Predicting risk of rupture and rupture-preventing reinterventions following endovascular abdominal aortic aneurysm repair

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Background: Clinical and imaging surveillance practices following endovascular aneurysm repair (EVAR) for intact abdominal aortic aneurysm (AAA) vary considerably and compliance with recommended lifelong surveillance is poor. The aim of this study was to develop a dynamic prognostic model to enable stratification of patients at risk of future secondary aortic rupture or the need for intervention to prevent rupture (rupture-preventing reintervention) to enable the development of personalized surveillance intervals.
Methods: Baseline data and repeat measurements of postoperative aneurysm sac diameter from the EVAR-1 and EVAR-2 trials were used to develop the model, with external validation in a cohort from a single-centre vascular database. Longitudinal mixed-effects models were fitted to trajectories of sac diameter, and model-predicted sac diameter and rate of growth were used in prognostic Cox proportional hazards models.
Results: Some 785 patients from the EVAR trials were included, of whom 155 (19·7 per cent) experienced at least one rupture or required a rupture-preventing reintervention during follow-up. An increased risk was associated with preoperative AAA size, rate of sac growth and the number of previously detected complications. A prognostic model using predicted sac growth alone had good discrimination at 2 years (C-index 0·68), 3 years (C-index 0·72) and 5 years (C-index 0·75) after operation and had excellent external validation (C-index 0·76–0·79). More than 5 years after operation, growth rates above 1 mm/year had a sensitivity of over 80 per cent and specificity over 50 per cent in identifying events occurring within 2 years.
Conclusion: Secondary sac growth is an important predictor of rupture or rupture-preventing reintervention to enable the development of personalized surveillance intervals. A dynamic prognostic model has the potential to tailor surveillance by identifying a large proportion of patients who may require less intensive follow-up.

Introduction

Endovascular aneurysm repair (EVAR) has become the primary choice of repair for many patients with an intact abdominal aortic aneurysm (AAA)[1] and is a less invasive alternative to traditional open repair of AAA. Evidence from RCTs of EVAR *versus* open repair has shown that EVAR has an early mortality benefit; however, this survival benefit is eroded within a few years after operation[2−5], with significantly higher AAA-related mortality and rates of secondary rupture[2,6]. Guidelines[7] therefore recommend

lifelong clinical and imaging surveillance after EVAR in order to detect complications that require timely reintervention.

Compliance with lifelong surveillance is, however, poor. Among Medicare beneficiaries in the USA, 50 per cent of patients were lost to annual imaging follow-up by 5 years[8]. Compliance also dropped off in the EVAR-1 trial[2], where only half of the surviving patients in the EVAR group still underwent annual CT 6 years after randomization. This loss to follow-up could partly be explained by an ageing

population (in EVAR-1, over 40 per cent of patients still alive after 6 years were aged over 80 years). However, there are also concerns about the frequent use of CT and resulting radiation burden that might suggest a less intensive CT surveillance protocol is required[7], with colour duplex ultrasonography recommended as a reasonable alternative to CT[9,10]. In addition, the costs associated with lifelong CT surveillance are high; one-third of the total costs of EVAR follow-up in the first 5 years is associated with yearly postoperative radiological surveillance[11], which influences the long-term cost-effectiveness of EVAR[12].

Interest is therefore growing in developing prognostic models to determine long-term results following EVAR, which may lead to changes in the level of surveillance required for some patients. A number of prognostic variables measured either before or soon after surgery have been shown to be associated with long-term freedom from aneurysm-related morbidity, including early absence of endoleak, migration and kinking[13,14], smaller initial aneurysm diameter, younger age at operation[15], and morphological variables such as smaller maximum common iliac diameter, aortic sac volume and maximum sac diameter[16]. However, there has been relatively little investigation of dynamic measures that change over follow-up, such as the patient's surveillance and surgical history and, in particular, aspects of a patient's aneurysm sac diameter trajectory. The advantages of incorporating dynamic measurements of secondary sac diameter history into a prognostic model are twofold; first, they can be used to update an individual's risk prediction and hence recommended time of next visit at each surveillance scan; and, second, they can be measured accurately, cheaply and safely throughout follow-up using ultrasonography.

The aim of this study was to develop and identify aspects of sac diameter trajectory that predict future secondary rupture or rupture-preventing reintervention (RPR) at three distinct times during follow-up when reassessment of an individual's surveillance protocol may be necessary.

Methods

Data from the EVAR-1 and EVAR-2 trials[2,17] were used to develop a prognostic model for predicting secondary rupture or RPR following EVAR. The trials implanted EVAR devices between 1999 and 2004, which did not have the advances of devices today, including imaging sizing and improved techniques and technologies. Therefore, to validate the risk predictions on a contemporary series, a consecutive prospective cohort of patients who had elective EVAR was recruited from Helsinki University Hospital (HUH) in Finland.

The prognostic model was developed for risk prediction purposes. The model was dynamic in nature and used a landmarking approach[18]. Models were developed at three preselected times after operation (2, 3 and 5 years), chosen because there may be uncertainty at these times whether patients should be invited back regularly, and for which a prediction model could be used as a decision aid. At each of these time points (landmark times), updated information on the predicted current sac diameter and rate of sac growth was incorporated into the prognostic model.

Data sets

The design and selection of participants in the EVAR-1 and EVAR-2 trials have been described previously[19]. Briefly, between 1 September 1999 and 3 August 2004, patients aged over 60 years with an AAA of at least 5·5 cm and suitable for an operation were randomized to either EVAR or open repair (EVAR-1 trial) or, if ineligible for open repair, to EVAR *versus* no operation (EVAR-2 trial). For the purposes of this study, only patients who underwent elective EVAR were included. Patient follow-up was planned for 1 month, 3 months and 1 year after operation, and annually thereafter, comprising abdominal CT and recording of any complications or adverse events. The management of aneurysm-related complications was left to the discretion of the trial centre. The present study used CT imaging data that were recorded comprehensively between 1999 and 2009. Patients were followed up for reinterventions from 1 September 1999 to 1 September 2009 using local hospital records, and from 1 September 2009 to 31 March 2015 using predominantly record linkage to Hospital Episode Statistics. Dates and causes of death were extracted using record linkage from the Office of National Statistics from 1 September 1999 to 30 June 2015.

Validation data were obtained from HUH, which is the only hospital providing vascular surgical services and EVAR to 2·0 million inhabitants in Southern Finland. All patients who underwent EVAR for intact elective infrarenal AAA in HUH during 2000–2015 were included in the present analysis. Basic demographics were extracted from the hospital's vascular registry. Data on the primary EVAR procedure, possible aneurysm-related reinterventions and imaging (digital subtraction angiography, CT, magnetic resonance angiography (MRA) and ultrasound examinations) during follow-up were collected retrospectively from the case histories. CT images were reviewed for endoleaks, migration and kinking, and sac diameter was measured if not clearly stated in the radiological records. Dates and causes of death were extracted from the hospital records until the end of July 2017, and confirmed where possible

with data from the Cause of Death registry of Statistics Finland, which were available up to 31 December 2016. In 2000–2010, the surveillance protocol after EVAR included CT at 1, 6 and 12 months, and annually thereafter. However, if there were reinterventions or endoleaks, additional CT was undertaken if considered necessary. After 2010, the surveillance protocol was simplified to CT at 3 and 12 months after the procedure, and annual ultrasonography if no complications were detected (with a reference ultrasound examination at 6 months). However, when there was suspicion of a sac diameter increase from the ultrasound images, CT (or MRA in selected patients if CT was contraindicated) was scheduled to determine the reason for sac diameter increase and the need for reintervention.

Measurements and outcomes

The outcome investigated in this study was the time to the next rupture or RPR after the three landmark times. RPR events were included in the outcome as many ruptures could possibly have been prevented by early reintervention. The aim was to develop a risk model that could predict severe sequelae that would require immediate reintervention. RPR was defined as any reintervention to prevent sac growth and rupture. All candidate procedures were reviewed and categorized as RPR or not. Reintervention for a type II endoleak without sac expansion was not considered to be a RPR.

Statistical analysis

The TRIPOD guidelines[20] for prediction model development and validation were followed. A longitudinal mixed-effects model was developed using EVAR trials data on repeat measurements of sac diameter taken from imaging scans. Fractional polynomial modelling[21] was used to select the best-fitting form for the trajectory function over time. Individual variability around the mean trajectory function was incorporated by including random effects for the coefficients of the fractional polynomial. Baseline characteristics were also investigated as possible explanatory variables. Three separate models were fitted using individuals still alive and under follow-up at 2, 3 and 5 years after operation; each incorporated all sac diameter measurements up until the landmark time of interest. The best linear unbiased predictors (BLUPs) of the random effects were extracted to obtain the predicted sac diameter and rate of growth for each individual at each landmark time. For patients in the Helsinki cohort, BLUPs of the random effects were derived based on the model coefficients estimated in the EVAR trials. Observed diameter

measurements in the Helsinki data were obtained from a mixture of scan modalities. Non-CT measurements (ultrasonography and MRA) were adjusted using the difference in the mean diameter between these modalities and those on CT (estimates of which were obtained from a mixed-effects model). Further details may be found in *Appendix S1* (supporting information).

A prognostic model was developed to predict the time to next RPR or rupture following each landmark time, using a Cox proportional hazards model. Risk factors considered in the model included the predicted current aneurysm sac diameter, the predicted rate of sac growth, the patients' age at operation, sex, BMI, preoperative aneurysm diameter, graft shape, smoking status, diabetes status, and the number of previous complications detected and reinterventions performed. Individuals without any longitudinal sac measurements before the preselected landmark times were dropped from the analyses when developing the prognostic models. This study used a simple selection procedure that avoided overfitting to obtain a parsimonious model[22]. Risk factors that had at least one univariable *P* value smaller than 0·010 across the three landmark models were included in a multivariable model. From this multivariable model the following prognostic models were compared: M1, risk factors in the multivariable model excluding predicted sac diameter and rate of sac growth; M2, model M1 plus predicted sac diameter; M3, model M1 plus predicted rate of growth; M4, model M1 plus predicted sac diameter and rate of growth; M5, predicted rate of growth only. In addition, a further model (M6) considered only a crude rate of sac growth as a predictor (calculated by taking the difference between the previous diameter measurement and the preoperative diameter, and dividing by the time between the measurements).

Risk scores were created at each landmark time and were based on the linear predictor of the Cox model. The predictive accuracy of the risk scores developed from the EVAR trials was assessed by various methods: discriminative ability was measured using C-indices, with 20-fold cross-validation for internal validation; the 2-year predicted risk of rupture or requirement for RPR following the landmark time was calculated by combining the risk score with the estimated baseline survivor function, and risk predictions were compared with observed 2-year risks via a calibration plot; and patients were classified as high or low risk based on a chosen cut-off point of the 2-year predicted risk and compared with observed event numbers in the 2 years following the landmark time. The sensitivity and specificity of the risk classification were obtained with patients who were censored during the 2 years excluded from the calculations. External validation

of the risk scores was undertaken using data from the Helsinki cohort.

Results

EVAR trials

Some 1656 patients were randomized in the EVAR trials (1252 in EVAR-1 and 404 in EVAR-2). Patients who did not undergo elective EVAR or whose operation was converted to open repair during initial surgery (807 patients), had no postoperative CT images or sac diameter measurements available (60), or who underwent EVAR but had a straight graft fitted (4) were excluded from the analyses (*Fig. S1a*, supporting information). The remaining 785 patients were available for analysis (*Table 1*). Of these individuals, 700 (89·2 per cent) were men and the mean age was 74·5 years. The mean preoperative maximum external AAA diameter was 6·49 (range 5–10·5) cm and a mean of 5·4 CT scans per patient were acquired over a mean follow-up of 4 years after operation (maximum 10 years). Mean follow-up for RPR or rupture was 7·1 years (maximum 15·6 years).

During follow-up, 155 patients (19·7 per cent) had a secondary rupture or RPR. There were 42 patients with at least one secondary rupture and 138 with at least one RPR. Twenty-five patients had both a rupture and RPR recorded during follow-up. The rate of rupture remained relatively stable across the landmark time points at approximately one per 100 person-years, whereas the rate of RPR decreased slightly over time from three per 100 person-years after 2 years to two per 100 person-years after 5 years.

Helsinki cohort

A total of 402 patients were studied in the Helsinki cohort. After excluding 12 patients without any postoperative diameter measurements, 390 remained and were used for external validation of the derived risk score (*Fig. S1b*, supporting information). The patient characteristics of the cohort were very similar to those in the EVAR-1 and EVAR-2 trials in terms of proportion of men (87·7 per cent), mean age (74·6 years), number of scans during follow-up (mean 5·8) and duration of follow-up imaging (mean 3·52 (range 0·003 to 14·2) years) (*Table 1*). The mean preoperative AAA size was 6·30 cm, slightly smaller than that in the EVAR trials. Postoperative aneurysm (sac) diameters were measured using a mixture of CT (63·6 per cent), ultrasound imaging (35·8 per cent) and MRA (0·6 per cent).

Seventy-three patients (18·7 per cent) experienced at least one secondary sac rupture or RPR during follow-up. Eleven patients had at least one secondary rupture and

66 underwent at least one RPR; four patients had both a rupture and RPR recorded during follow-up. The rates of secondary rupture were similar to those in the EVAR trials at one per 100 person-years across the three landmark times. However, the rate of RPR was more than double that of the EVAR trials, ranging from a maximum of seven per 100 person-years after 3 years to five per 100 person-years after 5 years. Although the proportions of patients who underwent RPR during follow-up were similar in both the EVAR trials and the Helsinki cohort, reinterventions occurred sooner in the Helsinki cohort, at a mean of 2·8 years after operation compared with 3·7 years in the EVAR trials.

Aneurysm sac trajectory modelling

The observed aneurysm sac trajectories of patients in the EVAR trials and Helsinki cohort over a 10-year follow-up interval were stratified by type of event (no rupture or RPR, RPR with no subsequent rupture and secondary sac rupture) (*Fig. 1*). Loess smoothers were added to the profile plots to capture the average trajectory trends. In general, the reduction in sac diameter occurred non-linearly over follow-up, with a sharp decrease initially after operation, before stabilizing. In patients in the EVAR trials who underwent RPR during follow-up, the initial reduction in sac diameter was less pronounced and the mean diameter remained relatively high throughout follow-up. Patients in the Helsinki cohort showed similar trajectories. In patients whose aneurysm ruptured during follow-up, there was a clear increase in the mean sac diameter over time for patients both in the EVAR trials and Helsinki cohort. However, the heterogeneity between patients was large, with some who experienced AAA rupture still showing a declining sac trajectory over time.

Longitudinal models were fitted to the EVAR data; functions of time, patient age and preoperative AAA size were statistically associated with postoperative sac diameters (*Table S1*, supporting information). Mean trajectory functions for each model fitted to data up to the three landmark times are shown in *Fig. S2* (supporting information).

### Risk prediction of secondary sac rupture and rupture-preventing reinterventions

The univariable associations between possible risk factors and rupture or RPR in the EVAR trials are shown in *Table S2* (supporting information). Patients with a larger preoperative maximum aneurysm size had an increased risk of RPR or rupture. The numbers of previous complications and reinterventions were also significantly associated with an increased risk of secondary rupture or RPR after EVAR.

Table 1 Patient characteristics in the EVAR trials and the Helsinki cohort

	EVAR-1 and EVAR-2 trials		Helsinki cohort	
	n	No. of patients*	*n*	No. of patients*
Preoperative AAA size (cm)†	785	6·49(0·91)	390	6·30(0·90)
Age (years)†	785	74·5(6·4)	390	74·6(7·9)
Men	785	700 (89·2)	390	342 (87·7)
BMI (kg/m²)†	784	26·7(4·6)	390	27·3(5·3)
Diabetes	782	88 (11·3)		78 (20·0)
Smoking status	784			
Current		159 (20·3)		98 (25·1)
Past		548 (69·9)		–
Never		77 (9·8)		–
Graft shape	765		389	
Uni-iliac		57 (7·5)		7 (1·8)
Bi-iliac		708 (92·5)		382 (98·2)
No. of postoperative sac measurements†	785	5·4(2·7)	390	5·8(3·1)
Interval from operation to last follow-up imaging (years)†	785	4·03(2·51)	390	3·52(2·73)
Follow-up for RPR or rupture (years)†	785	7·1(4·1)	389	4·0(3·0)
Type of imaging used for sac diameter measurement	4230		2250	
CT		4230 (100)		1430 (63·6)
Ultrasonography		0 (0)		806 (35·8)
Magnetic resonance angiography		0 (0)		14 (0·6)
No. of previous complications after surgery†				
2 years	666	0·28(0·53)	287	0·74(1·33)
3 years	609	0·34(0·59)	226	0·96(1·72)
5 years	495	0·42(0·70)	121	1·10(2·00)
No. of previous reinterventions†				
2 years	666	0·10(0·38)	287	0·19(0·52)
3 years	609	0·14(0·44)	226	0·32(0·76)
5 years	495	0·22(0·57)	121	0·47(0·91)
Predicted sac diameter after surgery (cm)†				
2 years	659	5·85(1·31)	285	5·49(1·26)
3 years	607	5·77(1·50)	226	5·39(1·59)
5 years	495	5·66(1·69)	121	5·18(1·76)
Predicted rate of sac growth after surgery (cm/year)†				
2 years	659	0·083(0·364)	285	0·041(0·364)
3 years	607	0·143(0·323)	226	0·101(0·336)
5 years	495	0·142(0·233)	121	0·114(0·255)
Secondary rupture or RPR	785		390	
0		630 (80·3)		317 (81·3)
≥ 1		155 (19·7)		73 (18·7)
No. of deaths	785	615 (78·3)	389	163 (41·9)
Causes of death	615		163	
Aneurysm-related after repair		13 (2·1)		2 (1·2)
Aneurysm rupture after repair (secondary)		33 (5·4)		7 (4·3)
Coronary heart disease		154 (25·0)		39 (23·9)
Stroke		37 (6·0)		9 (5·5)
Other vascular disease		23 (3·7)		12 (7·4)
Lung cancer		59 (9·6)		13 (8·0)
Other cancer		104 (16·9)		27 (16·6)
Respiratory		93 (15·1)		19 (11·7)
Renal		15 (2·4)		2 (1·2)
Other		81 (13·2)		17 (10·4)
Unknown		3 (0·5)		16 (9·8)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). AAA, abdominal aortic aneurysm; RPR, rupture-preventing reintervention.
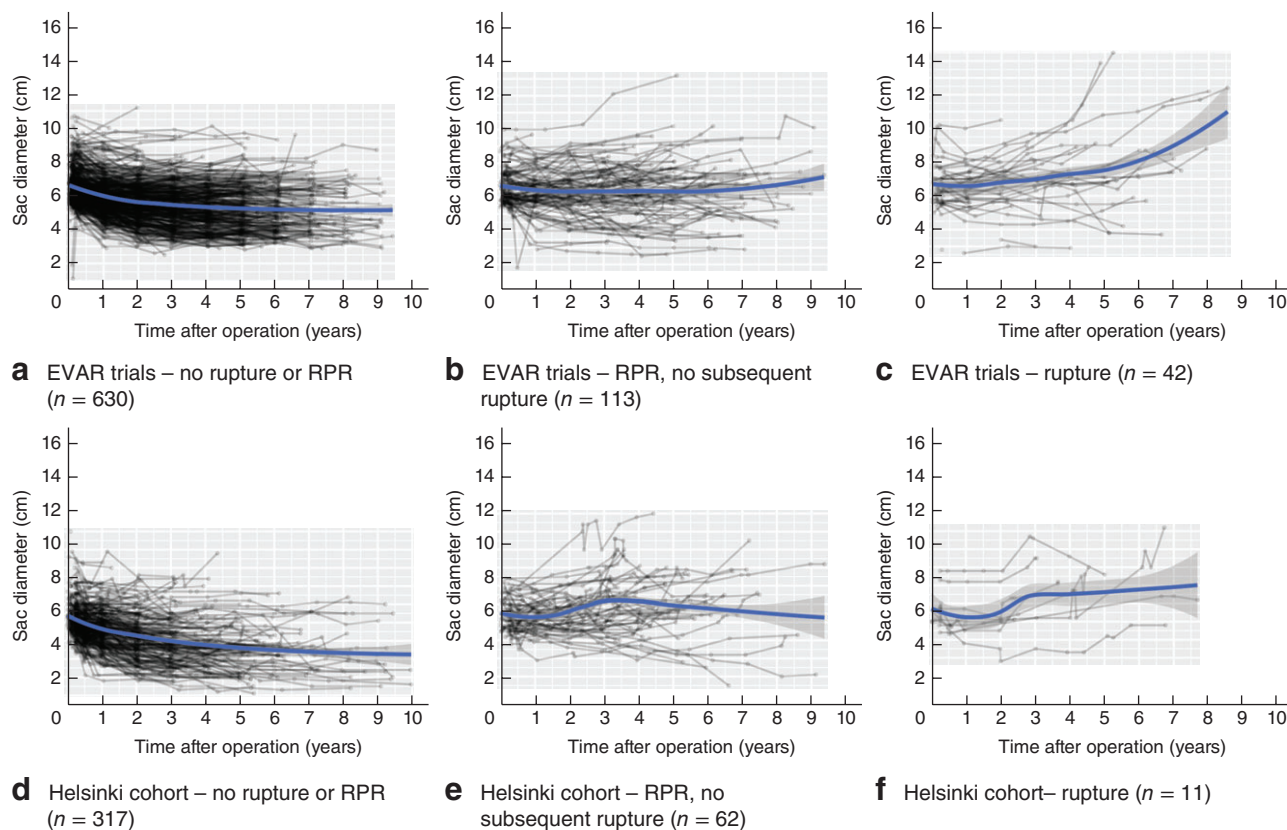
Fig. 1 Trajectories of aneurysm sac diameter in the EVAR trials and Helsinki cohort over 10 years of follow-up, with loess smoothers superimposed. Shaded areas represent 95 per cent confidence intervals. RPR, rupture-preventing reintervention

The number of previous complications was subdivided into five types of complication to investigate the association of each type with rupture or RPR separately. The occurrence of migration and type I and II endoleaks during the study interval was strongly associated with an increased risk of rupture or RPR, and there was also a non-significant positive association for type III endoleaks. There was statistically significant evidence that both the current sac diameter and the rate of sac growth increased the risk of rupture or RPR.

Table 2 Multivariable hazard ratios from prognostic model M4 for risk of rupture or rupture-preventing reintervention at 2, 3 and 5 years after operation

	2 years (n = 116 events)			3 years (n = 103 events)			5 years (n = 66 events)		
	n	Hazard ratio	P	n	Hazard ratio	P	n	Hazard ratio	P
Preoperative AAA size (per cm)	659	1·94 (1·25, 3·02)	0·003	607	1·55 (0·98, 2·45)	0·062	495	1·09 (0·73, 1·63)	0·666
No. of previous complications	659	1·76 (1·29, 2·42)	<0·001	607	1·56 (1·15, 2·11)	0·004	495	1·16 (0·83, 1·62)	0·384
No. of previous reinterventions	659	0·97 (0·65, 1·47)	0·899	607	1·28 (0·92, 1·80)	0·144	495	0·89 (0·56, 1·40)	0·613
Current sac diameter (per cm)	659	0·68 (0·44, 1·05)	0·084	607	0·86 (0·54, 1·37)	0·532	495	1·21 (0·82, 1·78)	0·344
Current rate of sac growth (per 2 mm per year)*	659	1·64 (1·31, 2·06)	<0·001	607	1·79 (1·25, 2·55)	0·001	495	1·80 (1·12, 2·89)	0·015

Values in parentheses are 95 per cent confidence intervals. *2 mm/year is the standard deviation of the rate of sac growth. AAA, abdominal aortic aneurysm. Hazard ratios were obtained by Cox proportional hazards analysis.
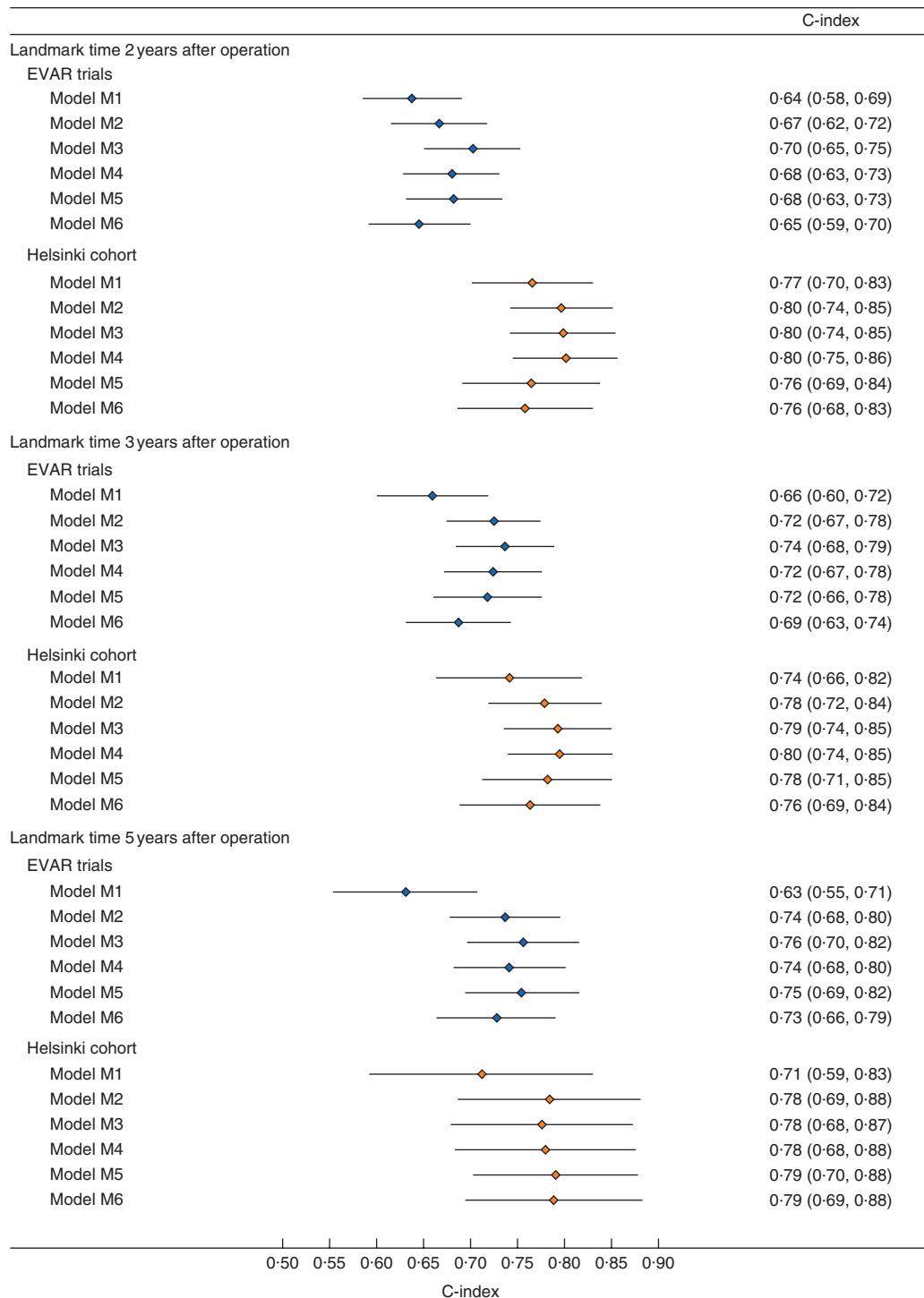
Fig. 2 Predictive accuracy (C-index with 95 per cent c.i.) of six prognostic models (M1–M6) based on the EVAR trials and Helsinki cohort. Model M1, preoperative abdominal aortic aneurysm size, previous numbers of complications and previous numbers of reinterventions; model M2, model M1 + predicted sac diameter; model M3, model M1 + predicted rate of sac growth; model M4, model M1 + predicted sac diameter + predicted rate of growth; model M5, predicted rate of growth; model M6, crude rate of growth

Table 3 Performance of prognostic model M5 incorporating predicted sac growth only in classifying patients as low or high risk based on a risk score threshold

Landmark time after operation	2-year risk threshold (%)	Approximate threshold based on growth rate (mm/year)	Cases classified high risk*	Non-cases classified low risk†	PPV: high-risk patients who are cases	NPV: low-risk patients who are non-cases	% classified low risk
2 years							
EVAR			n = 47	n = 519			
	> 4	>−2	43 (91)	111 (21)	10	97	20
	> 5	> −1	42 (89)	172 (33)	11	97	31
	> 6	> 0	40 (85)	228 (44)	12	97	42
	> 8	> 2	33 (70)	325 (63)	15	96	60
	> 10	> 3	27 (57)	401 (77)	19	95	74
Helsinki			n = 35	n = 142			
	> 4	> −2	32 (91)	44 (31)	25	94	27
	> 5	> −1	29 (83)	59 (42)	26	91	37
	> 6	> 0	29 (83)	71 (50)	29	92	44
	> 8	> 2	27 (77)	93 (65)	36	92	57
	> 10	> 3	20 (57)	121 (85)	49	89	77
3 years							
EVAR			n = 45	n = 462			
	> 4	> 0	37 (82)	157 (34)	11	95	33
	> 5	> 1	36 (80)	211 (46)	13	96	43
	> 6	> 2	34 (76)	253 (55)	14	96	52
	> 8	> 3	32 (71)	309 (67)	17	96	64
	> 10	> 3	30 (67)	355 (77)	22	96	73
Helsinki			n = 30	n = 108			
	> 4	> 0	28 (93)	53 (49)	34	96	40
	> 5	> 1	27 (90)	62 (57)	37	95	47
	> 6	> 2	25 (83)	69 (64)	39	93	54
	> 8	> 3	23 (77)	77 (71)	43	92	61
	> 10	> 3	20 (67)	90 (83)	53	90	69
5 years							
EVAR			n = 26	n = 378			
	> 4	> 1	22 (85)	209 (55)	12	98	53
	> 5	> 2	20 (77)	246 (65)	13	98	62
	> 6	> 2	18 (69)	274 (72)	15	97	70
	> 8	> 3	14 (54)	315 (83)	18	96	81
	> 10	> 4	12 (46)	334 (88)	21	96	86
Helsinki			n = 12	n = 48			
	> 4	> 1	10 (83)	31 (65)	37	94	55
	> 5	> 2	9 (75)	33 (69)	38	92	60
	> 6	> 3	8 (67)	33 (69)	35	89	62
	> 8	> 3	6 (50)	41 (85)	46	87	78
	> 10	> 4	6 (50)	41 (85)	46	87	78

Values in parentheses are percentages (*sensitivity and †specificity). Cases are the patients who will have a ruptured aneurysm or rupture-preventing reintervention during follow-up. PPV, positive predictive value; NPV, negative predictive value.

After adjusting for other predictors, only a few co-variables remained significantly associated with the risk of rupture or RPR. *Table 2* shows the hazard ratios (HRs) contributing to the full multivariable prediction model (M4). Full regression coefficients and 2-year baseline hazards for models M1–M6 at each of the three landmark times are available in *Table S3* (supporting information). In particular, preoperative AAA size was still an important predictor at 2 years, but its effect attenuated by 5 years after operation. Similarly, the number of previous complications was associated with a higher risk at 2 and 3 years after surgery, but was not a significant predictor by 5 years. Current sac diameter was no longer an important predictor once sac growth and preoperative AAA size had been accounted for, whereas rate of sac growth remained associated with an increased risk throughout follow-up. At 2 years, the risk of rupture or RPR increased by 64 per cent (HR 1·64, 95 per cent c.i. 1·31 to 2·06; $P < 0·001$) for every 2-mm/year increase in the rate of sac growth. For the same increase in rate of growth at 5 years, the

risk increased by 80 per cent (HR 1·80, 1·12 to 2·89; $P = 0.015$).

Calibration and predictive accuracy of the risk scores

Two-year risk predictions from the full multivariable model (model M4) were well calibrated with observed risks at all three landmark time points in the EVAR trials data (*Fig. S3*, supporting information). Predictive discrimination was calculated for the six prognostic models (M1–M6). *Fig. 2* shows the C-index value at 2, 3 and 5 years after operation for patients in the EVAR trials and those in the Helsinki cohort. The difference in C-index from model M1 is shown in *Fig. S4* (supporting information). At all landmark times there was an improvement in the C-index when the rate of growth was included in the model (model M3 *versus* M1); the C-index values from the EVAR trials increased from 0·64 to 0·70 at 2 years (difference 0·06, 95 per cent c.i. 0·02 to 0·11; $P = 0.004$), from 0·66 to 0·74 at 3 years (difference 0·08, 0·02 to 0·13; $P = 0.006$) and from 0·63 to 0·76 at 5 years (difference 0·13, 0·04 to 0·21; $P = 0.003$), representing good discriminatory performance. Using rate of growth alone as a predictor (model M5) also showed good discriminatory performance, whereas using a crude rate of growth performed poorly (model M6).

The prognostic models performed even better in the external Helsinki cohort, with higher C-index values for all landmark times and models. As with the EVAR trials, there was an improvement in predictive accuracy, albeit less pronounced, when rate of growth was included in the models. There was an increase in C-index from 0·77 in model M1 to 0·80 in model M3 at 2 years, and from 0·71 to 0·78 at 5 years.

Developing a classification rule

The performance of model M5 (using predicted sac growth alone) in correctly classifying individuals as high or low risk was investigated. Patients in the EVAR trials and Helsinki cohort were classified according to whether their 2-year risk prediction was greater or less than a threshold value. *Table 3* shows the estimated sensitivity, specificity, and positive and negative predictive values for various 2-year risk thresholds. Each 2-year risk threshold approximates to an equivalent growth rate threshold. To ensure high sensitivity (classifying the patients who will have an aneurysm rupture or RPR (cases) that will occur in the next 2 years as high risk), the threshold needs to be set low (for example, considering a 2-year risk of more than 4–10 per cent as high risk). The results show that any patient with a positive aneurysm growth rate (greater than

0 mm/year) could be flagged as high risk at 2 or 3 years after operation. This would identify more than 80 per cent of all cases (in both the EVAR trials and the Helsinki cohort), while enabling between 30 and 45 per cent of all patients to be classified as low risk, with a potential change in surveillance. At 5 years after operation, around 85 per cent of patients who have an RPR or aneurysm rupture within the following 2 years have a growth rate over 1 mm/year. Using this as a threshold would allow over 50 per cent of patients to be classified as low risk at this time point.

Discussion

A prognostic model was developed to predict secondary rupture or RPR following EVAR for AAA. After controlling for other predictors, an increased risk was found to be associated with larger preoperative AAA diameters, a greater frequency of previous complications and higher rates of sac growth. A longitudinal model that used a series of repeat sac diameter measurements was used to obtain a prediction of current sac growth that is less prone to measurement error than a crude estimate of rate of growth calculated using change from baseline (operation). The rate of growth is an important predictor as it shows a consistent association with risk throughout follow-up and can be used to update individual risk to potentially enable personalized surveillance.

The prognostic model based on changes in sac diameter showed good predictive accuracy within the EVAR trials and performed significantly better when the external data set of patients who underwent EVAR in the Helsinki region was used. This may be because there was larger variation in patient characteristics (age, number of previous complications and reinterventions) in the Helsinki cohort, which enables better discrimination of the population. Another possible explanation could be improved imaging quality, leading to potentially more accurate estimates of sac diameter and growth, and better detection of underlying endoleaks leading to reinterventions that are more closely aligned with sac growth. With this knowledge, a centre would have greater enthusiasm for annual follow-up with the expectation of reducing the risk of rupture in an individual patient. A third possible reason for better predictive accuracy in the Helsinki data could be good adherence to patient follow-up.

Although the model performed well on the external data, there are several inconsistencies between the EVAR trials and the Helsinki cohort. Data collection for the Helsinki

region was mainly focused on five main complication categories: type I, II and III endoleaks, migration and kinking; the EVAR trials registered additional complications such as thrombosis and graft infection. The authors attempted to standardize the definitions used across the two data sets, and focused on the five categories referred to above. Similarly, reinterventions were often coded differently in the two data sets; a standardized coding of RPR was required to harmonize the outcome. Use of the surrogate outcome of rupture or RPR was chosen partly owing to small numbers of ruptures, which precluded the use of rupture as an independent outcome in a prognostic model.

A risk score incorporating sac growth opens the door to simple yet safe personalized surveillance. Sac diameter can be measured reliably on an ultrasound device and could potentially be measured in primary care, not requiring a hospital visit. This would not only reduce costs, but may also be more acceptable to the patient and keep more patients in follow-up. Calculation of an individual's predicted rate of AAA growth would need to be implemented within a computer algorithm, although many risk calculators are now available on mobile phones[23]. A patient undergoing EVAR has a vested interest in ensuring that the sac around the repair does not expand; if it does, more imaging would be required to identify and correct the underlying endoleak causing the sac diameter to increase. A safe and acceptable lifelong follow-up schedule is therefore imperative. More use of ultrasonography would dispense with the need for annual exposure to radiation that occurs with CT. The higher rates of cancer death late in follow-up after EVAR in the EVAR-1 trial[2] may have been related to the reliance on follow-up by CT.

In EVAR-1, aneurysm-related mortality and all-cause mortality were higher after 8 years in the EVAR group than the open repair group[2]. The main cause of AAA-related mortality was secondary sac rupture resulting from failure to comply with annual imaging and reinterventions. It follows that smarter surveillance protocols could reduce not only mean costs but also rates of secondary sac rupture and AAA-related mortality, thus improving the cost-effectiveness of EVAR.

Future work should focus on the cost implications, quality-of-life assessments and the cost-effectiveness of various surveillance strategies after EVAR, including comparing how surveillance might be delivered (for example, an annual close-to-home ultrasound sac diameter measurement compared with a visit to secondary care for CT). It is also important to study the efficacy of this predictive model prospectively, to check the correlation between sac growth and underlying correctable endoleak complication, kinking or migration, and to investigate whether the correction of these brings about a lower rate of secondary sac rupture and improved survival.

A dynamic prognostic model incorporating secondary sac growth has the potential to be used to tailor surveillance by identifying a large proportion of patients who may require less intensive follow-up as well as those who have a high risk of secondary rupture or RPR within the next 2 years.

Acknowledgements

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.