Appendix D – Clinical evidence tables

Full citation	**Brown L C, and Powell J T (1999) Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Annals of surgery 230(3), 289-96; discussion 296-7**
Study details	Study design: Prospective cohort study Location(s): UK Aim of the study: To investigate risk factors associated with aneurysm rupture. Study dates: 1991 to 1998 Follow-up: 3 years Sources of funding: The trial was supported by grants from the UK Medical Research Council, the British Hearth Foundation.
Participants	Sample size: 2,557 Inclusion criteria: People with AAAs between, 60 and 76 years, who were entered into either UKSAT trial or the “Small Aneurysm Study”. Patients who were eligible for randomisation into the trials had aneurysm diameters between 4.0 and 5.5 cm. Patients who were ineligible for randomisation into the trials were also included. These patients were ineligible if they had an AAA diameter < 4.0 cm or > 5.5 cm, if they refused randomisation or if surgery was considered unsuitable. Exclusion criteria: Not specified
Methods	Data collection: Patients were assessed by a clinical interview and physical examination to collect data on risk factors. The maximum antero-posterior diameter of aneurysms was determined using ultrasound imaging: imaging intervals were not specified. Analysis: Cox regression analysis, adjusting for age, sex and initial AAA diameter. Baseline characteristics: • Mean age: 69 years • Sex: 79.4% male • Mean aneurysm diameter: 4.6 cm • History of diabetes: 4.4% • History of hypertension: 41.2%
Outcomes	Outcome: Aneurysm rupture (ascertained either from a death certificate or from ultrasound imaging) Risk factors: Age; sex; initial AAA diameter (cm); smoking status; body mass index (BMI); mean blood pressure (mmHG); ankle-brachial pressure index measurement; forced expiratory volume in 1 second (FEV_1); total cholesterol (mmol/L)
Risk of bias assessment	1. Did the study address a clearly focused issue? Yes

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(using CASP tool)	2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes - measured in accordance of UKSAT trial protocols 4. Was the outcome accurately measured to minimise bias? Yes 5 (a) Have the authors identified all important confounding factors? Unclear (b) Have they taken account of the confounding factors in the design and/or analysis? Unclear 6 (a) Was the follow up of subjects complete enough? Yes (b) Was the follow up of subjects long enough? Yes Overall risk of bias: Low Directness: directly applicable

Full citation	**Ferguson Craig D, Clancy Paula, Bourke Bernard, Walker Philip J, Dear Anthony, Buckenham Tim, Norman Paul, and Golledge Jonathan (2010) Association of statin prescription with small abdominal aortic aneurysm progression. American heart journal 159(2), 307-13**
Study details	Study design: Prospective cohort study Location(s): Australia and New Zealand Aim of the study: To assess the association between statin usage and AAA growth. Study dates: Follow-up: Median of 5 years Sources of funding: Grants were received from the National Institute of Health (USA), Townsville Hospital Private Practice Fund, National Heart Foundation and National Health and Medical Research Council.
Participants	Sample size: 652 Inclusion criteria: People with small AAAs between 3.0 and 5.0 cm in diameter for whom the recruiting clinician had no plan to perform surgical repair. Exclusion criteria: Not specified Baseline characteristics: • Mean age: 73 years • Sex: 94% male • Mean aneurysm diameter: 3.3 cm • Diabetes: 13%

Full citation	**Ferguson Craig D, Clancy Paula, Bourke Bernard, Walker Philip J, Dear Anthony, Buckenham Tim, Norman Paul, and Golledge Jonathan (2010) Association of statin prescription with small abdominal aortic aneurysm progression. American heart journal 159(2), 307-13**
	• Hypertension: 60% • Coronary heart disease: 46% • Peripheral arterial disease: 20%
Methods	Data collection: Patients were assessed by a clinical interview and physical examination plus their medical records were reviewed to collect data on risk factors. The maximum antero-posterior diameter of aneurysms was determined using ultrasound imaging performed at 6 month intervals (for aneurysms 4.5 to 5.0 cm in diameter) or yearly intervals (for aneurysms 3.0 to 4.4 cm in diameter). Analysis: Multivariate logistic regression, adjusting for initial aortic diameter presence of diabetes, and presence of coronary heart disease
Outcomes	Outcome: Aneurysm growth (binary outcome) Risk factors: Age; sex; diabetes; hypertension; coronary heart disease; peripheral artery disease; smoking status; initial aortic diameter; taking ACE inhibitors; taking aspirin; taking beta-blockers; taking statins
Risk of bias assessment (using CASP tool)	1. Did the study address a clearly focused issue? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5 (a) Have the authors identified all important confounding factors? Unclear (b) Have they taken account of the confounding factors in the design and/or analysis? Unclear 6 (a) Was the follow up of subjects complete enough? Yes (b) Was the follow up of subjects long enough? Yes Overall risk of bias: Low Directness: directly applicable

Full citation	**Nakayama Atsuko, Morita Hiroyuki, Miyata Tetsuro, Ando Jiro, Fujita Hideo, Ohtsu Hiroshi, Akai Takafumi, Hoshina Katsuyuki, Nagayama Masatoshi, Takanashi Shuichiro, Sumiyoshi Tetsuya, and Nagai Ryozo (2012) Inverse association between the existence of coronary artery disease and progression of abdominal aortic aneurysm. Atherosclerosis 222(1), 278-83**
Study details	Study design: Retrospective cohort study Location(s): Japan Aim of the study: To investigate the coronary artery disease on the progression of AAA and the onset of major adverse cardiovascular events after elective surgical repair Study dates: January 2003 to March 2010 Follow-up: minimum of 2 years Sources of funding: This research is supported by the Japan Society for the Promotion of Science
Participants	Sample size: 665 Inclusion criteria: People who underwent elective surgical repair for AAA at a specialist centre. Surgical repair was offered to patients when aneurysms were greater than 5.0 cm in diameter. Exclusion criteria: Patients with AAAs that were diagnosed as being a direct consequence of a specific cause such as trauma, infection, inflammatory disease, or Marfan syndrome were excluded.
Methods	Data collection: The details of surgical management and patient clinical characteristics, before and after surgical repair, were obtained from medical records. Diameters of aneurysms were evaluated by computed tomography. Imaging intervals were not specified. Analysis: Multivariate logistic regression and Cox regression analysis, adjusting for age, sex, BMI, hypertension, dyslipidaemia, diabetes, smoking status, haemodialysis, coronary artery disease Baseline characteristics: • Mean age: 73.3 years • Sex: 83% male • Mean aneurysm diameter: 53.5cm • Diabetes: 13% • Hypertension: 60% • Coronary heart disease: 46% • Peripheral arterial disease: 20%
Outcomes	Outcome: Accelerated growth, defined as expansion rate greater than 5 mm per year Risk factors: Age; sex; BMI; hypertension; dyslipidaemia; diabetes; smoking status; haemodialysis; creatine levels (mg/dL); family history of AAA; family history of coronary artery disease; existence of preoperative coronary artery disease; ischaemic changes on ECG; presence of cerebral artery disease; presence of COPD; taking beta-blockers; taking ACE inhibitors; taking calcium-channel blockers; taking statins

Full citation	**Nakayama Atsuko, Morita Hiroyuki, Miyata Tetsuro, Ando Jiro, Fujita Hideo, Ohtsu Hiroshi, Akai Takafumi, Hoshina Katsuyuki, Nagayama Masatoshi, Takanashi Shuichiro, Sumiyoshi Tetsuya, and Nagai Ryozo (2012) Inverse association between the existence of coronary artery disease and progression of abdominal aortic aneurysm. Atherosclerosis 222(1), 278-83**
Risk of bias assessment (using CASP tool)	1. Did the study address a clearly focused issue? Yes 2. Was the cohort recruited in an acceptable way? No – only patients who underwent elective surgical repair were included. Data from patients who had growing aneurysms that did not reach the threshold for surgical repair or patients who opted not to receive surgery were not included in the analysis. This may potentially lead to over- or under-estimations of effect sizes. 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5 (a) Have the authors identified all important confounding factors? Unclear (b) Have they taken account of the confounding factors in the design and/or analysis? No 6 (a) Was the follow up of subjects complete enough? Yes (b) Was the follow up of subjects long enough? Yes Overall risk of bias: High Directness: directly applicable

Full citation	**Norman Paul, Spencer Carole A, Lawrence-Brown Michael M, and Jamrozik Konrad (2004) C-reactive protein levels and the expansion of screen-detected abdominal aortic aneurysms in men. Circulation 110(7), 862-6**
Study details	Study design: Retrospective cohort study Location(s): Australia Aim of the study: To assess the relationship between C-reactive protein (CRP) levels and small AAA expansion rates. Study dates: Not specified Follow-up: minimum of 1 year Sources of funding: Grants were received from the National Health and Medical Research Council (Australia), the National Heart Foundation (Australia), and Royal Perth Hospital Research Foundation
Participants	Sample size: 545 Inclusion criteria: Men, between 65 and 83 years, with small AAAs (size range not specified) who were enrolled in a population-based screening study. Exclusion criteria: Not specified. Baseline characteristics: • Mean age: not reported • Sex: 100% male • Mean aneurysm diameter: not reported • History of acute myocardial infarction: 28% • History of angina: 28% • History of stroke: 11% • History of diabetes: 10% • Hypertension: 46%
Methods	Data collection: Data was used from databases of the Western Australia AAA screening study. In the screening study participants completed a question air on risk factors that included the Edinburgh Claudication questionnaire, had their height, weight, blood pressure, and circumference at the waist and hips recorded. C-reactive protein was measured by a high-sensitivity assay. Aneurysm diameters were determined using ultrasound imaging performed at 6 month intervals (for aneurysms ≥ 4.0 cm in diameter) or yearly intervals (for aneurysms 3.0 to 3.9 cm in diameter). Analysis: Multivariate logistic regression adjusting for age
Outcomes	Outcome: Aneurysm growth ≥ 3 mm (binary outcome) Risk factors: Initial aorta size; smoking status; C-reactive protein levels (mg/L)
Risk of bias assessment	1. Did the study address a clearly focused issue? Yes 2. Was the cohort recruited in an acceptable way? Yes

Full citation	Norman Paul, Spencer Carole A, Lawrence-Brown Michael M, and Jamrozik Konrad (2004) C-reactive protein levels and the expansion of screen-detected abdominal aortic aneurysms in men. Circulation 110(7), 862-6
(using CASP tool)	3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5 (a) Have the authors identified all important confounding factors? Unclear (b) Have they taken account of the confounding factors in the design and/or analysis? No 6 (a) Was the follow up of subjects complete enough? Yes (b) Was the follow up of subjects long enough? Yes Overall risk of bias: Moderate Directness: directly applicable

Full citation	**Santilli S M, Littooy F N, Cambria R A, Rapp J H, Tretinyak A S, d'Audiffret A C, Kuskowski M A, Roethle S T, Tomczak C M, and Krupski W C (2002) Expansion rates and outcomes for the 3.0-cm to the 3.9-cm infrarenal abdominal aortic aneurysm. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, and North American Chapter 35(4), 666-671**
Study details	Study design: Retrospective cohort study Location(s): USA Aim of the study: To determine expansion rates and outcomes of people with AAA Study dates: December 1992 to November 2000 Follow-up: mean of 3.89 years Sources of funding: Not reported
Participants	Sample size: 790 Inclusion criteria: People with AAAs between 3.0 and 3.9 cm in diameter who were screened for the ADAM randomised controlled trial (including those patients who were not randomised into the trial). All participants had at least 1 follow-up aneurysm diameter measurement taken at least 90 days following initial screening. Exclusion criteria: Not specified Baseline characteristics: Mean age: 69.1 years Sex: 100% male Mean aneurysm diameter: 3.3 cm Comorbidities: not reported
Methods	Data collection: Before the initial ultrasound screening, all patients completed a brief questionnaire to obtain demographic and risk factor information. The patients were asked whether they had ever been told by a physician that they had the risk factors in question. Aneurysm diameters (antero-posterior and lateral planes) were obtained using ultrasound imaging. Imaging intervals were not specified. Analysis: Multivariate logistic regression. No further details were provided
Outcomes	Outcome: aneurysm growth (ordinal outcomes) and aneurysm rupture Risk factors: initial infrarenal aortic diameter; age; family history of AAA; smoking status; cardiovascular disease (history of angina, stroke, myocardial infarction, or coronary artery bypass grafting); claudication; diabetes; hypertension (previous diagnosis or current medication); or hypercholesterolemia (previous diagnosis or current medication)
Risk of bias assessment (using CASP tool)	1. Did the study address a clearly focused issue? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? No - Before the initial ultrasound screening, all patients completed a brief questionnaire to obtain demographic and risk factor information. The patients were asked whether they had ever been told by a physician that they had the risk factors in question.

Full citation	**Santilli S M, Littooy F N, Cambria R A, Rapp J H, Tretinyak A S, d'Audiffret A C, Kuskowski M A, Roethle S T, Tomczak C M, and Krupski W C (2002) Expansion rates and outcomes for the 3.0-cm to the 3.9-cm infrarenal abdominal aortic aneurysm. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, and North American Chapter 35(4), 666-671**
	4. Was the outcome accurately measured to minimise bias? Yes 5 (a) Have the authors identified all important confounding factors? Unclear (b) Have they taken account of the confounding factors in the design and/or analysis? No 6 (a) Was the follow up of subjects complete enough? Yes (b) Was the follow up of subjects long enough? Yes Overall risk of bias: Moderate Directness: directly applicable

Full citation	**Thompson S G, Brown L C, Sweeting M J, Bown M J, Kim L G, Glover M J, Buxton M J, and Powell J T (2013) Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. Health technology assessment (Winchester, and England) 17(41), 1-118**
Study details	Study design: Individual patient data meta-analysis using data from randomised controlled trials and disease registries Location(s): UK Aim of the study: To inform the evidence base for small AAA surveillance strategies. Study dates: literature searched up to September 2012 Follow-up: mean of 4.0 years Sources of funding: Funding was received from the National Institute for Health Research Health Technology Assessment programme.
Participants	Sample size: 18 studies, including 15,475 Inclusion criteria: Studies including more than 100 patients with AAAs between 3.0 and 5.5 cm in diameter. Exclusion criteria: Studies in which patient data were duplicated, non-human studies, editorials, letters, case reports, studies using patients previously treated by AAA surgery or aneurysms of other arteries, and studies reporting on patients with Marfan syndrome were excluded Baseline characteristics: baseline characteristics of the pooled study cohort were not reported. Instead, baseline characteristics of patients in each individual study were reported separately.
Methods	Data collection: Data sets for were identified through a systematic literature search. Upon identification of relevant studies requests for individual patient data were sent to principal investigators of each study. Data requested included age, sex, sequential aneurysm diameters, ethnicity, smoking history, BMI, presence of diabetes, dates of aneurysm repair, aneurysm rupture or death. A pragmatic definition of aneurysm rupture was used, based on locally used definitions and reporting. Aneurysm diameters were measured using ultrasound imaging or computed tomography. For each individual, the baseline measurement was defined as the first measurement recorded between 3.0 and 5.4 cm. Any measurements taken before the aneurysm reached 3.0 cm were not considered in the analysis. All data following baseline measurements were used up until the point that aneurysms exceeded 5.5 cm in diameter, the patient received underwent elective surgical repair, the patient died of non-related causes or the date of administrative censoring of the data set. Aneurysm growth analysis: Each predictor was considered in a quadratic random-effects model. To allow studies that recorded both ultrasound imagine and computed-tomography to be included, a dummy variable was added to distinguish between the 2 imaging modalities. Multivariate analysis was performed adjusting for age, calendar year, sex, smoking, diabetes, mean arterial blood pressure/pulse pressure, history of cardiovascular disease, and additionally any recorded use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium-channel blockers, statins or lipid-lowering medicines, and antiplatelet use. Studies that did not collect all these covariates were adjusted for as many covariates in the list as possible. Aneurysm rupture analysis: Cox regression analysis was performed, adjusting for aneurysm diameter (entered as a time-varying covariate)
Outcomes	Outcome: Aneurysm growth and aneurysm rupture Risk factors: Age; sex; smoking status; BMI; diabetes; mean arterial blood pressure (per 10 mmHg); pulse pressure (per 10 mmHg); history of cardiovascular disease.

Full citation	**Thompson S G, Brown L C, Sweeting M J, Bown M J, Kim L G, Glover M J, Buxton M J, and Powell J T (2013) Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. Health technology assessment (Winchester, and England) 17(41), 1-118**
Appraisal of study quality	1. Did the review follow a protocol? Yes 2. Did inclusion criteria allow the right studies to be identified? Yes 3. Were restrictions based on study characteristics and information sources appropriate? Yes 4. Did the search include a range of databases and other sources for published and unpublished reports? Yes 5. Were the terms and structure of the search strategy suitable? Yes 6. Were efforts made to minimise errors in selection of studies? Yes 7. Did authors provide a description of how IPD were requested, collected and managed? Yes 8. Did authors describe which aspects of IPD were subject to data checking and how this was done? Yes 9. Were efforts made to minimise errors in data collection? Yes 10. Were sufficient study characteristics reported? Yes 11. Were all relevant study results included? Yes 12. Was the integrity of IPD assessed? Yes 13. Did the authors describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome? Unclear – Authors do not report whether a risk of bias tool was used to assess the quality of identified studies 14. Was heterogeneity minimal or addressed in the synthesis? Heterogeneity varied according to risk factor assessed (up to 98%). Not all patient demographics data was available from included studies. Most studies used ultrasound imaging to measure the diameters of aneurysms; however, a few of the studies used computed-tomography. Some studies measured external (outer-to-outer) wall diameters, whereas others (n=3) measured internal diameters. Study-specific thresholds for surgical intervention varied from 4.5 cm up to 6.0 cm 15. Were the findings robust? Unclear – no regression or sensitivity analyses were performed Overall risk of bias: Moderate Directness: directly applicable