esomeprazole or rabeprazole at high doses.[11] Additionally, amoxicillin three times a day could have been prescribed as it was proposed in east Asia, potentially increasing the eradication frequency.[12] Furthermore, these results might not be generalisable to other populations; Asians tend to be smaller and lighter than individuals of other ethnic origins and therefore the smaller volume of antibiotic distribution might have positively affected the outcome of treatments.

With regard to adverse events, beyond the usual symptoms, there was a consequence of treatment not yet assessed—ie, the effect on gut microbiota with long-term effects on the patients that might be different according to the compounds used. Also the discrepancy (up to 5%) between the results of phenotypic and genotypic resistance for both clarithromycin and fluoroquinolones raises a question about the most accurate method for susceptibility testing.

Overall, this study shows that some empirical treatments, especially bismuth quadruple therapy, can lead to excellent eradication frequencies, thanks to bismuth salts and tetracycline for which no resistance is usually found and can therefore be an alternative to the tailored treatments after antimicrobial susceptibility testing. If concomitant therapy, the other effective regimen in the study, is used, the recommended treatment duration should be 14 days unless 10 days are proven effective locally.[11]

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We declare no competing interests.

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Selection, technique, and follow-up: keys to success in EVAR

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Short-term survival benefits of endovascular aneurysm repair (EVAR) versus open repair of elective abdominal aortic aneurysms have been shown in randomised trials, but this early survival benefit is lost within a few years.[1–3] The long-term survival benefit of EVAR remains unclear.[4]

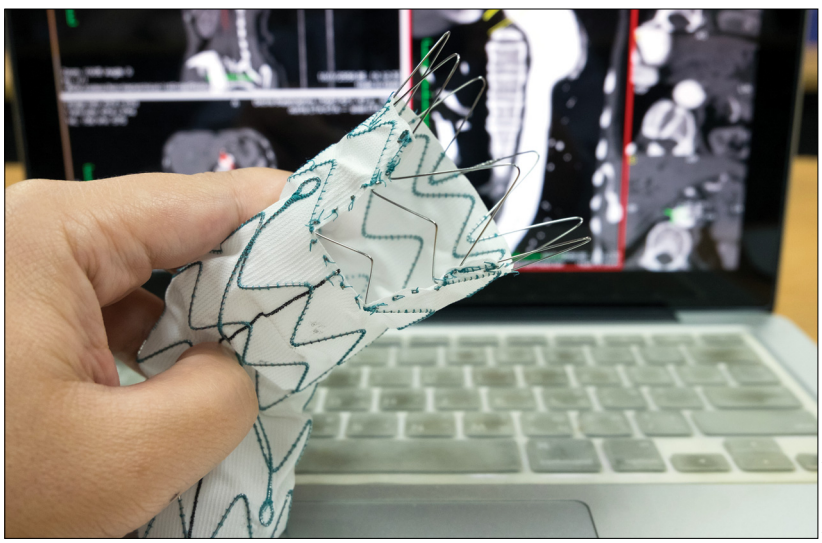
The randomised controlled EVAR trial 1 was initiated in 1999, and the EVAR trial participants and authors are to be congratulated for their persistence to obtain these long-term data in this aneurysm population suitable for both open repair and EVAR.[1] In Rajesh Patel and colleagues' EVAR trial 1[5] reported in *The Lancet*, over a mean of 12·7 years' follow-up (max 15·8 years), they show no significant difference between the randomly assigned groups in total mortality (9·3 deaths per 100 person-years in the EVAR group *vs* 8·9 deaths per 100 person-years in the open-repair group) or aneurysm-related mortality

(1·1 deaths per 100 person-years in the EVAR group *vs* 0·9 deaths per 100 person-years in the open-repair group). An early and significant survival benefit was noted in the EVAR group at 6 months after randomisation (adjusted hazard ratios 0·61, 95% CI 0·37–1·02 for total mortality; and 0·47, 0·23–0·93, p=0·031 for aneurysm-related mortality), and only after 8 years did open repair have a significantly lower mortality (1·25, 1·00–1·56, p=0·05 for total mortality; and 5·82, 1·64–20·65, p=0·006 for aneurysm-related mortality). The increased aneurysm-related mortality beyond 8 years was mainly attributable to secondary aneurysm sac rupture post-EVAR. Overall, aneurysm re-intervention rates were higher in the EVAR than in the open-repair group (4·1 and 1·7 per 100 person-years; p<0·0001) with most re-interventions taking place within 4 years of the initial treatment.[5]

In this trial, patients were treated more than 12 years ago and, fortunately, medical and endovascular management have since progressed. Case selection, device choice,[6] and planning with technical skills by use of simulation,[7] imaging modalities with decreased radiation, best practices in medical treatment, and surveillance programmes in centralised aortic units have all improved the overall management of aortic aneurysmal disease.[8] Although the EVAR trial 1 will always be a landmark trial, the long-term findings with only 57% of patients being alive at the end of follow-up should be interpreted with caution because of the following limitations.

The data collection from 10–15 years risks bias since it was done both retrospectively and prospectively, and relies on data from NHS records for procedures at the time of patient discharge (Hospital Episode Statistics) and trial-based data. The benefit was that patients lost to follow-up were retrieved and that re-interventions after open repair, such as incisional hernia repair, not collected before 2009, could be included in a retrospective manner. Follow-up for mortality (the primary outcome) was unchanged between 1999 and 2015.

In 1999, the mean age at randomisation for the EVAR trial 1 was 74 years, indicating that patients were a high-risk group for malignancy based on age rather than radiation exposure. The difference in total malignancy deaths at 15 years is small (126 in the EVAR group *vs* 123 in the open-repair group) and in fact more malignancy deaths were noted in the open-repair group at time intervals 6 months to 4 years and at 4–8 years. Appropriate investigation and robust data are needed and any insinuation that EVAR predisposes to or increases the risk of cancer might be dangerously misleading.



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The long-term surveillance after aneurysm repair in the UK trial, a country known for its evidence-based medicine, was astonishingly low despite reports warning the endovascular community about the importance of lifelong follow-up.[9]

Unfortunately, imaging data have not yet been included to explain why aneurysms excluded with second and third generation devices still rupture during long-term follow-up. Was this aneurysm growth or rupture caused by true device failures[10] (eg, fractures, migration, endoleak type I or III), or was the initial stent graft not deployed within 3 mm of the lowest renal artery? Was surveillance continued for long enough (median CT surveillance six scans [IQR 3–8] in EVAR group *vs* three scans [1–6] in open-repair group[5]) and were serious and life-threatening complications managed appropriately by secondary interventions (such as by relining, coiling, proximal fenestrated cuff) to save the patient's life?[10] Local investigators in this trial by Patel and colleagues[5] were at liberty to treat patients to their best knowledge, but some complications that are now known to cause aneurysm rupture were not treated.[11]

EVAR has gained enormous popularity worldwide with a lower initial operative mortality than open repair. Secondary ruptures after EVAR account for the long-term increase in aneurysm-related mortality. These findings, confirmed by 15 years of follow-up data from the EVAR 1 trial,[5] should alert physicians managing abdominal aortic aneurysms and might have implications for case

selection, patients' treatment choices, and continuous surveillance after EVAR. These results also show that long-term follow-up of surgical innovations is crucial.[12]

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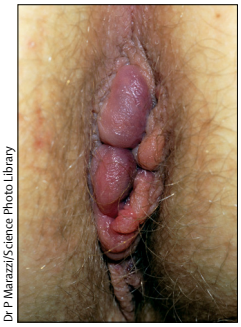
eTHoS piles pressure on haemorrhoidopexy



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Surgical innovation strives to address the perceived shortcomings and potential pitfalls associated with traditional therapeutic techniques. New devices are often recommended to patients on the basis of incomplete clinical datasets that highlight specific short-term gains over standard treatment but may not confirm long-term benefit. Enthusiasm for new technology in surgery should be balanced by the requirement to undertake objective, high-quality studies to establish the overall clinical and economic effect of surgical therapies.[1]

In *The Lancet*, Angus Watson and colleagues present eTHoS,[2] a randomised, non-blinded, multicentre, phase 3 study assessing clinical outcomes and cost-effectiveness for treatment of moderate or severe haemorrhoids using novel stapled haemorrhoidopexy versus the long-established traditional excisional haemorrhoidectomy.[2] These outcomes are of importance as each year millions of people are affected by haemorrhoids worldwide;[3] the UK National Health Service carries out in excess of 20 000 haemorrhoidal treatments.[4]

Traditional haemorrhoidectomy excises symptomatic tissue from the anal canal leaving wounds that usually take 6 weeks to heal.[5] Surgeons often contend that traditional haemorrhoidectomy is a good treatment for haemorrhoids, the axiom of "6 weeks' pain for 5 years' gain" has long been touted, although surprisingly little high-quality evidence exists to support this position.[6] Patients experience short-term discomfort after traditional haemorrhoidectomy until their anal canal wounds heal, and, if severe, this pain might give rise to additional problems such as a fear of evacuation, constipation, and an inability to pass urine requiring catheterisation.

Stapled haemorrhoidopexy was specifically developed to tackle the problem of early pain after traditional haemorrhoidectomy.[7] A ring of tissue is excised from the relatively insensate, viscerally innervated upper anal canal, with the cut edges simultaneously brought together and fixed by a circle of staples. Traction draws the prolapsing haemorrhoids into the anal canal where they remain fixed (pexy). Stapling might also interrupt the submucosal blood flow to haemorrhoids, thereby reducing symptoms of bleeding. Initial experience reinforced the view that stapled haemorrhoidopexy was less painful for patients than traditional haemorrhoidectomy, however, severe

Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial

*Rajesh Patel, Michael J Sweeting, Janet T Powell, Roger M Greenhalgh, for the EVAR trial investigators**

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*The EVAR trial investigators are listed in the appendix

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See Online for appendix

Summary

Background Short-term survival benefits of endovascular aneurysm repair (EVAR) versus open repair of intact abdominal aortic aneurysms have been shown in randomised trials, but this early survival benefit is lost after a few years. We investigated whether EVAR had a long-term survival benefit compared with open repair.

Methods We used data from the EVAR randomised controlled trial (EVAR trial 1), which enrolled 1252 patients from 37 centres in the UK between Sept 1, 1999, and Aug 31, 2004. Patients had to be aged 60 years or older, have aneurysms of at least 5·5 cm in diameter, and deemed suitable and fit for either EVAR or open repair. Eligible patients were randomly assigned (1:1) using computer-generated sequences of randomly permuted blocks stratified by centre to receive either EVAR (n=626) or open repair (n=626). Patients and treating clinicians were aware of group assignments, no masking was used. The primary analysis compared total and aneurysm-related deaths in groups until mid-2015 in the intention-to-treat population. This trial is registered at ISRCTN (ISRCTN55703451).

Findings We recruited 1252 patients between Sept 1, 1999, and Aug 31, 2004. 25 patients (four for mortality outcome) were lost to follow-up by June 30, 2015. Over a mean of 12·7 years (SD 1·5; maximum 15·8 years) of follow-up, we recorded 9·3 deaths per 100 person-years in the EVAR group and 8·9 deaths per 100 person-years in the open-repair group (adjusted hazard ratio [HR] 1·11, 95% CI 0·97–1·27, p=0·14). At 0–6 months after randomisation, patients in the EVAR group had a lower mortality (adjusted HR 0·61, 95% CI 0·37–1·02 for total mortality; and 0·47, 0·23–0·93 for aneurysm-related mortality, p=0·031), but beyond 8 years of follow-up open-repair had a significantly lower mortality (adjusted HR 1·25, 95% CI 1·00–1·56, p=0·048 for total mortality; and 5·82, 1·64–20·65, p=0·0064 for aneurysm-related mortality). The increased aneurysm-related mortality in the EVAR group after 8 years was mainly attributable to secondary aneurysm sac rupture (13 deaths [7%] in EVAR *vs* two [1%] in open repair), with increased cancer mortality also observed in the EVAR group.

Interpretation EVAR has an early survival benefit but an inferior late survival compared with open repair, which needs to be addressed by lifelong surveillance of EVAR and re-intervention if necessary.

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Introduction

Abdominal aortic aneurysm is a common disease that particularly affects men older than 60 years. As the size of the aneurysm increases the risk of rupture increases. Since 1951, surgical repair has been practised.[1] Minimally invasive vascular repair was first reported in 1986.[2] Three principal, randomised controlled trials[3–5] for abdominal aortic aneurysm have shown marked benefits of endovascular aneurysm repair (EVAR) with respect to 30-day mortality. However, the total mortality benefit was lost (catch-up of mortality) in these randomised controlled trials after 2 years (in the UK Endovascular Aneurysm Repair trial 1 [EVAR trial 1]),[6] 1–2 years (DREAM),[7] and 5 years (OVER).[8]

Schermerhorn and colleagues[9] assessed peri-operative and long-term survival, re-interventions, and complications after endovascular repair compared with open repair of abdominal aortic aneurysm in cohorts of US Medicare beneficiaries (US Government health-care insurance programme) matched by propensity score who underwent repair during 2001–08 and followed up until 2009. They found that endovascular repair, compared with open repair, was associated with early survival advantage that gradually decreased over time, with catch-up of mortality after 3 years.[9] The rate of rupture after aneurysm repair was significantly higher in those who had EVAR than in those who had open repair. An observational study[10] from a single institution in Queensland, Australia, reported no differences in 5-year, 10-year, and 15-year survival between open repair (n=982; median follow-up 6·5 years) and EVAR (n=358; median follow-up 4·0 years), but had incomplete patient reporting.

The EVAR trial 1[6] previously reported aneurysm-related mortality and total mortality up to 10 years of follow-up, at which point no difference was reported

Research in context

Evidence before this study

We searched MEDLINE and Embase on June 7, 2016, for all articles published from Jan 1, 2006, to May 31, 2016, using search terms "15 year follow up of EVAR for intact abdominal aortic aneurysm", "long-term elective repair", "abdominal aortic aneurysm", "minimally invasive surgery", "vascular surgical procedures", endovascular surgery", and "open surgery". Three principal randomised controlled trials for abdominal aortic aneurysm have shown marked benefits of endovascular aneurysm repair (EVAR) for 30-day mortality, but total mortality benefit was lost in these trials after 2 years (EVAR trial 1), 1–2 years (DREAM), and 5 years (OVER; catch-up of mortality). A comparison of endovascular with open repair of abdominal aortic aneurysm in propensity-score matched cohorts of Medicare beneficiaries found that endovascular repair was associated with early survival advantage that gradually decreased over time, with catch-up of mortality after 3 years. The rate of rupture after aneurysm repair was significantly higher in those who had EVAR than open repair. The UK EVAR trial 1 previously reported follow-up for aneurysm-related and total mortality up to 10 years, at which point no difference was recorded between EVAR and open abdominal aneurysm repair. No previous trial has used follow-up of endovascular repair or open repair after this time. An observational study done during 1990–2013, published in 2016, from a single institution in Queensland, Australia, reported no differences in 5-year, 10-year, and 15-year survival between open repair (n=982; median follow-up 6·5 years) and EVAR (n=358; median follow-up 4·0 years), but had incomplete patient reporting. A previous report from the EVAR trials data defined a "cluster" of complications (eg, type I endoleak, type III endoleak, type II endoleak with sac expansion, kinking, and migration), which was associated with secondary aortic sac rupture with 67% risk of death. The Eurostar database reported that the rate of secondary sac rupture after endovascular repair is low for the first 4 years, but after this time the rate appears to increase, particularly in those with known sac expansion.

Added value of this study

Late aneurysm-related and total mortality were both greater in patients who were randomly assigned to EVAR than those who had open repair. The rate of re-interventions, including those free from re-intervention after 2 years or 5 years, was higher in the EVAR group at all timepoints. Despite the operative benefit for the EVAR group with lower aneurysm and total mortality after 6 months, this benefit was lost partly due to secondary rupture and aneurysm-related causes of death. The main cause of aneurysm-related mortality in the EVAR group was secondary aortic sac rupture which together with a larger contribution from cancer-related deaths led to higher total mortality in late follow-up. We followed up patients for 15 years; no previous comprehensive report of comparative follow-up longer than 10 years of EVAR versus open repair seemed to have been reported.

Implications of all the evidence available

The loss of early EVAR survival benefit, followed by inferior late survival benefit and durability compared with open repair, needs to be addressed by lifelong surveillance of EVAR and prompt re-intervention if necessary. There is no time when it is safe to discontinue surveillance in patients who have had EVAR. Sac expansion needs to be tracked for all time periods and the underlying cause corrected. Novel ways to sense sac expansion would be useful to prompt early awareness of risk of secondary aortic sac rupture. Efforts should be made to understand the underlying aortic dilating disease process and to attempt to limit it. Device design might take into account the expected ongoing dilating process of the aorta. A possible increase in cancer deaths in the EVAR group in very late (>8 years) follow-up merits further consideration.

between endovascular and open abdominal aneurysm repair, but the problem of secondary sac rupture after EVAR was emerging.[11] The original trial protocol stated that if concerns became apparent about the durability of EVAR, the trial should be extended to address the issue. No previous comprehensive report of follow-up longer than 10 years of EVAR or open repair exists. We report the long-term follow up results of up to 15 years of the EVAR trial 1, in terms of aneurysm-related and total mortality, cause of death, and aneurysm-related re-interventions.

Methods

Study design and participants

In this randomised controlled trial, our participants were from the EVAR trial 1.[12] The EVAR trial 1 enrolled men and women who were aged 60 years or older between Sept 1, 1999, and Aug 31, 2004, from 37 hospitals in the UK. Patients were offered enrolment if they had an aortic aneurysm of at least 5·5 cm in diameter (assessed with CT), with aortic morphology compatible with endograft placement within the manufacturers' instructions for use, and were deemed fit for open repair (decided by surgeon, radiologist, anaesthetist, and cardiologist) with an acceptable risk of postoperative death for both procedures. Our exclusion criteria have been previously reported[13] and included unsuitability for an EVAR device, abdominal aortic aneurysm smaller than 5·5 cm in diameter, refusal to enter into the trial, or refusal to any CT scan or further treatment. The protocol is available online. We gained ethical approval for our extended patient follow-up after Sept 1, 2009,[6] from the UK's North West Multicentre Research Ethics Committee, who did not require patients to provide consent again for the ongoing follow-up of the EVAR trial 1 of up to 15 years.

For the **UK EVAR trial protocol** see https://www1.imperial.ac.uk/biosurgerysurgicaltechnology/clinical_trials_outcomes/vasculardisease/clinicaltrials/evar_trials/

Randomisation and masking

Participants were randomly allocated (1:1) to undergo either open repair or endovascular repair by computer-generated sequences of randomly permuted blocks stratified by centre, at the trial hub (Charing Cross Hospital, London, UK). Patients and treating clinicians were aware of group assignment.

Procedures

The procedures we used have been previously described.[13] Participating trial centres were reminded that all patients should continue in regular follow-up (the protocol specified annual follow-up) and all patients, including those with lapsed follow-up, should be recalled for a final clinical and imaging follow-up in 2014. The maximum aortic or sac diameter and presence of complications were recorded at each patient follow-up. Patients were followed up once a year for clinical and imaging assessment and serum creatinine concentrations. The management of aneurysm-related complications was left to the discretion of the trial centre. For our extended follow-up of patients, the grading of aneurysm-related re-interventions and the associated use of high-dependency or intensive care were obtained by questionnaire to the principal investigators at the trial centres (appendix). The Trial Endpoint Committee adjudicated the cause of death, aneurysm-related mortality, and other events based on International Classification of Diseases (version 10) causes listed and dates of aneurysm-related re-interventions. The committee were unaware of study group assignment.

For the **pre-defined statistical analysis plan** see https://www1.imperial.ac.uk/biosurgerysurgicaltechnology/clinical_trials_outcomes/vasculardisease/clinicaltrials/evar_trials/

Outcomes

Our primary outcome was aneurysm-related mortality and total mortality. Aneurysm-related mortality was defined as all deaths from aneurysm rupture before repair, within 30 days of the primary procedure, within 30 days of any re-intervention attributable to the aneurysm, from other aneurysm-related causes (including graft infection or fistula), or from secondary aneurysm rupture after repair. Our secondary outcomes included re-intervention (time to first re-intervention, first re-intervention for a life-threatening problem, and first serious re-intervention); complications, sac growth and risk of late complications, and costs and cost-effectiveness will be reported separately.

For the primary mortality outcome, patients were followed up from Sept 1, 1999, to June 30, 2015 (using record linkage from the Office of National Statistics, with death classification based on death certificates and clinical information provided to the endpoint committee[6]). Patients were followed-up for graft-related complications and re-interventions from Sept 1, 1999, to March 31, 2015. For graft-related re-interventions between Sept 1, 2009, and March 31, 2015, follow-up was predominantly using record linkage to administrative data for hospital readmissions and re-interventions via Hospital Episode Statistics. Re-interventions, including incisional hernia repair throughout the trial, and other operative procedures preceding death were subsequently checked with the trial centres, with 89% concordance between administrative and clinical site data (appendix). Graft-related complications and re-interventions were also directly obtained from the trial centres with a new case record form for our follow-up between Sept 1, 2009, and March 31, 2015 (appendix). The primary analysis compared rates of total mortality and aneurysm-related mortality until June 30, 2015.

Statistical analysis

As of Sept 1, 2009, 711 patients with an mean age of 80 years were reported alive and under follow-up in the EVAR trial 1 (357 in the EVAR group and 354 in the open repair group). This number gave us 80% power at the 5% significance level to detect a hazard ratio (HR) of 1·25 during the extended period from Sept 1, 2009, to June 30, 2015, assuming 10% of patients to be still alive at the end of June 30, 2015. We completed all analyses according to a pre-defined statistical analysis plan and were based on the intention-to-treat principle, with outcomes assessed from the time of randomisation. We used Cox regression modelling to compare total mortality, aneurysm-related mortality, and time to first graft-related re-intervention. Hazard ratios (HR) were presented as the EVAR group relative to the open-repair group. Due to non-proportional hazards during the first 8 years of follow-up,[6] we analysed data by splitting follow-up into four groups of time: from randomisation to 6 months, 6 months to 4 years, 4 years to 8 years, and after 8 years' follow-up. We assessed deviations from the proportional hazards assumption as overall and within these periods by regressing-scaled Schoenfeld residuals against log of time. Regression estimates are presented both unadjusted and adjusted for baseline covariates. We used Kaplan-Meier estimates to show survival probabilities up to 15-years' follow-up in each group.

Additionally, we did a per-protocol analysis on data from patients who had undergone their randomly assigned treatment and did two sensitivity analyses to allow inclusion of patients with missing covariates in the adjusted models (appendix).

We completed time to first re-intervention analyses separately for any graft-related re-intervention, any serious re-intervention and any life-threatening condition (appendix). The criteria used to censor individuals are provided in the appendix. We also did further analyses for patients without any re-intervention between randomisation and at 2 years of follow-up and without any re-intervention between randomisation and 5 years of follow-up. We did all analyses with Stata (version 13). The oversight committee, data monitoring and ethical committee, approved the statistical analysis plan. The trial is registered at ISCRTN (ISRCTN55703451).

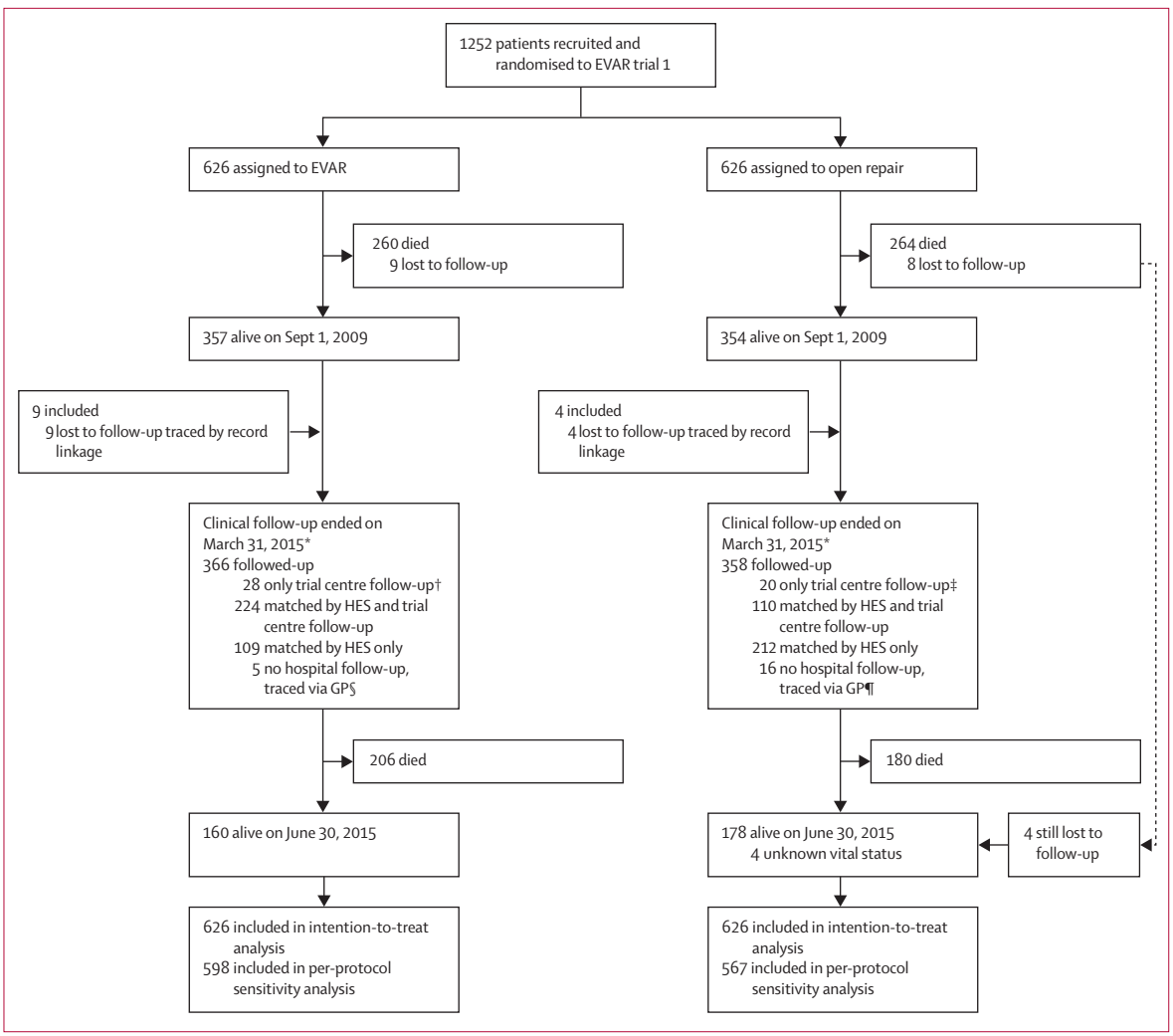

Figure 1: **Trial profile for mortality and re-interventions**
EVAR=endovascular aneurysm repair. HES=hospital episode statistics (record linkage to administrative data for hospital readmissions and re-interventions). GP=general practitioner. *End of clinical follow-up. †One English patient unmatched by HES and 27 patients from Northern Ireland or Scotland. ‡One English patient unmatched by HES and 19 patients from Northern Ireland or Scotland. §One English patient unmatched by HES and four patients from Northern Ireland or Scotland. ¶Four English patients unmatched by HES and 12 patients from Northern Ireland or Scotland.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, reporting of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
From Sept 1, 1999, to Aug 31, 2004, we recruited 1252 patients to participate in this trial, who were equally randomly assigned to the two treatment groups (626 patients per group; figure 1; appendix). No substantial differences were noted in baseline characteristics between the groups. Overall mean age of patients was 74 years, and 1135 (91%) were men (appendix).[12]

Patients were followed up until June 30, 2015 (mean 12·7 years; median 12·4 years; range 1·8–15·8 years); mean person-years observation to either death or end of the study was 8·0 years. By June 30, 2015, only four patients were lost to follow-up for mortality and 25 for re-interventions (five in the EVAR group and 20 in the open-repair group), but data were available from record linkage for 13 [76%] of 17 patients previously lost to mortality follow-up (figure 1). For these 13 individuals found from record linkage, a cause of death was established on the basis of only a death certificate. Annual clinical follow-up with either CT or duplex imaging reduced steadily over the trial and was consistently lower in the open-repair group than in the EVAR group (appendix). Over the course of follow-up a median of six CT scans (IQR 3–8) were done per patient in the EVAR

	Endovascular repair (N=626)		Open repair (N=626)		Hazard ratio (95% CI)		p value†
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Unadjusted	Adjusted*	
Total mortality							
All patients	466/626 (74%)	9·3	444/626 (71%)	8·9	1·05 (0·92–1·19)	1·11 (0·97–1·27)	0·14
0–6 months	26/626 (4%)	8·5	45/626 (7%)	15·0	0·57 (0·35–0·92)	0·61 (0·37–1·02)	0·06
>6 months to 4 years	126/600 (21%)	6·7	116/581 (20%)	6·3	1·07 (0·83–1·38)	1·13 (0·87–1·47)	0·35
>4–8 years	135/474 (28%)	8·3	129/464 (28%)	8·0	1·03 (0·81–1·31)	1·07 (0·83–1·37)	0·62
>8 years	179/339 (53%)	14·9	154/333 (46%)	12·7	1·18 (0·95–1·47)	1·25 (1·00–1·56)	0·048
Aneurysm-related mortality							
All patients	56/626 (9%)	1·1	45/626 (7%)	0·9	1·24 (0·84–1·83)	1·31 (0·86–1·99)	0·21
0–6 months	14/626 (2%)	4·6	30/626 (5%)	10·0	0·46 (0·24–0·87)	0·47 (0·23–0·93)	0·031
>6 months to 4 years	12/599 (2%)	0·6	8/581(1%)	0·4	1·48 (0·60–3·62)	1·46 (0·56–3·83)	0·44
>4–8 years	14/474 (3%)	0·9	4/464 (1%)	0·2	3·46 (1·14–10·52)	3·11 (0·99–9·72)	0·05
>8 years	16/339 (5%)	1·3	3/333 (1%)	0·2	5·50 (1·60–18·89)	5·82 (1·64–20·65)	0·0064

*Hazard ratios adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 s, log creatinine, statin use, body-mass index, smoking status, systolic blood pressure and total cholesterol; 77 individuals excluded due to missing data. †p value adjusted for covariates.

Table 1: **Deaths from any cause and aneurysm-related causes, according to time since randomisation in the intention-to-treat population**

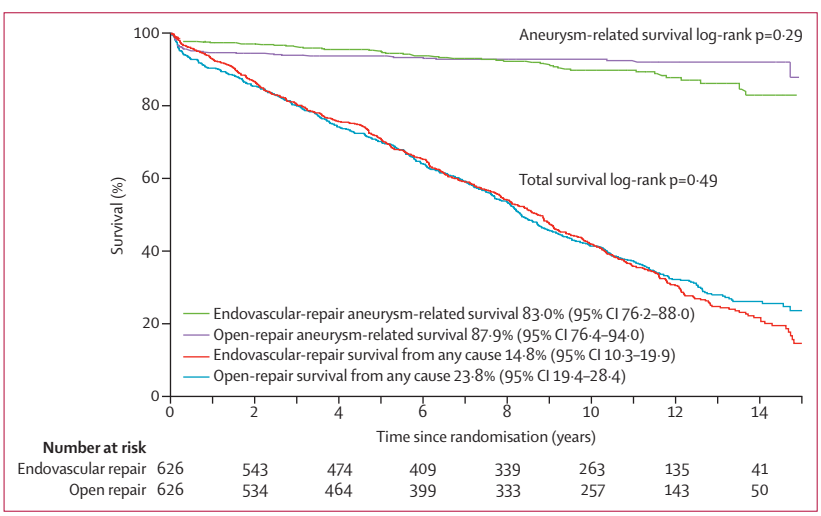

Figure 2: **Kaplan-Meier estimates for total survival and aneurysm-related survival up to 15 years of follow-up**
The hazard ratio is 1·05 (95% CI 0·92–1·19) for total mortality, and is 1·24 (0·84–1·83) for aneurysm-related mortality.

group and three (1–6) per patient in the open-repair group. Of the patients who had not had death reported by Sept 1, 2009, 655 (90%) of 728 patients were tracked with Hospital Episode Statistics, including 13 patients previously lost to follow-up, with local hospital follow-up reported in 48 (70%) of the 69 remaining patients (21 [3%] patients had no further hospital admissions or follow-up; figure 1). After publication of the 30-day mortality results from the EVAR trial 1,[3] 26 of the 37 trial centres remained in equipoise and continued recruitment into a separate study from Sept 1, 2004, to June 15, 2005, when primary outcome results were published,[12] with a further 175 patients (appendix) not previously reported but used in our sensitivity analyses for only mortality.

During 9968 person-years of follow-up 910 deaths occurred, 101 (11%) of which were aneurysm related (table 1). Overall aneurysm-related mortality was 1·1 deaths per 100 person-years in the EVAR group and 0·9 deaths per 100 person-years in the open-repair group (adjusted HR 1·31, 95% CI 0·86–1·99, p=0·21). For total mortality, we recorded 9·3 deaths per 100 person-years in the EVAR group and 8·9 deaths per 100 person-years in the open-repair group (adjusted HR 1·11, 95% CI 0·97–1·27, p=0·14). Our results for sensitivity analyses that included patients with missing baseline covariates were similar for aneurysm-related and total mortality (appendix).

We noted evidence of deviation from proportional hazards assumption for aneurysm-related mortality (p<0·0001), with a significant early benefit of EVAR during the first 6 months after randomisation, counteracted by an increase in aneurysm-related mortality after 4 years, the difference being most significant after 8 years (table 1). Additionally, we reported deviation from the proportional-hazards assumption for total mortality (p=0·0232), with a significant early benefit of EVAR during the first 6 months after randomisation, similar mortality between the groups from 6 months to 8 years, but after 8 years a significant increase in patient mortality in the EVAR group (table 1). Kaplan-Meier curves for patient survival for aneurysm-related and any cause are shown in figure 2. Aneurysm-related mortality curves cross-over between 6 years and 8 years and total mortality curves diverge after 10 years. Survival was not significantly improved in EVAR compared with open repair (median 8·7 years in EVAR group *vs* median 8·3 years in open-repair group; log-rank p=0·49). Sensitivity analyses including the additional 175 patients from the separate 2004–05 study yielded very similar results (appendix).

The full causes of death, by time since randomisation, are in table 2. Overall, rupture after aneurysm repair resulted in 31 deaths in the EVAR group and five in the open-repair

	Endovascular repair	Open repair
Randomisation to 6 months	n=26	n=45
Aneurysm rupture before repair (primary)	5 (19%)	5 (11%)
Aneurysm-related after repair	7 (27%)	24 (53%)
Aneurysm rupture after repair (secondary)	2 (8%)	1 (2%)
Coronary heart disease	4 (15%)	4 (9%)
Stroke	0	1 (2%)
Other vascular disease	2 (8%)	2 (4%)
Cancer		
Lung	1 (4%)	0
Other	2 (8%)	0
Respiratory	0	5 (11%)
Renal	2 (8%)	0
Other	1 (4%)	3 (7%)
Unknown	0	0
>6 months to 4 years	n=126	n=116
Aneurysm rupture before repair (primary)	2 (2%)	5 (4%)
Aneurysm-related after repair	2 (2%)	2 (2%)
Aneurysm rupture after repair (secondary)	8 (6%)	1 (1%)
Coronary heart disease	27 (22%)	25 (22%)
Stroke	11 (9%)	6 (5%)
Other vascular disease	6 (5%)	5 (4%)
Cancer		
Lung	19 (15%)	20 (17%)
Other	20 (16%)	29 (25%)
Respiratory	10 (8%)	16 (14%)
Renal	4 (3%)	1 (1%)
Other	15 (12%)	6 (5%)
Unknown	2 (2%)	0
>4–8 years	n=135	n=129
Aneurysm rupture before repair (primary)	0	1 (1%)
Aneurysm-related after repair	6 (4%)	2 (2%)
Aneurysm rupture after repair (secondary)	8 (6%)	1 (1%)
Coronary heart disease	31 (23%)	28 (22%)
Stroke	16 (12%)	12 (9%)
Other vascular disease	7 (5%)	7 (5%)
Cancer		
Lung	12 (9%)	16 (12%)
Other	22 (16%)	27 (21%)
Respiratory	16 (12%)	22 (17%)
Renal	4 (3%)	3 (2%)
Other	13 (10%)	10 (8%)
Unknown	0	0
(Table 2 continues in next column)		

	Endovascular repair	Open repair
(Continued from previous column)		
>8 years	n=179	n=154
Aneurysm rupture before repair (primary)	0	1 (1%)
Aneurysm-related after repair	3 (2%)	0
Aneurysm rupture after repair (secondary)	13 (7%)	2 (1%)
Coronary heart disease	33 (18%)	35 (23%)
Stroke	10 (6%)	15 (10%)
Other vascular disease	4 (2%)	12 (8%)
Cancer		
Lung	13 (7%)	10 (6%)
Other	37 (21%)	21 (14%)
Respiratory	29 (16%)	30 (19%)
Renal	5 (3%)	4 (3%)
Other	31 (17%)	24 (16%)
Unknown	1 (1%)	0

***Table 2*: Causes of death in patients, by time since randomisation in the intention-to-treat population**

group. Two patients in the open-repair group had ruptures in 2010 and 2012, having refused the operation. Overall there was no difference in cancer-related mortality between the groups (adjusted HR 1·09, 95% CI 0·84–1·40, p=0·53), although an increase was recorded in the EVAR group after 8 years (adjusted HR 1·87, 95% CI 1·19–2·96, p=0·0072; appendix).

No significant interactions were noted between patients randomly assigned treatment group and age, sex, or aneurysm diameter for either aneurysm-related or total mortality (p>0·10 for all comparisons; appendix).

Per-protocol analysis was of 598 patients in the EVAR group and of 567 patients in the open-repair group, and again strongly showed the benefit of EVAR during the first 6 months, counteracted by an increase in aneurysm-related mortality at all subsequent time periods (appendix), the increase being proportionately greater than for the analysis by randomised group. Overall aneurysm-related mortality was significantly higher in the EVAR group (1·0 per 100 person-years) than in the open repair group (0·6 per 100 person-years; adjusted HR 1·76, 95% CI 1·07–2·89, p=0·026). Total mortality was not significantly higher in the EVAR group at 9·1 per 100 person-years than in the open-repair group at 8·4 per 100 person-years (adjusted HR 1·14, 95% CI 0·99–1·31, p=0·07).

During 9715 person-years of follow-up, 258 graft-related re-interventions were undertaken in 165 patients in the EVAR group and 105 were done in 74 patients in the open-repair group, with higher rates to first re-intervention in the EVAR group (table 3). The re-intervention rate was significantly higher in the EVAR group for any re-intervention and serious re-interventions in the first 4 years and for life-threatening re-interventions (including conversion to open repair, repeat EVAR and treatment of graft infection) in the follow-up of 6 months to 4 years and after 8 years (table 3, figure 3). Even after 2-years or 5-years follow-up without any life-threatening

	Endovascular repair (n=626)		Open repair (n=626)		Hazard ratio (95% CI)		p value†
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Unadjusted	Adjusted*	
Any re-intervention							
All patients	164/626 (26%)‡	4·1	74/626 (12%)	1·7	2·37 (1·80–3·12)	2·42 (1·82–3·21)	<0·0001
0–6 months	67/626 (11%)	23·7	36/626 (6%)	12·5	1·89 (1·26–2·83)	1·95 (1·28–2·98)	0·0020
>6 months to 4 years	56/536 (10%)	3·5	9/559 (2%)	0·5	6·81 (3·37–13·77)	6·29 (3·09–12·78)	<0·0001
>4–8 years	21/381 (6%)	1·6	16/436 (4%)	1·1	1·48 (0·77–2·84)	1·60 (0·81–3·15)	0·17
>8 years	20/264 (8%)	2·3	13/282 (5%)	1·3	1·76 (0·88–3·54)	1·51 (0·71–3·19)	0·29
Any serious re-intervention							
All patients	140/626 (22%)	3·3	57/626 (9%)	1·3	2·60 (1·91–3·54)	2·62 (1·90–3·61)	<0·0001
0–6 months	45/626 (7%)	15·5	19/626 (3%)	6·5	2·38 (1·39–4·06)	2·46 (1·39–4·33)	0·0019
>6 months to 4 years	52/557 (9%)	3·1	8/570 (1%)	0·5	6·93 (3·29–14·58)	6·45 (3·04–13·68)	<0·0001
>4–8 years	21/403 (5%)	1·5	16/444 (4%)	1·1	1·43 (0·75–2·74)	1·45 (0·73–2·88)	0·29
>8 years	22/277 (8%)	2·5	14/289 (5%)	1·4	1·76 (0·90–3·44)	1·59 (0·78–3·26)	0·20
Life-threatening re-intervention							
All patients	85/626 (14%)	1·9	41/626 (7%)	0·9	2·12 (1·46–3·08)	2·09 (1·42–3·08)	0·0002
0–6 months	22/626 (4%)	7·4	19/626 (3%)	6·5	1·14 (0·62–2·11)	1·08 (0·57–2·08)	0·81
>6 months to 4 years	27/576 (5%)	1·5	2/570 (<1%)	0·1	13·77 (3·27–57·92)	12·78 (3·01–54·23)	0·0006
>4–8 years	15/434 (3%)	1·0	11/450 (2%)	0·7	1·41 (0·65–3·06)	1·41 (0·63–3·14)	0·40
>8 years	21/302 (7%)	2·1	9/300 (3%)	0·8	2·50 (1·14–5·45)	2·44 (1·05–5·68)	0·039

*Hazard ratios adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 s, log creatinine, statin use, body-mass index, smoking status, systolic blood pressure, total cholesterol, top neck diameter, neck length, and maximum common iliac diameter (91 individuals excluded due to missing data). †p value adjusted for covariates. ‡Re-interventions were done in 165 patients with endovascular repair, but one patient who had re-intervention is excluded from analyses because of unknown time of re-intervention.

Table 3: **First re-interventions in patients, according to time since randomisation in the intention-to-treat population**

re-intervention, new life-threatening re-interventions occurred at any time up to 15-years of follow-up (figure 3). The relative difference in re-intervention rate between the groups was highest from 6 months to 4 years after randomisation, particularly for the most serious re-interventions (table 3). A similar pattern, by timepoint, was observed for second and subsequent re-interventions (appendix).

Discussion

Our long-term results showed aneurysm-related and total mortality are greater in late follow-up for patients who had EVAR than those who had open repair, but over the whole follow-up the mean total and aneurysm-related mortality were not significantly different between groups. The significant late divergence of the survival curves in favour of open repair (figure 2) can be partly explained through greater increase in late mortality from aneurysm-related deaths in the EVAR group.

Total and aneurysm-related mortality were lower in patients who received EVAR in the first 6 months. However, after this time deaths in the EVAR group increased, and after 8 years of follow-up both total and aneurysm-related mortality were significantly higher in the EVAR group than in the open repair group. After the first 6 months, the increased aneurysm-related deaths in the EVAR group were predominantly from secondary sac rupture. Over the whole follow-up, two aneurysm-related deaths followed re-intervention, but the 31 deaths from secondary sac rupture were partly due to not having underlying causes of sac expansion from endoleak corrected.[11] Of patients allocated to open repair, five secondary ruptures occurred, of which four were originally assigned to open repair but received EVAR, and the last secondary rupture occurred more than 8 years after the open-repair procedure. Secondary sac rupture is much more common after EVAR, occurring at any period after the procedure, whereas sac rupture after open repair is rare and tends to occur in late follow-up.

Re-interventions occurred in both groups throughout our study follow-up, including in patients who were free from re-intervention after 2 years or even 5 years. The rate of re-intervention was higher in the EVAR group at all follow-up timepoints. These late re-interventions included those with a high severity score, indicating that it was not safe to stop follow-up for patients with EVAR. However, in this trial some patients were discharged from surveillance and therefore lost the option of planned re-intervention. With a mean age of 74 years at randomisation, there could have been some pressing clinical reasons not to re-intervene for some patients after long-term follow-up because of old age and frailty. A criticism of earlier reports from this trial that not all incision-related re-interventions, after open repair, were reported was addressed in this long-term follow-up.

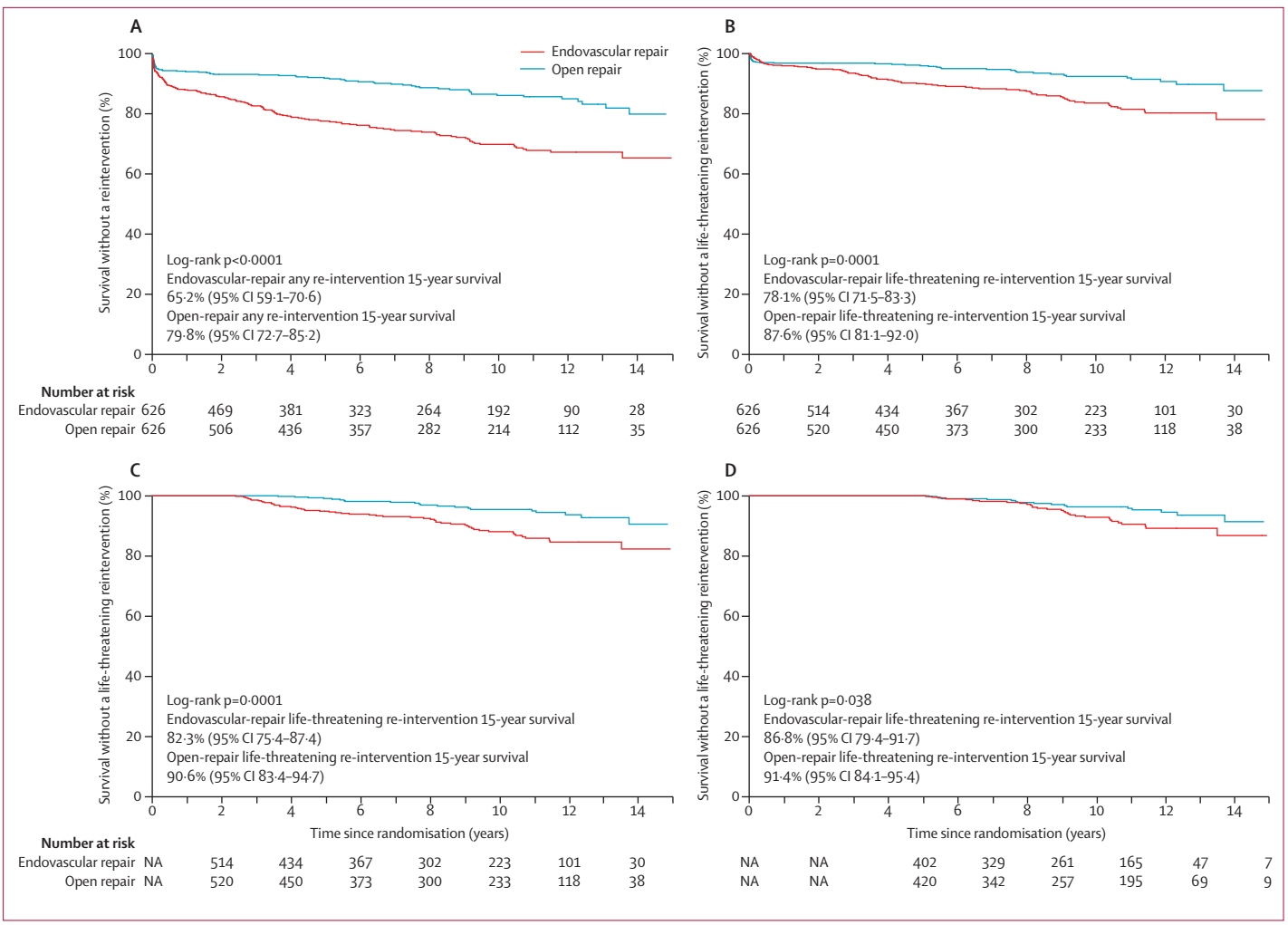

Figure 3: **Kaplan-Meier estimates of time to first re-intervention in the EVAR and open repair groups during 15 years of follow-up**
The time to first re-intervention (A), to first life-threatening re-intervention (B), to first life-threatening re-intervention for individuals who have survived 2 years free of a life-threatening re-intervention (C), and the time to first life-threatening re-intervention for individuals who have survived 5 years free of a life-threatening re-intervention (D). EVAR=endovascular aneurysm repair. NA=not applicable.

Limitations of this trial include that devices we used were implanted between 1999 and 2004 and newer devices since then might be expected to have better results.[14] Additionally, imaging to establish size and placement of endografts has improved since 2004. The original trial protocol was for annual follow-up by CT scan, which was used in the early stages of the trial. However, in the later stages, many of the patients in the EVAR group were followed up with ultrasonography. This change from CT to ultrasonography was affected by increasing concern about radiation exposure.[15] Moreover, imaging follow-up declined over time, particularly for the patients in the open-repair group. Consequently, re-interventions became less likely once surveillance ceased. We cannot assume that follow-up practice is the same in the rest of the world as it is in the UK where many patients were discharged from surveillance after several years. Since the patients in the EVAR group had more diligent follow-up than those in the open-repair group, aneurysm-related mortality might have been underestimated in the open-repair group, although this factor does not affect our findings for total mortality. A further limitation is that because of decreasing clinical follow-up at the original trial hospitals the methodology to identify re-interventions changed after 2009 to predominantly use record linkage through the Hospital Episode Statistics administrative dataset, with these re-interventions subsequently being validated at the trial hospitals. However, these data also captured information for patients whose care had moved to non-trial hospitals and recovered some patients who had been previously lost to follow-up.

Patients seem to prefer EVAR[16] to open repair, and currently it is the method of choice for repair of abdominal aortic aneurysm. EVAR devices are constantly being improved and sizing and imaging methods available for

deployment are better now than they were between 1999 and 2004: a corollary is that experience in open repair is declining. However, aortas with aneurysmal disease continue to dilate and over time a good device could leak or migrate and even an open repair can rupture. Challenges in the future to maintain the initially better results of being in the EVAR group include the need to halt the dilating disease process as well as devices that allow for this inevitable dilating process over the years. The long-term results of this study can act as a benchmark against which new endovascular technologies for aneurysm repair can be compared with at each timepoint. In the meantime, surveillance must be addressed in clinical guidelines: to be diligent, regular, easy, and avoid CT scan if possible, and perhaps concentrate on the sac diameter after EVAR either by ultrasonography or novel implantable sensor devices.[17–21]

Contributors

RMG designed the trial with support from JTP. MJS, JTP, and RMG wrote the first draft of this manuscript. RP gathered data by trial centres of 2010 onwards. MJS did statistical analyses. The writing committee (RP, MJS, JTP, and RMG) did literature searches, interpreted the data, and wrote the paper with critical review, provided by the Trial Management Committee who decided to submit the paper for publication; but RMG had overall responsibility.

Declaration of interests

MJS reports grants from the National Institute for Health Research, during the conduct of the study. RMG serves as a salaried director of BIBA Medical and has an equity interest in the company, and also serves as an expert witness on behalf of patients with vascular disease. RP and JTP declare no competing interests.

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