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Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair (CAESAR): Results from a Randomised Trial

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Abstract *Background:* Randomised trials have failed to demonstrate benefit from early surgical repair of small abdominal aortic aneurysm (AAA) compared with surveillance. This study aimed to compare results after endovascular aortic aneurysm repair (EVAR) or surveillance in AAA <5.5 cm.
Methods: Patients (50–79 years) with AAA of 4.1–5.4 cm were randomly assigned, in a 1:1 ratio, to receive immediate EVAR or surveillance by ultrasound and computed tomography (CT) and repair only after a defined threshold (diameter ≥5.5 cm, enlargement >1 cm /year, symptoms) was achieved. The main end point was all-cause mortality. Recruitment is closed; results at a median follow-up of 32.4 months are here reported.
Results: Between 2004 and 2008, 360 patients (early EVAR = 182; surveillance = 178) were enrolled. One perioperative death after EVAR and two late ruptures (both in the surveillance group) occurred. At 54 months, there was no significant difference in the main end-point rate [hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.30–1.93; $p = 0.6$] with Kaplan–Meier estimates of all-cause mortality of 14.5% in the EVAR and 10.1% in the surveillance group. Aneurysm-related mortality, aneurysm rupture and major morbidity rates were similar. Kaplan–Meier estimates of aneurysms growth ≥5 mm at 36 months were 8.4% in the EVAR group and 67.5% in the surveillance group (HR 10.49; 95% CI 6.88–15.96; $p < 0.01$). For aneurysms under surveillance, the probability of delayed repair was 59.7% at 36 months (84.5% at 54 months). The probability of receiving open repair at 36 months for EVAR feasibility loss was 16.4%.
Conclusion: Mortality and rupture rates in AAA <5.5 cm are low and no clear advantage was shown between early or delayed EVAR strategy. However, within 36 months, three out of every five small aneurysms under surveillance might grow to require repair and one out of every six might lose feasibility for EVAR.

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Surveillance is safe for small AAA if close supervision is applied. Long-term data are needed to confirm these results.
Clinical Trial Registration Information: This study is registered, NCT Identifier: NCT00118573.

Previously published randomised controlled trials have demonstrated that there is no advantage of surgery versus surveillance in the treatment of patients with abdominal aortic aneurysms (AAAs) in the diameter range of 4.1–5.5 cm.[1–3]

However, since then, there has been an increasing application of endovascular aortic aneurysm repair (EVAR) as a less-invasive alternative to open surgery.[4–6] EVAR with last-generation devices has been claimed to significantly decrease the operative risks with respect to open surgery and proposed as a potential choice for early treatment of patients with small AAA to prevent the future risk of rupture.[5,6]

Although the natural history of AAA is that of a continuing growth, the rupture risk, at small aneurysm size, may be so low that early EVAR may result in over-treatment, exposing the patients to unnecessary risk of early or late procedure-related complications.[7,8] On the other hand, there is the potential risk that surveillance would miss unpredicted ruptures in small AAA.

The Comparison of surveillance versus Aortic Endografting for Small Aneurysm Repair study (CAESAR) is a randomised multicentre trial that was launched to compare early endovascular repair versus surveillance with ultrasonography and computed tomography (CT) in the treatment of aneurysms between 4.1 and 5.4 cm in diameter. Midterm results are presented.

Methods

Detailed methods of the CAESAR trial have been previously published.[9] Briefly, recruitment began on 30 August 2004, and ended on 31 December 2008 with 20 approved participating European/Western Asian hospitals. Data acquisition was stopped on 31 January 2010, for this report.

The trial was performed according to the CONsolidated Standards of Reporting Trials (CONSORT) Statement recommendations[10] and registered at http://www.clinicaltrials.gov with NCT Identifier: NCT00118573 (Study ID Numbers ICMJE 384/03).

The study was approved by a central human rights committee and the institutional review boards at each participating centre. An independent data monitoring committee reviewed the data at regular intervals. Trained trial coordinators at every centre were responsible for recruitment of patients and data collection. Data were collected centrally at the main trial office based at the Vascular Surgery Unit of Hospital S. Maria Misericordia, University of Perugia, Perugia, Italy.

Study participants: patients

Eligible patients had an AAA of 4.1–5.4 cm in diameter, 50–79 years of age, AAA suitable for EVAR as evaluated by CT scan (performed within 3 months) and at least a 5-year life expectancy.

Patients were excluded if they had severe co-morbidities or a suprarenal/thoracic aorta $\geq$4.0 cm, needed urgent repair, or were unable or unwilling to give informed consent or follow the protocol.

Entry evaluation included demographics, co-morbidities, medications, risk factors (defined according to the Society of Vascular Surgeons/American Association for Vascular Surgery (SVS/AAVS) reporting standards)[11] and measurements of various parameters from preoperative aortic imaging (e.g., aortic neck length and diameter) to assess the suitability for EVAR. EVAR suitability before and after randomisation was left at the discretion of the participating centre and based on CT evaluation. CT measurements were mandatory to determine aneurysm diameter and suitability for EVAR before randomisation, as well as need for repair during follow-up. Diameter of the aneurysm was defined on CT scan at the maximum external cross-sectional measurement in any plane but perpendicular to the vessel axis. The study included a central review of all CT imaging morphology data (core lab analysis).

Anonymised records of patients with AAA 4.1–5.4 cm not included in the trial were kept in a separate database and reasons for exclusion recorded.

Participants: centres

The protocol specified that only centres performing both endovascular and open aortic repair could be approved to participate. For participation in the trial, individuals were required to have: (1) a minimum yearly volume of 50 AAA open or endovascular repairs, (2) performed at least 50 EVAR procedures in their experience and (3) provided track record of all aortic procedures performed during the past two years. Participating centres had to ensure high-quality CT scan and ultrasonography studies in validated laboratories by operators with documented experience in this field and adherence with the rules of the trial until the completion of the study.

Randomisation and masking

Randomisation was designed with equal probability (1:1 ratio) of assignment to either early EVAR or surveillance by means of a computed-generated random-number list, stratified by centre using a permuted block design and carried online through the Internet. After eligibility verification, allocated treatment was immediately available from the website (www.caesarstudy.com) to authorised accessed investigators.

Although patient assignment was necessarily unblinded, outcome data by treatment group were available during enrolment only to the biostatistician and data monitoring committee.

Procedures and follow-up

For patients assigned to early EVAR, the transluminal introduction of an aortic endograft system needed to be performed as soon as possible. To guarantee homogeneity of results, a single model of device (Zenith AAA Endovascular Graft; William Cook Europe, Bjaverskov, Denmark) was allowed for EVAR throughout the duration of enrolment.

Colour duplex ultrasound and plain X-ray of the abdomen were required before discharge. Follow-up visits were scheduled at 1 month and every 6 months thereafter, with clinical and ultrasound examination. Plain X-ray and contrast-enhanced CT scan were required yearly.

Patients assigned to the surveillance arm were seen every 6 months with clinical and ultrasonography studies and annual CT scan. Surveillance was continued until either the patients died, or repair was assigned or the trial ended. Repair was allowed only when the aneurysm grew to 5.5 cm diameter in size, rapidly increased in diameter ($>$1 cm/ year) or became symptomatic. Patients under surveillance, who met one or more threshold criteria for repair, were treated as soon as possible. EVAR was performed if anatomical suitability was maintained; alternatively open surgery was chosen.

Ultrasonography was not used to define aneurysm diameters but only to monitor aneurysm size and to assess achievement of threshold criteria that needed CT confirmation.

Outcome measures

The primary outcome measure was mortality from any cause. Secondary outcomes included: (1) aneurysm-related deaths (defined as any death caused directly or indirectly by aneurysm rupture or aneurysm repair), (2) aneurysm rupture, (3) perioperative (30 days or inpatient) or late adverse events (defined according to the SVS/AAVS reporting standards),[11] (4) conversion to open repair, (5) loss of treatment options (anatomical suitability for EVAR) and (6) aneurysm growth rate.

Statistical analysis

We originally calculated that 740 patients (i.e., 370 patients per group) needed to be enrolled to detect a 5% and a 15% difference in survival rates at 36 and 54 months, respectively, between the early EVAR and the control groups with a statistical power of 80% at the 5% significance level. The values for the surveillance group were those observed in the UK Small Aneurysm Trial Participants.[13] To reach this number, we planned a 2-year enrolment period and an additional follow-up of 3 years, assuming 3% loss to follow-up.

After 2 years of enrolment, on the basis of the observed adverse events, it was estimated that more than 3000 patients were needed to be enrolled.

Consequently, the study was reconfigured to reflect lower than planned enrolment rate and lower all-cause mortality rate. Enrolment was continued for an additional 2 years and 4 months. Nevertheless, following a futility analysis (major outcome difference 1.4%), the Committee stopped recruitment on 31 December 2008.

Primary analysis was by intention-to-treat. Outcomes were given in absolute numbers and in cumulative incidences. Rates of cumulative event after 36 and 54 months' rates were calculated by the Kaplan–Meier method to compensate for patient dropouts and estimates between the two randomisation groups were compared with the log-rank and Wilcoxon tests. Interactions of covariate on outcome were estimated with Cox proportional hazard regression models and expressed as hazard ratios (HRs) with confidence intervals (CIs), coefficient and standard errors. Covariates in the Cox model were selected through stepwise regression using the maximum partial likelihood ratio (enter 0.10; remove 0.15). Variables were compared by using χ^2, Fisher's exact test, *t*-test and analysis of variance (ANOVA) when appropriate. Mean with Standard Deviation (SD) and median with interquartiles ranges (IQRs) were used to describe continuous variables. Aneurysm growth over time in the two groups was assessed with linear regression. *P*-values were two-sided and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using BioMedical Data Processing (BMDP) Statistical Software Package, version 2009 (Statistical Software Inc., Los Angeles, CA, USA).

The protocol originally specified publication of 54-month results when available on all patients to ensure that short-term postoperative risks after early EVAR would be distanced and balanced with the surveillance arm risks. Because of important changes in survival and aneurysm growth noted during the second year of follow-up, allowing higher than expected repair rates in the surveillance arm, this plan was amended to reveal midterm results of the trial in a report.

Role of the funding source

The trial was originally funded with a grant by Cook Medical. In December 2006, the sponsorship withdrew. Enrolment and follow-up fees for patients included in the study after 1 January 2007 were not paid by any sponsorship and the trial continued as a full spontaneous research unfunded trial. However, study design, data collection, data analysis, data interpretation and the writing of the report were at all times conducted independently from the sponsor. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between 30 August 2004 and 31 December 2008, 432 patients potentially eligible for the trial were screened. As many as 72 were excluded before randomisation. Fig. 1 shows the trial profile. Reasons for exclusion consisted mainly in patients' refusal (79.2%) and less commonly in investigators' choice (20.8%). Enrolment was stopped when only 50% of the desired inclusion population was reached after 3 years, based on futility analysis results. Fig. 2 shows patients enrolment over time.

A total of 360 patients, who consented, were randomised at 20 centres: 182 were assigned to undergo early EVAR and 178 to undergo surveillance.

There were 345 (95.8%) males and 15 (4.2%) females, aged ≥50—79 years; and mean aneurysm diameter was 47.2 mm (SD 3.24). The two groups were similar at baseline except for mean distal aortic diameter, which was about 1.5 mm smaller in the surveillance group (27.5 versus 29.0 mm) (Tables 1—3).

Of the 182 patients randomly assigned to early EVAR, seven did not undergo endovascular repair after randomisation: six declined treatment and one underwent open repair according to patient's choice. Overall, the treatment was started according to the randomised assignment in 96.0% of patients (175 of 182).

Of the 178 patients assigned to surveillance, one received immediate EVAR and the treatment started according to randomised assignment in 99.4% of patients (177 of 178).

Following the enrolment, of the aneurysms in the EVAR group, four had open surgery, all according to protocol: three because of immediate EVAR failure (immediate conversion) and one was a late conversion. Of the aneurysms under surveillance, 172 did not undergo repair until the diameter of the AAA was more than 5.5 cm, increased more than 1 cm/ year or became tender (per-protocol repair). Five patients assigned to surveillance underwent repair against the protocol: four requested early EVAR and one had surgery performed by a surgeon not participating in the trial.

Therefore, by the time of the present analysis (31 January 2010), 96.4% of patients overall adhered to their assigned treatment (347 of 360). Aneurysm repair had been performed overall in 175/182 of the patients in the early EVAR group (171 EVAR and four open) and in 85/178 in the surveillance group. The median time between randomisation and repair was 22 days (IQR 14—35) in the early EVAR group and 741 days (IQR 443—937) in the surveillance group. Early-EVAR resulted in significantly reduced mean procedure time and mean estimated blood loss. Perioperative mortality (30 days or inpatient) and mean hospital stay were similar in the two groups (Table 4).

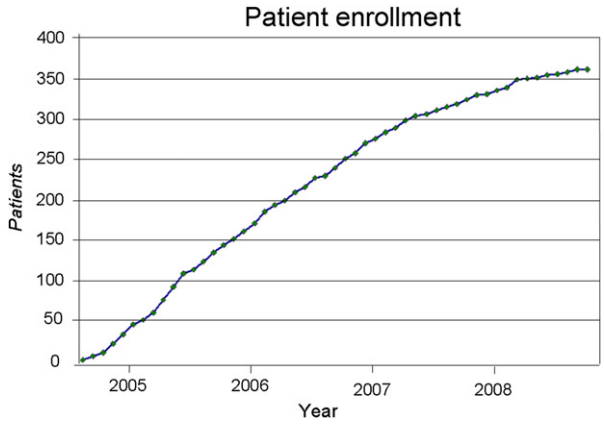


Figure 2 Patients' enrolment over years.

Median follow-up was 32.4 months (IQR 21.0—44.1) in the early EVAR group and 30.9 (IQR 18.3—45.3) in the surveillance arm. A total of 313 patients had either completed 12 months of follow-up or died before, 168 completed 36 months' and 64 completed 54 months of follow-up.

There was no difference in all-cause mortality between the two groups (HR 0.76; 95% CI 0.30—1.93; $p = 0.6$) and at 54 months' cumulative probability of mortality was 14.5% in the early EVAR and 10.1% in the surveillance group (Fig. 3).

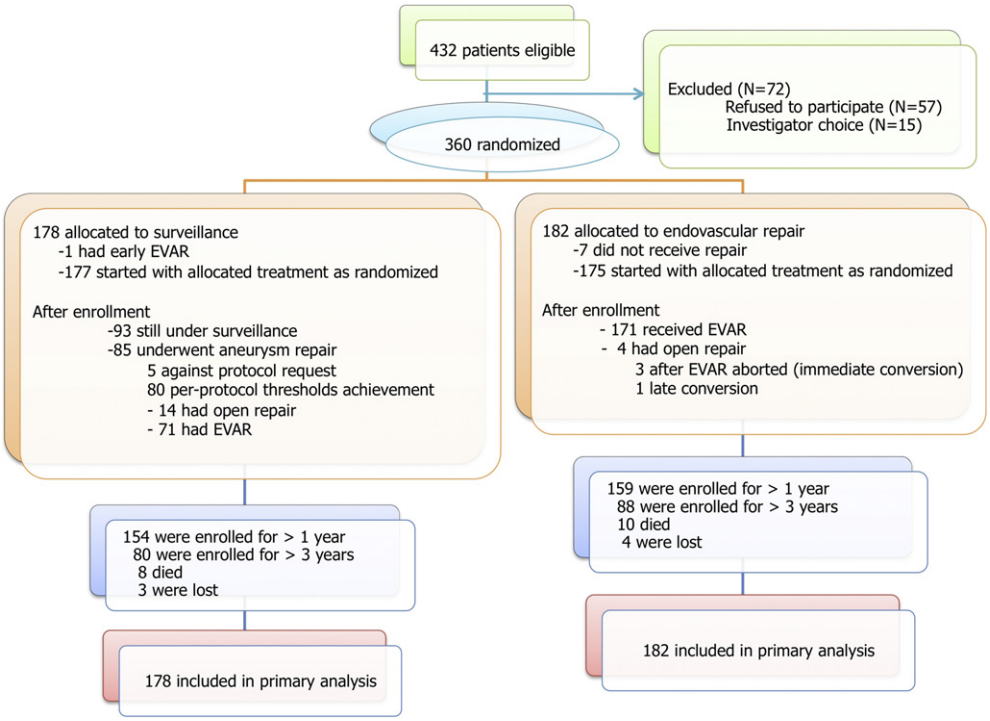


Figure 1 Trial profile.

Table 1 Risk factors and demographics at the time of randomisation.

Characteristics	Total (n = 360)	EVAR (n = 182)		Surveillance (n = 178)		P value
Age, mean (SD) y	68.9(6.8)	69	(6.4)	68.8	(7.2)	0.73
Female gender, No. (%)	15(4.2)	9	(4.9)	6	(3.4)	0.62
Smoking, No. (%)	199(55.3)	105	(57.7)	94	(52.8)	0.40
Hypertension, No. (%)	271(75.3)	135	(74.2)	136	(76.4)	0.71
Hyperlipemia, No. (%)	225(62.5)	113	(62.1)	112	(62.9)	0.95
Cardiac disease, No. (%)	141(39.2)	66	(36.3)	75	(42.1)	0.30
Chronic obstructive pulmonary disease, No.(%)	102(28.3)	57	(31.3)	45	(25.3)	0.24
Diabetes, No. (%)	49(13.6)	29	(15.9)	20	(11.2)	0.25
Renal disease, No. (%)	29(8.1)	13	(7.1)	16	(9.0)	0.65
Serum creatinine, mean (SD) mg/dL	1.08(0.26)	1.07	(0.24)	1.09	(0.28)	0.34
Cerebrovascular disease, No. (%)	54(15%)	21	(11.5)	33	(18.5)	0.08
Peripheral artery disease, No. (%)	46(12.8)	17	(9.3)	29	(16.3)	0.06
Previous laparotomy, No. (%)	72(20)	35	(19.2)	37	(20.8)	0.81
BMI >31 Kg/m^2, No. (%)	68(18.9)	35	(19.2)	33	(18.5)	0.97
Surgical risk (ASA score), No. (%)						0.85
ASA 1	44(12.2)	21	(11.5)	23	(12.9)	
ASA 2	180(50.0)	90	(49.5)	90	(50.6)	
ASA 3	136(37.8)	71	(39.0)	65	(36.5)	

Risk factors definitions were based and graded according to the SVS standards.[11]

Aneurysm-related mortality was similar in the two groups with one death occurring in each. In the early EVAR group, one patient died due to fatal perioperative pancreatitis while, in the surveillance group, there was one fatal aneurysm rupture. Overall, two late ruptures occurred (both in the surveillance group) in two aneurysms with 42.0 and 45.0 mm baseline diameter. At the time of rupture, respectively at 24 and 52 months after randomisation, the aneurysms were 56.0 and 55.0 mm in size and were both already scheduled for repair after CT assessment. One rupture was successfully treated by EVAR. Causes of late mortality are shown in Table 5.

As many as 55 adverse events of any type occurred in 45 patients and were more frequent in the early EVAR group compared with the surveillance group (Table 5). Estimated cumulative probabilities of adverse event in early EVAR versus surveillance patients were 19.8% versus 4.0% at 36 months and 21.2% versus 14.8% at 54 months ($P < 0.001$). As many as 13 adverse events occurring in 11 patients were major according to the SVS standard definitions[12] and were equally distributed between the two groups.

A total of 10 secondary therapeutic procedures (re-interventions) were needed after early EVAR repair, and none in the surveillance group (P = 0.03); seven were

Table 2 Morphological characteristics at the time of randomisation.

Characteristic	Total (n = 360)	EVAR (n = 182)		Surveillance (n = 178)		P value
AAA diameter, mm Mean (SD)	47.2(3.24)	47.5	(3.34)	47.0	(3.12)	0.14
	N (%)	N	%	N	%	
41–44 mm		40	(22.0)	42	(23.6)	
45–49 mm		83	(45.6)	96	(53.9)	
50–54 mm		59	(32.4)	40	(22.5)	
Eurostar classification	N (%)	N	%	N	%	0.33
A	120(33.3)	53	(29.1)	67	(37.6)	
B	181(50.3)	97	(53.3)	84	(47.2)	
C	42(11.7)	23	(12.6)	19	(10.7)	
D	10(2.8)	4	(2.2)	6	(3.4)	
E	7(1.9)	5	(2.7)	2	(1.1)	
Distal aortic diameter, mean (SD) mm	28.2(6.7)	29.0	(6.6)	27.5	(6.8)	0.04
Aortic neck length, mean (SD) mm	27.9(12.5)	28.1	(13.2)	27.6	(11.8)	0.69
Aortic neck diameter, mean (SD) mm	22.7(2.5)	22.8	(2.7)	22.5	(2.3)	0.19
Aortic neck 15 mm below renals, mean (SD) mm	23.4(2.77)	23.6	(2.8)	23.3	(2.7)	0.45

Table 3 Medications at the time of randomisation.

Medications	Total (n = 360)	EVAR (n = 182)		Surveillance (n = 178)		P value
	N (%)	N	%	N	%	
β −Blocker	81(24.8)	44	(26.0)	37	(23.6)	0.69
Aspirin	201(58.6)	102	(57.6)	99	(59.6)	0.78
ACE inhibitor	158(46.9)	70	(41.4)	88	(52.4)	0.06
Anticoagulants	19(5.9)	8	(4.8)	11	(7.1)	0.53
Diuretics	89(27.4)	47	(28.0)	42	(26.8)	0.90
Calcium channel Blocker	92(28.7)	52	(31.1)	40	(26.0)	0.36
Nitrates	29(9.2)	12	(7.4)	29	(9.2)	0.35
Statins	148(44.7)	76	(44.7)	72	(44.7)	1.00
Multiple drugs (3 or more)	85 (23.6)	44	(24.2)	41	(23.0)	0.98

associated with type II endoleak. Endoleak types and rates are shown in Table 5. No migration or loss of graft integrity occurred. Four open repairs were performed in the early EVAR group; three were intraprocedural conversions while the fourth was due to patient EVAR refusal.

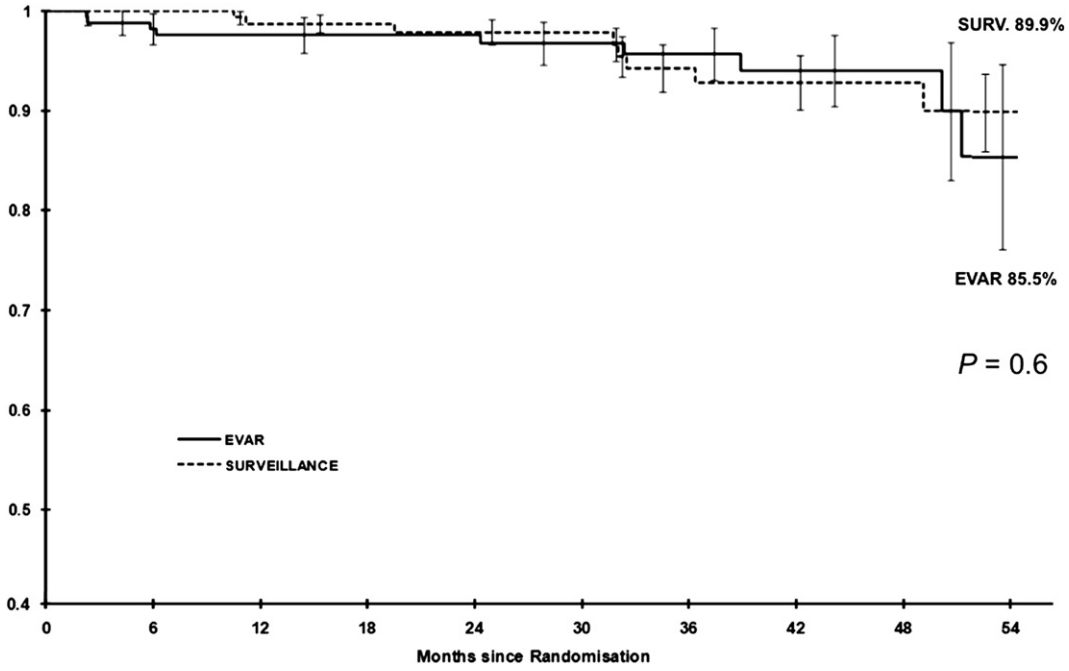
Reasons for delayed repair in the surveillance group included: n = 75 aneurysm diameter achievement of ≥5.5 cm, n = 20 aneurysm growth >1 cm/ year (in 11 associated with achievement of ≥5.5 cm diameter), n = 3 symptomatic aneurysm (in two associated with achievement of ≥5.5 cm, in one with rapid growth >1 cm/ year) and n = 1 development of iliac aneurysm. Of the 85 patients in the surveillance group undergoing delayed repair, 14 received open repair because EVAR feasibility was lost according to CT

Table 4 Early outcome and operative findings in patients receiving repair.

		EVAR		Surveillance		P value
Operative findings						
Time to repair, median (IQR),days		22	(1−593)	741	(443−937)	<0.0001
Procedure duration, median (IQR) min		100	(90−120)	117.5	(90−138.7)	0.0048
Estimated blood loss, median (IQR), mL		200	(100−300)	300	(150−500)	0.0023
Hospital stay, median (IQR), days		3	(2−4)	3	(2−5)	0.1626
Early outcome	Total	EVAR		Surveillance		P value
		N	(%)	N	(%)	
Mortality within 30 d or during hospitalization, No (%)	1	1	(0.6)	0	0	1.0
Patients with 30 day any morbidity related to repair, No (%)	36	31/175	(17.7)	5/85	(6)	0.01
Patients with 30 day any major morbidity, No (%)	10	6/175	(3.4)	4/85	(4.7)	0.7
Patients with 30 day device related any morbidity, No (%)	3	3/175	(1.7)	−	−	0.55
Patients undergoing any repair, No. (%)	260	175	(96.2)	85	(47.8)	<0.0001
Patients with open repair, No (%)	18	4/175	(2.3)	14/85	(16)	<0.0001
Patients with 30 day any morbidity related to repair, No (%)[a]	Total	EVAR (n = 242)		Open repair (n = 18)		P value
	36	33	(13.6)	3	(16.6)	0.722[a]

EVAR: Endovascular aortic aneurysm repair.

[a] 30 days morbidity events were reported from 260 patients with repair and included 175 patients of the early EVAR group and the 85 patients in the surveillance group requiring delayed repair. P value was measured for EVAR versus open repair.



MONTHS	0	6	12	18	24	30	36	42	48	54
EVAR	182	162	157	145	128	106	83	57	37	21
SURVEILLANCE	178	162	154	139	118	98	77	60	39	29

Figure 3 Kaplan—Meier estimates of survival at 54 months from time of randomisation in EVAR versus Surveillance groups. $P = 0.6$. Numbers at risk are shown.

scan evaluation. Reasons (one or more) are shown in Table 6. The 36-month probability of receiving open repair for feasibility loss was 16.4% and remained stable at 54 months.

Kaplan—Meier estimates of aneurysm growth of 5 mm or more (according to the first and last CT readings) for the early EVAR versus surveillance groups were 8.4% versus 67.5% at 36 months (HR 10.49; 95% CI 6.88—15.98; $P < 0.01$)(Fig. 4).

By linear regression models, aneurysm diameter decreased at a mean rate of 3.15 mm/ year after EVAR. In patients under surveillance, the initial enlarging diameter was counterbalanced by a decreasing diameter in those that were repaired resulting in a cumulative increase at mean rate of 0.5 mm/ year. The mean increase of aneurysm diameter in patients, who were never repaired at the time of the analysis, was 1.5 mm/ year and in those before receiving repair, 1.9 mm/ year.

In aneurysms under surveillance, estimated probability of receiving delayed repair was 59.7% at 36 months and 84.5% at 54 months. At 36 months, the cumulative probability to have repair was 23.3% in aneurysms of 4.1—4.4 cm diameter, 57.6% in those of 4.5—4.9 cm diameter, and 90.0% in those of 5.0—5.5 cm diameter (Fig. 5). After 54 months, the same probabilities were 76.1% for aneurysms of 4.5—4.9 cm and 95.6% for aneurysms larger than 5.0 cm. No valid information [standard error (SE) $>$ 10%] was available for the size category of 4.1—4.4 cm at 54 months.

The only significant positive predictors of delayed repair, according to Cox regression analysis, were larger aneurysm diameter (HR 1.27; 95% CI 1.18—1.37) and the absence of hypertension under drug treatment (HR 0.7; 95% CI 0.56—0.91). A trend towards positive association with delayed repair was found also for the absence of diabetes (HR 0.64; 95% CI 0.4—1.1) and of peripheral disease (HR 0.6; 95% CI 0.35—1.06) that were retained in the final Cox model.

Discussion

Two previous randomised trials on patients with small AAA failed to detect a benefit in survival with early open repair compared with surveillance.[2,3,7,12] The UK Small Aneurysms Trial (UKSAT), that randomly assigned 1090 patients with an aneurysm of size comparable to those of the CAESAR (4.0—5.5 cm) trial, demonstrated comparable long-term survival rates between early repaired aneurysms and those surveilled.[2,12] Similarly, the CAESAR trial showed that after 54 months, all-cause mortality, aneurysm-related mortality and major adverse event rates did not differ between patients randomised to early EVAR and those randomised to surveillance of AAA. However, the perioperative mortality risk of repair by the endovascular approach (0.55%) was significantly lower that that showed in the UKSAT with open repair (5.8%),[12] and aneurysm-related mortality rates after 54 months were close to zero, confirming the safety of EVAR. Nevertheless, the low risks of EVAR shown in the CAESAR could not translate into a benefit over surveillance because of similar safety shown with the surveillance strategy in which rupture (and aneurysm-related mortality) events were exceptional because only two ruptures occurred. The estimates of all-cause mortality (14.5% versus 10.1%) and

Table 5 Late outcomes.

Outcomes	Total	EVAR (n = 182)		Surveillance (n = 178)		P value
Mortality after 30 d or hospitalization	17	9	(4.9)	8	(4.5)	0.99
All-cause mortality (including 30-day), No (%)	18	10	(5.5)	8	(4.5)	0.80
Cause of death, No (%)						
AAA related	2	1	(0.5)	1	(0.6)	
Cardiovascular	6	4	(2.1)	2	(1.1)	
Cancer	7	3	(1.6)	4	(2.2)	
Other	1	1	(0.5)	—		
Unknown	2	1	(0.5)	1	(0.6)	
Patients with any morbidity (adverse event), No (%)	45	35	(19.1)	10	(5.1)	<0.01
Cause of morbidity, No (%)						
Atrial fibrillation	4	3	(1.6)	1	(0.6)	
AAA rupture	2	—		2	(1.1)	
Tender AAA	1	—		1	(0.6)	
Aortic neck rupture	1	1	(0.5)	—		
Cardiovascular	3	2	(1.1)	1/85	(1.2)	
Bleeding	10	8	(4.4)	2/85	(2.3)	
Limb ischemia	7	6	(3.3)	1/85	(1.2)	
Femoral or iliac dissection	2	2	(2.1)	—		
Blue toe syndrome	2	2	(2.1)	—		
Renal coverage/ embolization	8	7	(3.8)	1/85	(1.2)	
Buttock ischemia/erectile Dysfunction	4	4	(2.2)	—		
Wound infection	2	1	(0.5)	1/85	(1.2)	
Other	9	6	(3.3)	3	(1.7)	
Patients with any major morbidity, No (%)	11	6	(3.3)	5	(2.8)	0.99
Conversion to open surgery after EVAR (including 30 day), No (%)	4	4/175	(2.2)	0/71	—	0.32
Immediate conversion		3	(1.6)	—	—	
Late conversion		1	(0.5)	—	—	
Patients with secondary Procedures (reintervention), No (%)	10	10/175	(5.7)	0/85	—	0.03
Endoleak at 30 days, No (%)	35	28/175	(16)	7/71	(9.9)	0.23
Type I		2		1		
Type II		25		4		
Type III		—		1		
Unknown		1		1		
Endoleak at 1 year, No (%)	23	21/175	(12)	2/71	(2.8)	0.028
Type I		—		—		
Type II		19		2		
Type IV		1		—		
Unknown		1		—		
Loss of device integrity		—	—	—	—	—
Migration, No (%)		—	—	—	—	—

EVAR: Endovascular aortic aneurysm repair.

aneurysm-related mortality (<1%) at 54 months in both arms of the CAESAR trial were lower than those reported in previous studies on small AAA,[2,3] and mainly overlapped the results recently shown by the only other randomised trial that compared EVAR and surveillance on small AAA, the Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) trial.[6] Like the CAESAR trial, the PIVOTAL, that randomised 728 patients with 4.0—5.0 cm aneurysms to early EVAR versus surveillance, found very low mortality events: 4.1% mortality in each group after a mean follow-up of 20 months, with 0.6% perioperative mortality after EVAR. Authors were also surprised because of the

Table 6 Open repair in 14 patients assigned to surveillance.

	Age	Gender	AAA at baseline (mm)	AAA at repair (mm)	Randomisation date	Indication to repair date	Morphology changes and feasibility loss
1.	72	Male	52	57	5-12-2005	20-12-2006	Shortened aortic neck (<10 mm)
2.	69	Male	52	57	5-3-2008	30-3-2009	Shortened aortic neck (<10 mm)
3.	67	Male	43	50[a]	1-10-2004	24-10-2006	Neck dilatation; iliac aneurysm
4.	50	Male	49	55	7-3-2006	11-2-2007	Contrast allergy new onset
5.	67	Male	53.3	58.9	28-6-2006	30-1-2007	Neck thrombus; Funnel shape
6.	66	Male	52	58	11-5-2005	5-7-2007	Not defined
7.	70	Male	50	57	11-2-2005	6-4-2006	Neck thrombus; Funnel shape
8.	65	Male	48.4	55	5-5-2005	28-10-2005	Neck thrombus
9.	69	Male	48	55	19-1-2007	11-12-2008	Shortened aortic neck (<10 mm)
10.	70	Male	49	56	2-2-2006	8-11-2007	Neck thrombus; Funnel shape
11.	71	Male	5	57	10-2-2005	22-2-2007	Iliac access obstructive disease
12.	69	Male	48	55	21-9-2004	16-12-2005	Shortened aortic neck; neck angulation
13.	70	Female	45	55	24-7-2006	28-8-2008	Shortened aortic neck; Inverted funnel shape
14.	65	Male	49	55	22-12-2006	12-11-2008	Shortened aortic neck; neck dilatation

[a] Associated with iliac enlargement with iliac aneurysm development.

unexpectedly extremely low rupture risk: the 3-year risk of aneurysm-related mortality was close to zero with only two rupture occurring in both groups.

The CAESAR confirmed that rupture rate is very low in small AAA and probably below the 1% annual rate published before.[1,2] Nevertheless, expansion, even in aneurysms of small size, may be rapid and is associated with increased rupture risk and loss of feasibility for EVAR in 16.4% of patients at 36 months. The high rate of growth in small AAAs may have important implications for safety during surveillance and is a reason of concern in those patients with small aneurysms that cannot be properly managed under a strict surveillance programme. If an early EVAR strategy is not applied, close surveillance is needed to detect rapidly growing small aneurysms at increased rupture risk. It has been indeed recently shown that, for subjects with an AAA under surveillance, annual growth rate of 2 mm is significantly associated with clinical events.[13]

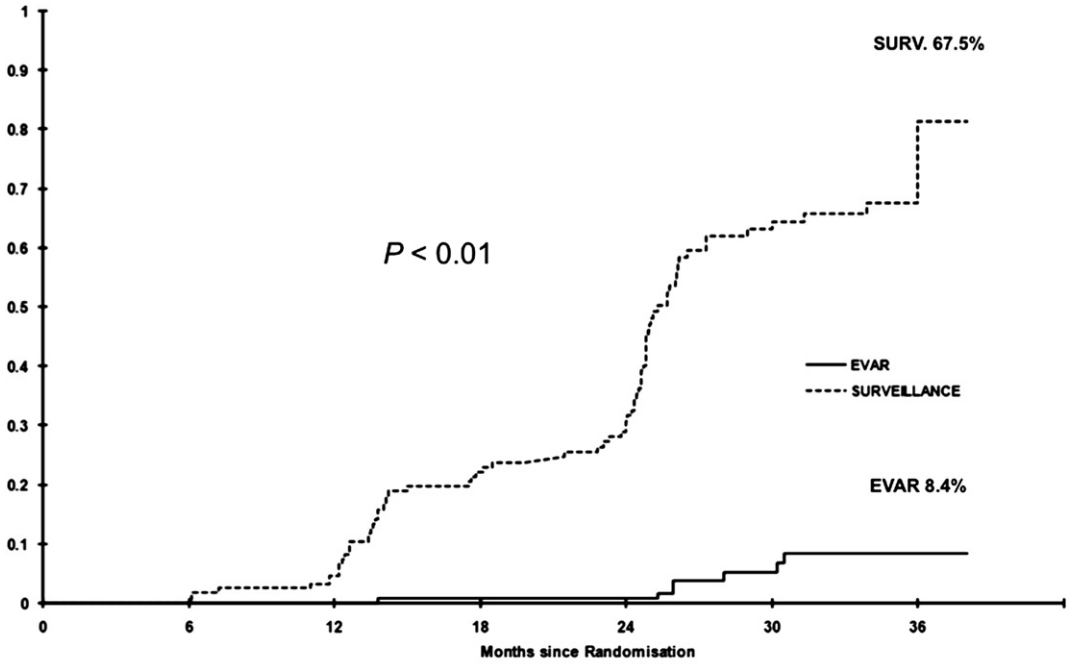
Surveillance provides a safe alternative method of management of patients with aneurysms 4.1—5.4 cm but requires to be based on accurate imaging and a careful close monitoring. For the CAESAR study, yearly CT scan was used to properly address any morphological change of the aneurysms or the stent graft. This allowed obtaining very low rupture and aneurysm-related death rates. Without strict surveillance strategies, within rigorous trial protocols, the same safe results are less likely to be reached.

A strict surveillance strategy resulted in repair for 59.7% of aneurysms under surveillance at 36 months and in 84.5% at 54 months. Because about 60% of aneurysms grow to require repair after less than 3 years, the option of anticipated endovascular treatment with low operative risk might be offered to selected patients with small AAA. Anticipated repair might be a choice particularly for patients with larger AAA size at baseline (>5.0 cm) as 90% of these will undergo repair within 36 months. In addition, from the CAESAR study, it was also remarkable that in aneurysms of smaller size (4.5—4.9 cm diameter) under surveillance estimates of repair at 36 months were as high as 57.6%.

The strategy of surveillance raises the question of loss of suitability for EVAR and the consequent increased probability to receive open repair.[14,15]

During the first 36 months of follow-up, 14 of 85 aneurysms enrolled in the surveillance arm of the CAESAR trial and requiring repair received open surgery because of loss of feasibility for EVAR. According to Kaplan—Meier estimates, at 36 months, one over six patients under surveillance will have changes in aneurysm morphology, mainly related to changes in the proximal aortic neck, not allowing delayed EVAR.

It has been suggested that best medical management, such as the use of statins, can optimise and improve natural history of patients under surveillance.[16,17] In the CAESAR trial, less than half the population (47.7%) was



MONTHS	0	6	12	18	24	30	36
EVAR	182	149	147	130	117	64	54
SURVEILLANCE	178	159	144	118	88	63	22

Figure 4 Kaplan–Meier estimates of aneurysm growth $\geq$5 mm at 36 months from time of randomisation in EVAR versus Surveillance groups. $P < 0.01$. Numbers at risk are shown.

under statins medication and the trial could not prove or disprove any advantage of these drugs. Nevertheless, 23% of patients were takers of three or more drugs, mainly for pressure control. Cox regression analysis suggested a potential link between aneurysm growth requiring repair and absence of history of diabetes, peripheral disease and hypertension. While other studies also confirmed the association between absence of diabetes and an increased rate of aneurysm enlargement in small AAA,[3,18] the use of anti-hypertensive drugs might have provided a protective effect on aneurysm growth from high blood pressure in our 'hypertensive' patients. However, our results might be affected by chance and variable patient adherence to therapy. How the findings of CAESAR may really influence the knowledge about the natural history of aneurysm growth remains uncertain: it could also be speculated that modification of atherosclerosis risk factors alone without repair may not prevent aneurysm from enlargement.

The low mortality rate in the CAESAR trial may be related to the experience of participating centres and to the per-protocol inclusion criteria of patients without high surgical risk, who would have benefited from early repair.

Of relevance, the rate of included women was particularly low (4.2%). It has been shown that the risk of rupture and the likelihood of a poor outcome after rupture are greater in women than in men.[19,20] The findings of the CAESAR trial could not be fit for a female population with small AAA.

The lack of difference in mortality risk between the two arms of the CAESAR trial persisted despite the presence of a higher number of adverse events and complications requiring secondary procedure in the early EVAR arm. Indeed, most adverse events were minor in clinical relevance and most re-interventions were performed for type II endoleak correction. No migration or loss of device integrity occurred, although follow-up length could not provide any strong message in favour of or against all the last-generation devices employed in the trial.

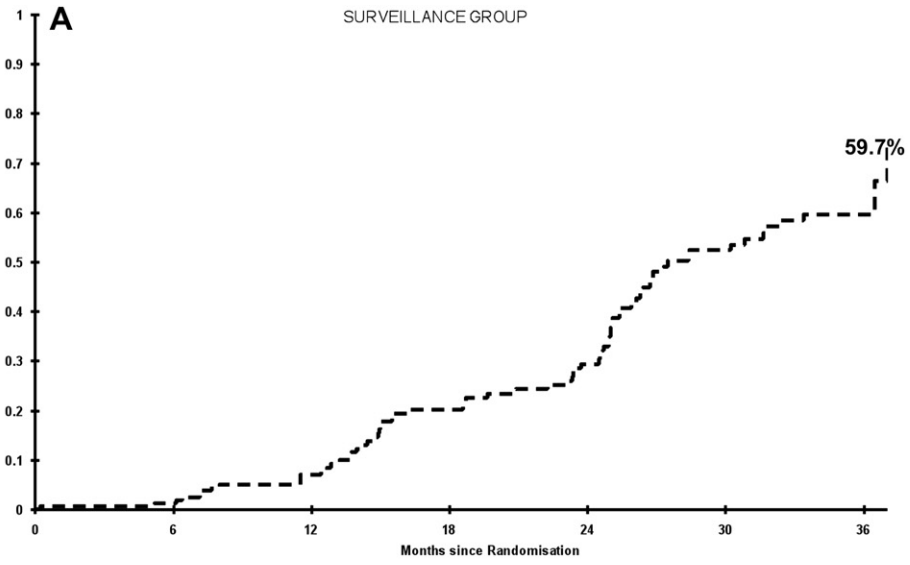
Limitations

The trial was stopped early and sample size was not achieved. We failed to prove the estimated difference in mortality between EVAR and surveillance, but secondary end points provided relevant information.

Furthermore, the length of follow-up was limited and changed findings could be expected when longer follow-up analyses will be achieved.[7,21]

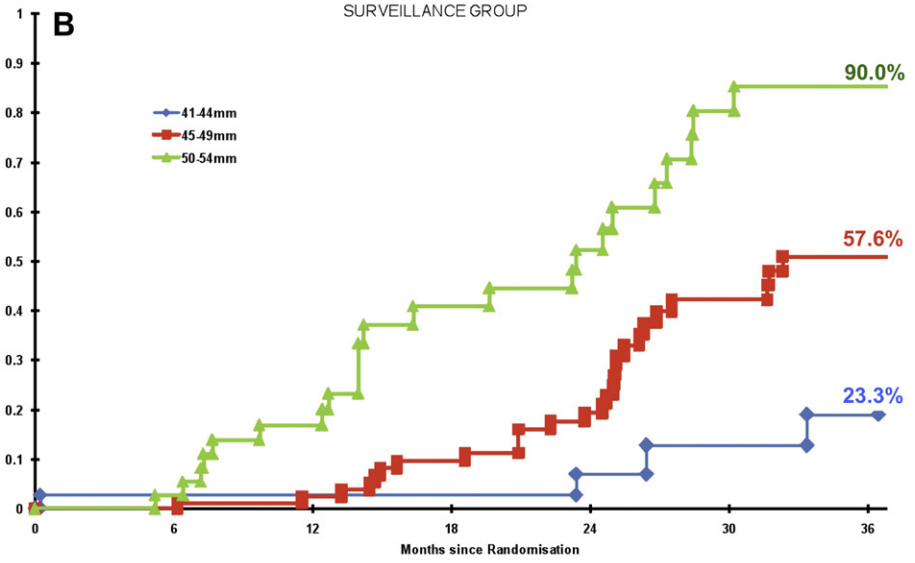
This report intentionally lacks detailed information on health-related quality of life analysis, which is ongoing.

In conclusion, mortality, aneurysm-related mortality and rupture rates in small AAA are low and no advantage was shown between early or delayed EVAR strategy. However, three out of five small AAA may grow, quickly reaching thresholds of high rupture and loss of EVAR suitability rates. Surveillance with delayed EVAR does result in 60% requirement of any repair and 16.4% of open repair after as little as 36 months from initial evaluation. The relevant aneurysm growth and need for repair rates in some small AAAs require close and alert surveillance with scheduled CT examination. Longer-term follow-up and detailed cost-effectiveness assessment data are needed to fully assess



N° at Risk

MONTHS	0	6	12	18	24	30	36
SURVEILLANCE	178	159	143	117	94	67	38



N° at Risk

MONTHS	0	6	12	18	24	30	36
41 - 44mm	39	35	29	25	23	16	14
45 - 49mm	99	87	78	64	54	35	20
50 - 54mm	40	37	33	23	15	10	3

Figure 5 Part A: Kaplan—Meier estimates of undergoing repair in the surveillance arm during 36 months follow-up. Part B: Kaplan—Meier estimates of undergoing repair in the surveillance arm during 36 months follow-up by baseline aneurysm diameter.

the relative merits of early EVAR versus surveillance strategies in small AAA management.

Disclosure Statement

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The sponsor had no role in the design and conduct of the study; in the collection, analysis and interpretation of the

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