak type 3  Endoleak type 4  Endoleak type 5  Secondary rupture  Rate of secondary rupture after EVAR per 100 person-years | 56 (35)  146 (39)  25 (15)  0 (0)  0 (0)  27 (10)  0.7 | 24 (17)  73 (12)  5 (1)  0 (0)  0 (0)  2 (2)  0.1 | 25 (19)  139 (38)  7 (7)  5 (2)  11 (3)  5 (4)  0.2 | 15 (8)  77 (10)  0 (0)  0 (0)  5 (0)  3 (3)  0.7 | 120 (79)  435 (99)  37 (23)  5 (2)  16 (3)  37 (19)  0.5 |

\*Values are mean(s.d.). †Values in parentheses are rate per 100 person-years. ‡Total number during primary admission and after discharge, allowing for patients to have recurring endoleaks; values in parentheses are number treated. Generally, reinterventions during the primary stay were not linked to the complications of graft migration, graft thrombosis and graft infection, so the total number of these complications receiving treatment cannot be reported. ‡In the DREAM trial after 2 years only complications with reinterventions reported.

**Table S6** Effects of treated and untreated type II endoleak on survival in patients who underwent EVAR.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | EVAR-1 | DREAM | OVER | ACE | Pooled | *P* | *I*2 (%) |
| No. contributing to unadjusted analysis  No. of. deaths  No. of AAA deaths | 629    255  32 | 171  59  7 | 440    143  8 | 163  18  7 | 1403  475  54 |  |  |
| Unadjusted hazard ratio  Untreated  Treated | 0.83  (0.57, 1.21)  1.87  (1.14, 3.08) | 1.19  (0.61, 2.30)  2.11  (0.65, 6.84) | 1.56  (1.05, 2.32)  0.50  (0.18, 1.37) | –†  –† | 1.14  (0.75, 1.76)  1.30  (0.56, 3.03) | 0.538  0.546 | 61  65 |
| No. contributing to adjusted analysis  No. of deaths  No. of. AAA deaths | 628  255  32 | 165  56  6 | 440  143  8 | 154  16  6 | 1387  470  52 |  |  |
| Adjusted hazard ratio\*  No type II endoleak  Untreated type II endoleak  Treated type II endoleak | 1.00 (reference)  0.86  (0.59, 1.26)  1.71  (1.04, 2.84) | 1.00 (reference)  1.22  (0.63, 2.38)  2.68  (0.81, 8.88) | 1.00 (reference)  1.46  (0.97, 2.19)  0.48  (0.18, 1.32) | –†  –† | 1.00 (reference)  1.14  (0.79, 1.62)  1.31  (0.54, 3.17) | 0.488  0.549 | 44  67 |

Values in parentheses are 95 per cent confidence intervals. Hazard ratios are shown for those with a detected type II endoleak, as-yet treated or untreated compared with patients without a detected type II endoleak. \*Adjusted for age, sex, aneurysm diameter and log creatinine. †Too few events to estimate a hazard ratio. A Cox regression model with a time-dependent variable indicating no detected, detected treated or detected untreated type II endoleak was used for this analysis.