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RANDOMISED CLINICAL TRIAL

Editor's Choice – Effect of Carotid Endarterectomy on 20 Year Incidence of Recorded Dementia: A Randomised Trial

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WHAT THIS PAPER ADDS

The Asymptomatic Carotid Surgery Trial (ACST-1) trial (surgery and medical treatment *vs.* medical treatment alone) showed that surgery for asymptomatic carotid stenosis significantly reduced long term stroke risk. In total, 1 601 patients in ACST-1 from the UK and Sweden, countries with good electronic patient record systems, were followed for 16 — 26 years, comparing dementia risk by previous treatment allocation. No difference in risk was found between randomised patient groups; the long term risk was higher in older patients, and those with brain infarcts or diabetes at randomisation. Carotid surgery for tight asymptomatic carotid stenosis reduced long term stroke risk, but this study has not shown that it reduces or increases the risk of dementia.

Objective: Stroke and carotid atherosclerosis are associated with dementia. Carotid endarterectomy (CEA) reduces stroke risk, although its effect on later dementia is uncertain. Participants in the Asymptomatic Carotid Surgery Trial (ACST-1), randomly allocated to immediate *vs.* deferral of CEA (i.e., no intervention unless or until triggered by ipsilateral transient ischaemic attack or stroke), were followed, to study effects on dementia.

Methods: From 1993 to 2003, ACST-1 included 3 120 participants with asymptomatic tight carotid stenosis. All UK and Swedish patients ($n = 1\ 601$; 796 immediate *vs.* 805 deferral) were followed with trial records, national electronic health record linkage, and (UK only) by post and telephone. Cumulative incidence and competing risk analyses were used to measure the effects of risk factors and CEA on dementia risk. Intention to treat analyses yielded hazard ratios (HRs; immediate *vs.* deferral) of dementia.

Results: The median follow up was 19.4 years (interquartile range 16.9 — 21.7). Dementia was recorded in 107 immediate CEA patients and 115 allocated delayed surgery; 1 290 patients died (1 091 [538 *vs.* 536] before any dementia diagnosis). Dementia incidence rose with age and with female sex (men: 8.3% aged < 70 years at trial entry *vs.* 15.1% aged ≥ 70; women: 15.1% aged < 70 years at trial entry *vs.* 22.4% aged ≥ 70 years) and was higher in those with pre-existing cerebral infarction (silent or with prior symptoms; 20.2% *vs.* 13.6%). Dementia risk was similar in both randomised groups: 6.7% *vs.* 6.6% at 10 years and 14.3% *vs.* 15.5% at 20 years, respectively. The dementia HR was 0.98 (95% confidence interval [CI] 0.75 — 1.28; $p = .89$), with no heterogeneity in the neutral effect of immediate CEA on dementia related to age, carotid stenosis, blood pressure, diabetes, country of residence, or medical treatments at trial entry (heterogeneity values $p > .05$).

Conclusion: CEA was not associated with significant reductions in the long term hazards of dementia, but the CI did not exclude a proportional benefit or hazard of about 25%.

Keywords: Carotid endarterectomy, Dementia, Long term follow up, National electronic health records, Randomised controlled trial, Stroke
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INTRODUCTION

Stroke, transient ischaemic attack (TIA), and cerebral small vessel disease are associated with vascular cognitive impairment and dementia.[1–4] Surgery for carotid stenosis (carotid endarterectomy [CEA]) prevents TIA and stroke in symptomatic and asymptomatic patients and could reduce the risk of later cognitive decline and dementia. However, there are no randomised trials of surgery or stenting for carotid stenosis with long term dementia assessment. Six cohort and longitudinal studies were identified with at least 500 patients, some of whom had carotid stenosis. One had follow up for at least 10 years but included very few patients with significant (> 50%) carotid stenosis and no formal selection process for surgery. Weak associations were found between carotid artery stenosis and dementia, but these were mostly related to age. Observational studies are prone to systematic error (or bias), but randomised trials are not.

CEA for tight asymptomatic carotid stenosis lowers stroke risk by about half within the next five years and this benefit persists after 10 years,[5] as successful removal of the stenosis reduces the risk of subsequent cerebral emboli and sudden cerebral hypoperfusion. Small, short term, observational studies have suggested that CEA or stenting might improve cognition, but, because cognitive decline and dementia rates are not measured routinely in randomised trials or registries, there is no clear evidence of longer term benefit or hazard.[6–10]

Prolonged follow up of trial participants is now possible with linkage to national electronic records and, as dementia records have good positive predictive value (PPV) for clinical diagnosis,[11–14] this provides the opportunity to investigate the longer term effects of CEA on incident dementia. Unlike observational studies, intention to treat (ITT) analyses of randomised trials allow an unbiased assessment of treatment effects.

The Asymptomatic Carotid Surgery Trial-1 (ACST-1) randomly allocated patients with tight carotid stenosis to early or deferred CEA, in order to determine the hazards and benefits of surgery on stroke. Between 1993 and 2003, 3 120 participants from 30 countries were entered, and the five and 10 year results of the trial were reported in 2004 and 2010, respectively.[5,15] Despite an early hazard from surgery, CEA clearly prevented later stroke, reducing the absolute risk of stroke by 6%–7% by five years, and this benefit was maintained to 10 years. Half the strokes prevented were disabling or fatal. As well as reducing the risk of emboli from the carotid stenosis, non-fatal stroke was prevented in about 5% of survivors. For this study, dementia outcomes 15 – 25 years after randomisation were investigated in the 1 601 ACST-1 participants from the UK and Sweden, where linkage to electronic health records is possible.

METHODS

Asymptomatic patients with substantial carotid artery narrowing, considered fit for surgery, were eligible for ACST-1,[5,15] a randomised trial comparing early ("immediate") CEA with deferral of operation until it seemed more clearly indicated (i.e., after stroke or TIA). All participants were to have appropriate contemporary stroke prevention medicines (referred to as "best' medical treatment), and all gave written informed consent when they joined the trial.

Participants were eligible if (1) they had severe uni- or bilateral carotid artery stenosis suitable for CEA (generally a carotid artery diameter reduction of 60% – 99%, although there was no fixed minimum percentage); (2) this stenosis had not caused ipsilateral stroke, TIA, or any other relevant neurological symptoms in the past six months; (3) no circumstance or condition precluding long term follow up; and (4) the doctor and patient were both substantially uncertain whether to choose immediate CEA or deferral of any CEA. The use of this uncertainty principle to define ACST eligibility is described in the study protocol.[16]

In the current study, risk of dementia was determined in UK and Swedish participants with review of ACST-1 trial paper records (1993 – 2008) and linkage to electronic centrally held health records for recorded dementia (Fig. 1). Data were also retrieved from the Swedish Dementia Registry. In addition, cognitive impairment in surviving UK ACST-1 participants was assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[17,18]

Ascertainment of dementia

Dementia was ascertained using multiple overlapping methods (Fig. 1), including review of study records, electronic health records, and informant questionnaires.

Adjudication of records to 2008. A single researcher (M.S.) hand searched and reviewed all participant patient files and identified participants with significant cognitive impairment or suspected dementia following a pre-specified review plan. A consultant geriatrician (S.T.P.) blinded to the original treatment allocation reviewed all cases of suspected dementia and a random subsample of 51 records from those without evidence of suspected dementia. Final allocation of dementia diagnosis was made by S.T.P. based on documented dementia diagnosis, or on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria after review of all available information in trial records, as previously described.[1]

Linkage. Participants were linked to centrally held national electronic health records in the UK and Sweden with name, date of birth, and UK National Health Service (NHS), Community Health Index, or personal patient identity number (for Sweden). Identification of dementia in these health records was by pre-specified International Classification of Diseases (ICD) coding (Table 1).

In England and Wales (956 patients), NHS Digital (https://digital.nhs.uk/) linked trial participants to the following datasets: mental health minimum dataset (2008 – 2015); mental health and learning disabilities (2014 – 2016); admitted patient care (1997 – 2017); outpatients (2003 –

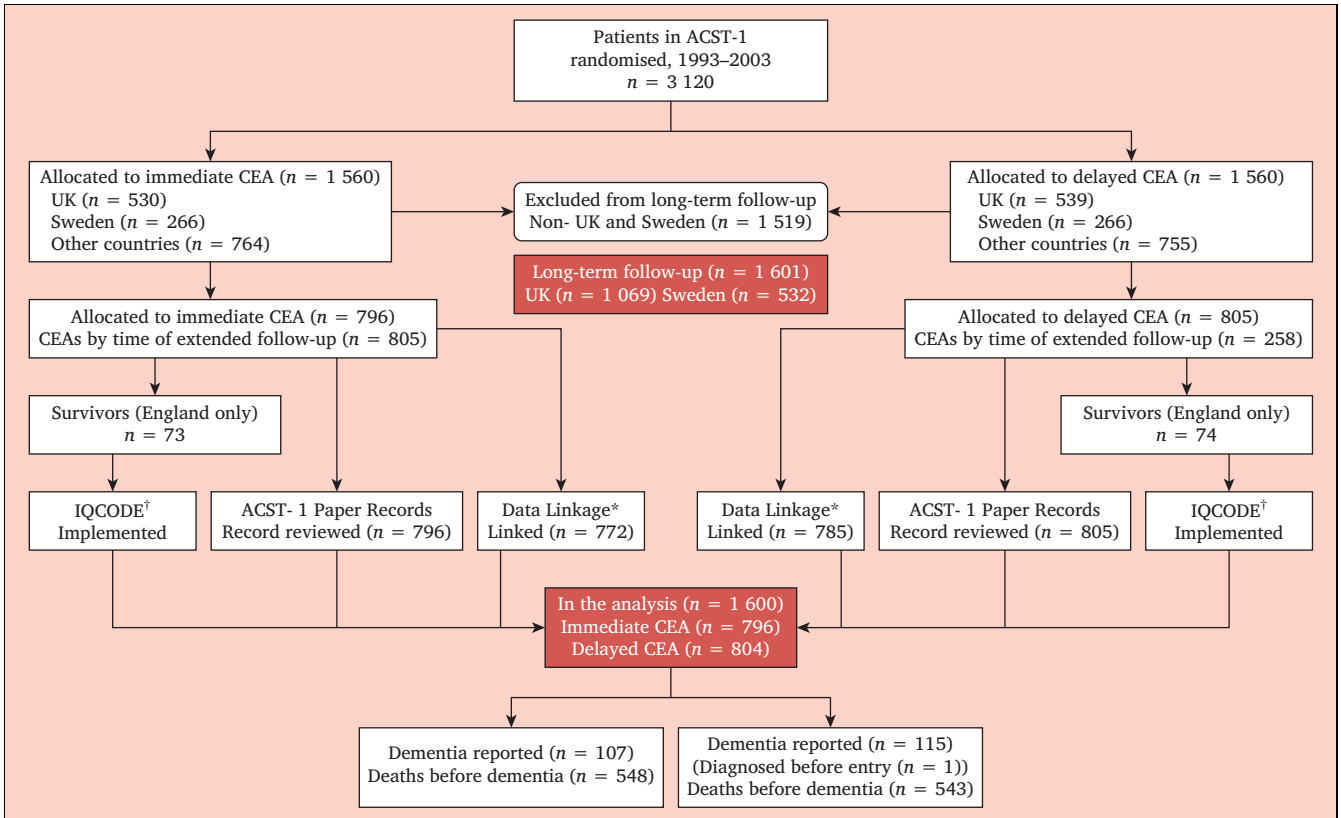


Figure 1. Trial profile, showing randomisation and follow up of the study patients undergoing immediate or deferred carotid endarterectomy (CEA) in the Asymptomatic Carotid Surgery Trial (ACST-1). *Reasons for non-linkage: National Health Service (NHS) number (England), Community Health Index (CHI) number (Scotland), or Socialstyrelsen (Sweden) not available or not matched with central record data; one exclusion as dementia found to be present at randomisation from data linkage (unknown at time of enrolment). †In England, 147 participants were alive in May 2019 through vital status from NHS Summary Care Records: Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) undertaken in May – August 2019. Nine had an IQCODE score of > 3.6, of those in whom an IQCODE was not done, two reported confirmed dementia diagnosis by relative, one self reported cognitive impairment, four deaths following initial contact, 57 active withdrawal, eight residing in a nursing home, five returned by Royal Mail, and 29 no response.

Table 1. Dementia type identified from all sources

Dementia type	ICD coding
Alzheimer's disease	ICD-9: 331.0
	ICD-10: F00, G30
Vascular dementia	ICD-9: 290.4
	ICD-10: F01, I67.3
Non-specific dementia	ICD-9: 290.0, 290.1x, 290.2, 290.3
	ICD-10: F02, F03, F05.1
Rare dementia	ICD-9: 046.19, 331.1, 333.4
	ICD-10: F020A, F021A, F022A, F023A, F024A, F028A
Possible dementia	ICD-9: 294.1, 294.9, 331.2, 331.9
	ICD-10: F050, G31.0, G31.1, G31.2, G31.8, G31.9

ICD = International Classification of Diseases.

2017); accident and emergency department admissions (2007 – 2017); the National Dementia and Antipsychotic Prescribing Audit of dementia care (2006 – 2011); and death records (1997 – 2017).

In NHS Scotland (69 patients) (https://www.informationgovernance.scot.nhs.uk/pbpphsc/), general/acute inpatient and day case records (1993 – 2017), mental health inpatient data (1993 – 2017), prescribing information system (2009 – 2017), and death records (1997 – 2018) were linked.

In Northern Ireland (44 patients), death records (up to 2018) were linked by the Northern Ireland Statistics and Research Agency (https://www.nisra.gov.uk/).

In Sweden (532 patients), the unique personal patient identity number was linked to hospitalisation, death, prescriptions, and dementia using the registry held by the National Board of Health and Welfare (Socialstyrelsen, https://www.socialstyrelsen.se/en/), and that of the Swedish Dementia Registry.

Contact with surviving ACST-1 UK participants. Surviving UK participants were contacted by post for consent to telephone their nominated informant (known to them for at least 10 years) in order to complete the validated IQCODE. On receiving consent from the ACST-1 participant, the IQCODE interview was conducted with the nominated relative or friend by the ACST-1 study nurse by telephone. These resources were unavailable for surviving Swedish participants.

Defined outcomes. The principal outcome was first dementia diagnosis of any type. Dementia was defined as an

ICD-9 or ICD-10 dementia code in any record; or medicines prescribed for dementia only in at least two records; or an adjudicated diagnosis from paper records; or an IQCODE score of > 3.6.[18] The date of dementia was defined as the first date on which dementia was recorded in any register, trial record, or from contact with survivors. Dementia was also identified by prescription of a medicine specifically for treatment of dementia, in at least two records. Dementia was defined in informant interviews for survivors either by the report of a confirmed dementia diagnosis or by an IQCODE score ≥ 3.6 of a possible total score of 5.0.[18]

One UK patient found to have had dementia before randomisation (from centrally held records), not known at the time of study enrolment, was excluded.

Statistical analysis

The first dementia event ascertained from any source was the main outcome of interest in the analysis. Death before diagnosis of dementia (i.e., death attributable to non-dementia causes) was considered as the competing risk. The 20 year absolute risk of dementia was estimated with cumulative incidence functions in the presence of competing risk[19] in participants in different baseline categories (including age, sex, and other risk factors) and in allocated treatment groups (immediate *vs.* deferral of CEA). Fine-Gray competing risk models, stratified by country (UK and Sweden), were implemented to identify risk factors for dementia and to evaluate the effect of immediate CEA on the long term risk of dementia.[20] The Fine-Gray regression analyses for the effect of CEA on dementia were performed according to ITT principle, and were adjusted for sex, age at entry, and prior brain infarct. In general, 95% confidence intervals (CIs) were used for the hazard ratios (HRs) of dementia from the Fine-Gray regressions. In the subgroup analyses of the effect of CEA on the risk of dementia, 99% CIs were used for HRs, to allow for subgroup multiplicity. All *p* values were two sided.

Ethical approval and trial registration

This study was approved in the UK by HRA Research Ethics Committee (16/SC/0406 and 19SC0149), the Confidentiality Advisory Group of NHS England and Wales, HRA (16/CAG/

Table 2. Characteristics of 1 600 patients randomised to immediate or deferred carotid endarterectomy (CEA) in the Asymptomatic Carotid Surgery Trial (ACST-1) study of dementia

	Immediate CEA (*n* = 796)	Deferral of CEA (*n* = 804)	Total (*n* = 1 600)
Country			
Sweden	266 (33.4)	266 (33.1)	532 (33.3)
UK	530 (66.6)	538 (66.9)	1 068 (66.8)
Male sex	510 (64.1)	513 (63.8)	1 023 (63.9)
Age at entry — y			
< 65	226 (28.4)	215 (26.7)	441 (27.6)
65–74	383 (48.1)	401 (49.9)	784 (49.0)
≥ 75	187 (23.5)	188 (23.4)	375 (23.4)
Pre-randomisation cholesterol — mmol/L			
< 6.5 (250 mg/L)	524 (65.8)	510 (63.4)	1 034 (64.6)
≥ 6.5	202 (25.4)	223 (27.7)	425 (26.6)
Not measured	70 (8.8)	71 (8.8)	141 (8.8)
Pre-randomisation systolic blood pressure — mmHg			
≥ 140	661 (83.0)	655 (81.5)	1 317 (82.3)
Ipsilateral carotid diameter reduction — % by ultrasound			
< 70	55 (6.9)	62 (7.7)	117 (7.3)
70–79	240 (30.1)	249 (31.0)	489 (30.6)
80–89	237 (29.8)	255 (31.7)	492 (30.8)
90–99	264 (33.2)	238 (29.6)	502 (31.4)
Ipsilateral plaque echolucency — % soft material			
< 25	135 (17.0)	148 (18.4)	283 (17.7)
≥ 25	159 (20.0)	187 (23.3)	346 (21.6)
Not estimated	502 (63.1)	469 (58.3)	971 (60.7)
Ipsilateral carotid territory status at entry: previous symptoms			
> 6 mo previous	135 (17.0)	131 (16.3)	266 (16.6)
Contralateral status at entry: previous symptoms, resultant CEA history, and patency			
No symptoms, patent	471 (59.2)	492 (61.2)	963 (60.2)
Previous symptoms, CEA, patent	134 (16.8)	150 (18.7)	284 (17.8)
Previous symptoms, no CEA, patent	102 (12.8)	88 (11.0)	190 (11.9)
Occluded	89 (11.2)	74 (9.2)	163 (10.2)
Diabetes or ischaemic heart disease recorded at entry			
Diabetes	127 (16.0)	123 (15.3)	250 (15.6)
Ischaemic heart disease — non-diabetic	222 (27.9)	237 (29.5)	459 (28.7)
Neither	447 (56.2)	444 (55.2)	891 (55.7)

0122, 18/CAG/0195), the Independent Group Advising on the Release of Data of NHS Digital, the Public Benefit and Privacy Panel for Health and Social Care (1617-0257) in NHS Scotland, and the Northern Ireland Statistics and Research Agency. In Sweden, the study was approved by the Swedish Ethical Review Authority, University of Lund on 6 December 2016 (2016/930).

The ACST-1 trial is registered (ISRCTN26156392).

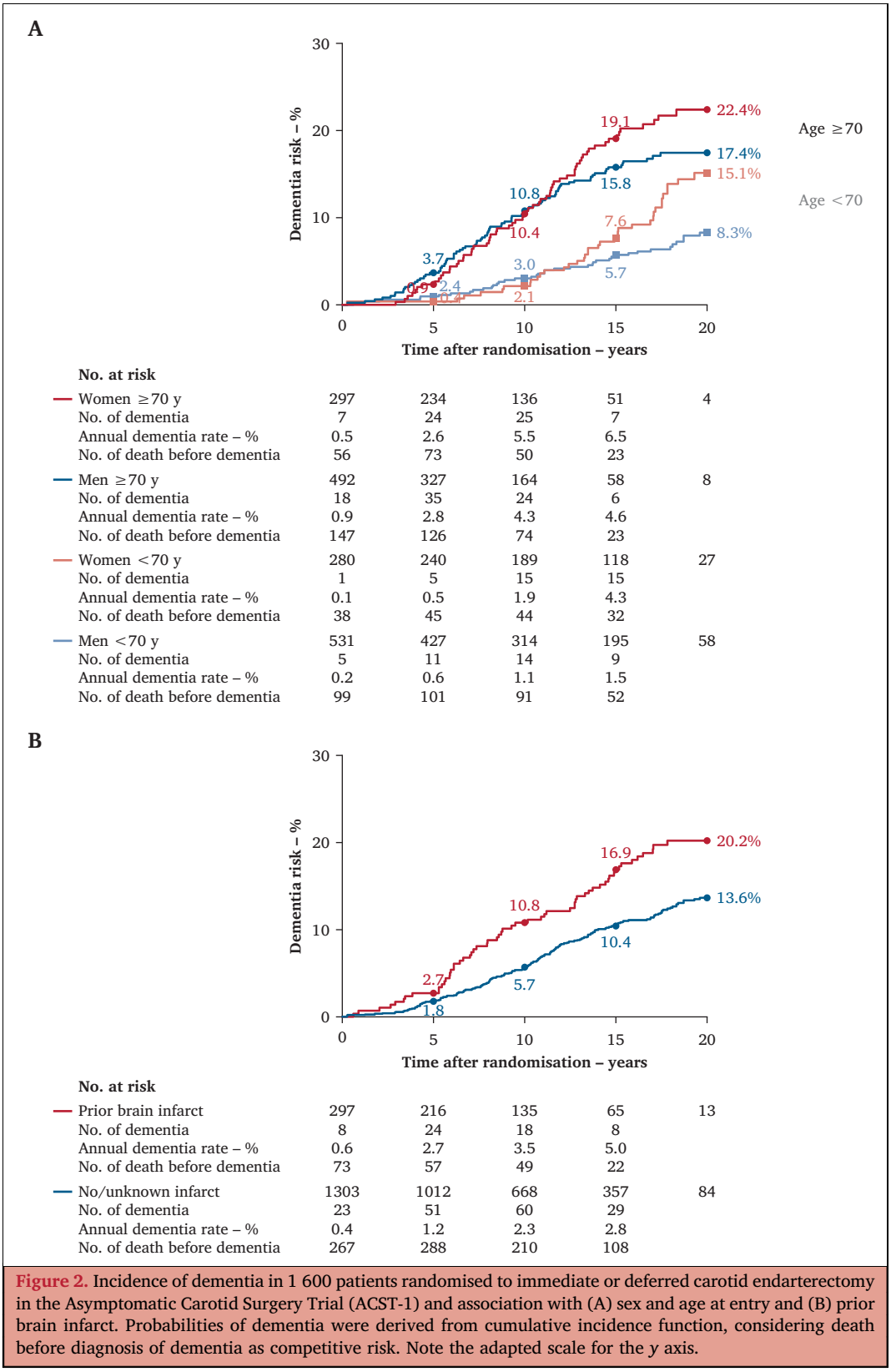


Figure 2. Incidence of dementia in 1 600 patients randomised to immediate or deferred carotid endarterectomy in the Asymptomatic Carotid Surgery Trial (ACST-1) and association with (A) sex and age at entry and (B) prior brain infarct. Probabilities of dementia were derived from cumulative incidence function, considering death before diagnosis of dementia as competitive risk. Note the adapted scale for the *y* axis.

	Dementia	Patients	Annual rate – %	Hazard ratio (95% CI)	p value
Sex					.028
Men	122	1023	1.2	1.00	
Women	99	577	1.6	1.38 (1.04–1.85)	
Age at entry – years					<.001
<65, mean 59	27	441	0.5	1.00	
65–74, mean 69	124	784	1.5	2.79 (1.84–4.24)	
≥75, mean 77	70	375	2.6	3.63 (2.28–5.76)	
Pre-randomisation cholesterol – mmol/L					.22
<5.5	92	600	1.5	1.00	
5.5–6.4	47	434	1.0	0.69 (0.48–0.99)	
≥6.5	56	425	1.2	0.79 (0.56–1.12)	
Not measured	26	141	2.1	0.91 (0.57–1.46)	
Pre-randomisation systolic blood pressure – mmHg					.48
<140	42	284	1.4	1.00	
≥140	179	1316	1.3	0.88 (0.62–1.25)	
Ipsilateral carotid diameter reduction – %					.14
<70, mean 59	23	117	1.8	1.00	
70–79, mean 72	79	489	1.5	0.85 (0.54–1.35)	
80–89, mean 81	58	492	1.2	0.66 (0.40–1.07)	
90–99, mean 92	61	502	1.2	0.63 (0.39–1.03)	
Prior brain infarct confirmed by CT or MRI					.004
Yes	58	297	2.1	1.81 (1.27–2.57)	
No	63	477	1.2	1.26 (0.91–1.75)	
Not done	100	826	1.2	1.00	
Contralateral status at entry: previous symptoms (yes/no)/CEA/patency					.059
No; no CEA; patent	127	963	1.2	1.00	
Yes; CEA; patent	36	284	1.3	0.87 (0.59–1.30)	
Yes; no CEA; patent	41	190	2.1	1.48 (1.02–2.14)	
Occluded	17	163	1.2	0.75 (0.45–1.24)	
Diabetes or ischaemic heart disease (IHD) at entry					.22
Diabetes	29	250	1.4	0.86 (0.56–1.32)	
IHD; non-diabetic	56	459	1.3	0.75 (0.54–1.04)	
Neither	136	891	1.4	1.00	
Antihypertensive therapy at entry					.68
Yes	146	1028	1.4	1.00	
No	75	572	1.2	0.94 (0.70–1.26)	
Antithrombotic therapy at entry					.14
Yes	205	1518	1.3	1.00	
No	16	82	2.0	1.49 (0.88–2.51)	
Lipid lowering therapy at entry					.25
Yes	84	583	1.3	1.00	
No	137	1017	1.4	0.84 (0.61–1.14)	

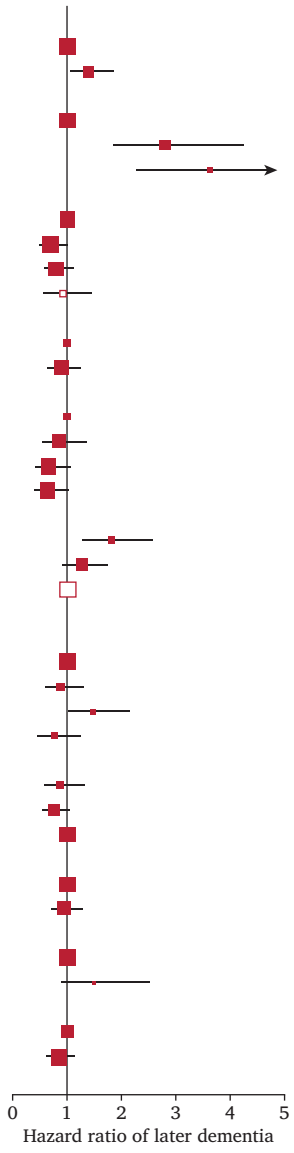


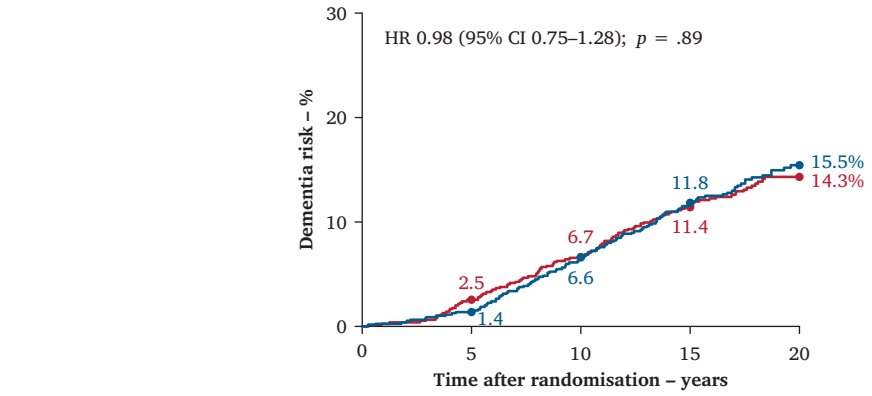
Figure 3. Associations of various factors in a study population of 1 600 patients of the Asymptomatic Carotid Surgery Trial (ACST-1) with hazard ratio of later dementia, assessed with the Fine-Gray model. Each of these Fine-Gray regressions was stratified by country (UK and Sweden) and adjusted for the features that were not being analysed. CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging; CEA = carotid endarterectomy.

RESULTS

The baseline characteristics and treatment allocation of the 1 600 participants included for analysis were well balanced between groups (Table 2). The mean ± standard deviation age of participants at trial entry was 69 ± 7 years. Nearly two thirds of patients were men (n = 1 023, 63.9%), 16.6% (n = 266) had a prior (> 6 months) history of stroke, 15.6% (n = 250) had diabetes, and a further 28.7% (n = 459) were known to have ischaemic heart disease.

Assuming no migration, 17 181 years of follow up were obtained. Median follow up for all patients was 19.4 years (interquartile range [IQR] 16.9 — 21.7 years); for UK patients it was 20.6 years (IQR 17.9 — 22.7 years) and for Swedish patients it was 17.3 years (IQR 15.1 — 19.9 years). The quality of data linkage from patient reported outcome measures and hospital episode statistics matching in the UK was deemed to be excellent, with almost all classed as matching rank 1 (best) or 2 out of 10.[21]

By end of follow up, 805 patients in the "immediate" group and 258 in the "delayed" group had undergone CEA (Fig. 1). In total, 1 290 deaths were reported: 134 (10.4%) patients died from stroke, 559 (43.3%) from cardiac or other vascular disease, 245 (19.0%) from cancer, and 352 (27.3%) from other causes. Altogether, 1 091 deaths (548 in the immediate CEA group *vs.* 543 in the deferred CEA group) occurred before the diagnosis of dementia.



No. at risk					
Deferral of CEA	804	624	411	214	48
No. of dementia	11	42	41	20	
Annual dementia rate – %	0.3	1.6	2.6	3.3	
No. of death before dementia	168	170	134	64	
Immediate CEA	796	604	392	208	49
No. of dementia	20	33	37	17	
Annual dementia rate – %	0.6	1.3	2.5	2.9	
No. of death before dementia	172	175	125	66	

Figure 4. Time to first recorded dementia in trial dataset or national electronic health records or telephone contact dataset in immediate and delayed carotid endarterectomy (CEA). Probabilities of dementia were derived from cumulative incidence function, considering death before diagnosis of dementia as competitive risk. Note the adapted scale for the *y* axis. HR = hazard ratio; CI = confidence interval

By May 2019, via NHS Summary Care Records, 147 UK patients were thought to be alive. They were contacted by mail and a telephone IQCODE interview was requested with a relative or friend (Fig. 1). Telephone IQCODE assessment was undertaken in the 41 participants who consented (20 from the immediate CEA group and 21 from the deferred surgery group). Significant cognitive decline or dementia was indicated from an IQCODE score of $\geq$ 3.6 in nine participants (22%) Dementia was confirmed by relatives in two cases, one participant's telephone reply confirmed cognitive impairment, eight further patients were described as resident in a nursing/care home, and four had died following initial contact. The remaining survivors either actively declined to take part in the IQCODE assessment, did not respond, or the invitation letter was returned by Royal Mail. The small number of responses to the IQCODE for those still alive were insufficient to make a meaningful comparison between treatments using the IQCODE groups alone, but the IQCODE findings were used in the total number of dementia outcomes in the study where dementia had not been reported from the other data sources.

Dementia

Dementia was diagnosed after randomisation in 221 of 1 600 patients. Dementia was first recorded in the ACST-1 trial records of 29 patients (n = 29/221, 13.1%; 24 UK patients and five Swedish patients). There was 100% agreement between assessors for written evidence of dementia or cognitive impairment, and for the subsample of files selected without suspected cognitive impairment or dementia.

In the UK electronic records, dementia was first identified in hospital admission records (n = 88/221, 39.8%), mental health records (n = 27/221, 12.2%), in another UK registry (n = 15/221, 6.8%), or in the IQCODE results (n = 9/221, 4.1%). In Sweden, dementia was recorded in the patient registry (covering diagnostic codes of both in hospital episodes and outpatient visits), the Swedish Medication registry (n = 42/221, 19.0%), or in the Swedish Dementia registry (n = 11/221, 5.0%).

There were 100 participants with a dementia diagnosis from a single data linkage source, 69 from two data linkage sources, and 52 with three or more sources.

Vascular dementia was the most frequently recorded first dementia diagnosis (n = 79, 35.7%), followed by Alzheimer's disease (n = 62, 28.1%), dementia of unspecified type (n = 61, 27.6%), possible dementia (n = 17, 7.7%), and rare dementias (n = 2, 0.9%).

The dementia incidence rose sharply with age and was higher in women at all ages (Fig. 2A). Risk of dementia was highest in older female patients (> 70 years at trial entry). Patients with prior brain infarction (Fig. 2B) had approximately double the hazard of dementia (p = .001) compared with those without. The incidence of dementia was similar in participants, with 60% — 79% *vs.* 80% — 99% carotid stenosis in the asymptomatic artery and in those with higher or lower baseline systolic blood pressure, respectively (Fig. 3).

There were 107 (13.4%) dementia cases in those allocated immediate CEA and 114 (14.2%) in those allocated delayed surgery. Risks of dementia were similar in both treatment groups: 6.7% *vs.* 6.6 % at 10 years and 14.3% *vs.* 15.5% at 20 years. The HR of dementia was 0.98 (95% CI 0.75 — 1.28;

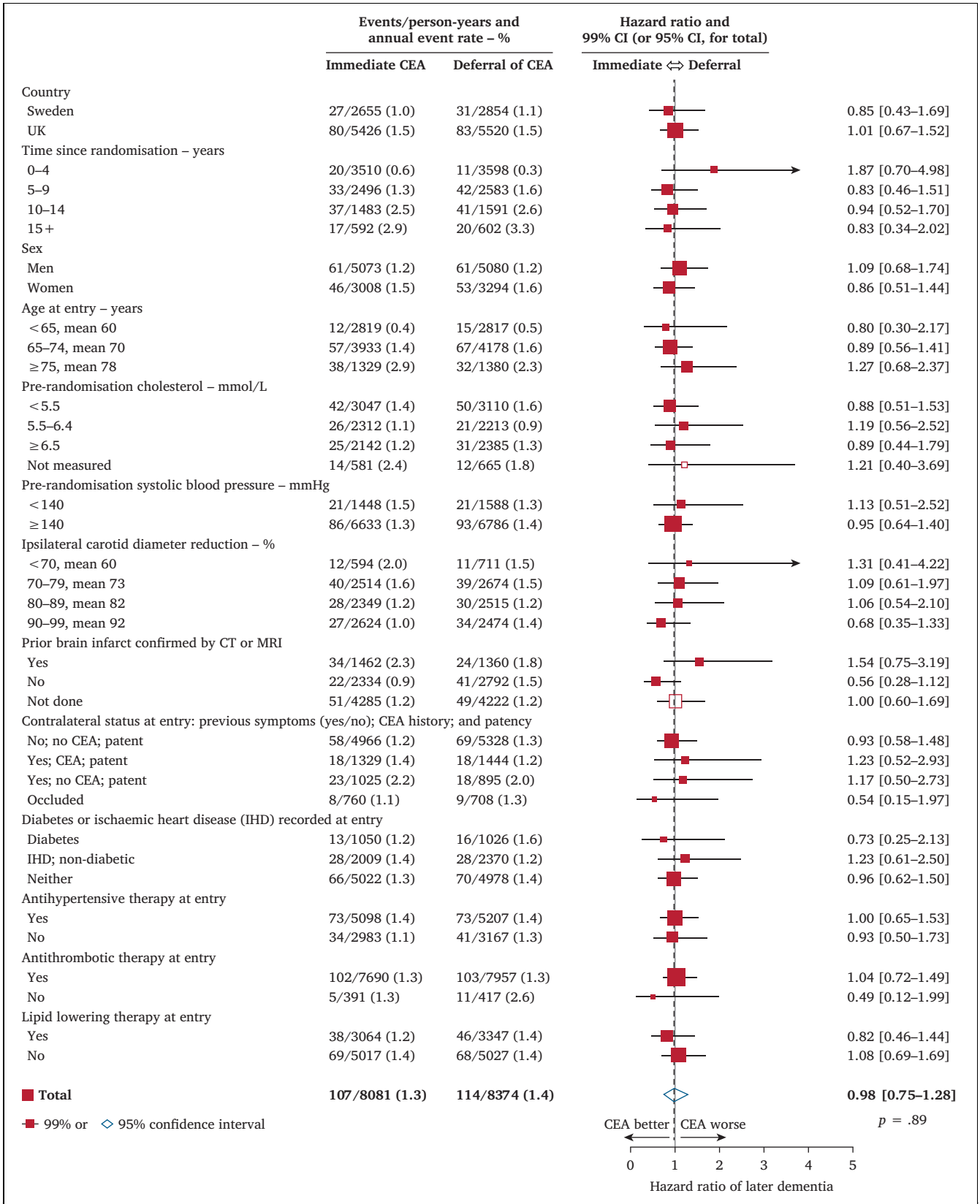


Figure 5. Multiple subgroup analyses of effects of carotid endarterectomy (CEA) on incidence of dementia during years 0 − 20 since randomisation to the Asymptomatic Carotid Surgery Trial (ACST-1). The Fine-Gray regression analyses for the effect of CEA on dementia were intention to treat, stratified by country (UK and Sweden) and adjusted for sex, age at entry, and prior brain infarct. CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging.

$p = .89$) (Fig. 4). This proportional difference was unchanged by adjustment for age at baseline and sex, and was consistent across various subgroups, including prior brain infarction, diabetes, country of residence, or medical treatments at trial entry (all had heterogeneity values of $p > .05$) (Fig. 5).

DISCUSSION

This study of 1 600 ACST-1 trial participants has shown that, after 20 years follow up, there is no significant increase or reduction in recorded dementia risk in asymptomatic patients randomised to early CEA. However, the CI did not exclude a proportional benefit or hazard of about a quarter.

Both incident stroke and cerebral hypoperfusion are associated with a higher risk of dementia, and both are reduced by endarterectomy.[5,8,9,15] About one third of patients develop new dementia within five years following stroke, perhaps due to "unmasking" of an underlying neurodegenerative illness by the stroke, or to a direct effect of stroke on dementia pathogenesis.[1] Cerebral hypoperfusion is also associated with cognitive decline and dementia in population based studies, and has been shown to be present before the onset of symptoms.[22] Although severe stroke is associated with greater degrees of cognitive ageing (TIA for approximately 3 years, mild stroke for approximately 6 years, severe stroke for approximately 9 years of cognitive aging),[1,4] it is infrequent, even in a high risk population like ACST-1. In the trial, non-fatal stroke was prevented in only about 5% of surviving participants. If reduction of symptomatic non-fatal stroke was the sole mechanism by which endarterectomy could have prevented dementia, the numbers of expected cases of dementia prevented by surgery, as a proportion of the total number of cases of dementia due to any cause would be too few to detect a benefit in this trial.

An effect after endarterectomy may not have been seen because vascular cognitive impairment is caused by pathology other than symptomatic stroke, for example by progression of cerebral small vessel disease. An increase in ipsilateral carotid stenosis is not clearly associated with a greater number of ipsilateral white matter lesions (largely due to small vessel disease),[23] and if cerebral small vessel disease is an important contributor to dementia, CEA might not be expected to have a significant effect on the incidence of dementia.

This paper has several strengths. Early CEA was randomly allocated, so intervention and control groups were matched for known confounders at recruitment. The use of electronic health records enables the ascertainment of dementia (which was not part of the original trial protocol) and reduces potential bias because the electronic health record includes participants who may not respond to active follow up.[24] The PPV of an electronic health record for dementia is high (87% — 100% for all cause dementia).[11,25,26] Importantly, underdiagnosis or overdiagnosis of dementia is unlikely to be materially different in either randomised group.

There were a number of limitations. Face to face interviews of participants throughout follow up would have been the ideal method to detect cognitive impairment and dementia, but this was not possible. Studies attempting this often have high rates of loss to follow up.[24] Dementia may be under ascertained using electronic records with limited sensitivity for diagnosed dementia (between 65% and 78%),[14,25,26] although that effect should be similar in both randomised groups. Hospital coding, although it has a high PPV, is recorded only for patients with a dementia diagnosis.[11,25,26] Only 20% of hospitalised patients over 75 years of age have a dementia diagnosis, although more than 50% may have moderate or severe cognitive deficits, and rates of undiagnosed dementia are high.[27,28]

So, the proportion of true dementia cases coded may be substantially lower than the 70% reported for diagnosed dementia, perhaps around 35% of the true total.[25,26] However, the retrospective prolonged follow up and overlapping methods may have improved dementia ascertainment, especially where participants had multiple admissions.[11,25] Finally, there was no consistent dementia ascertainment over time because some datasets (e.g., National Dementia and Antipsychotic Prescribing Audit[29]) only covered short time periods and because earlier years are likely to have missed more cases.

It has been shown that it is possible to use electronic health records to follow participants over a long time, despite considerable differences between the UK and Sweden in both regulatory burden and costs for data access, factors that are not addressed in this study.

In conclusion, in this study of 1 600 patients, random allocation to immediate or deferred CEA did not appear to reduce dementia risk, despite a reduction in stroke risk at five and 10 years.[5] The incidence of dementia in this population is high, especially in those over 75 years of age, and prior diabetes or cerebral infarcts at trial entry were risk factors for dementia. Because stroke is closely associated with dementia risk, it remains possible that the prevention of stroke in specific high risk populations may be beneficial in preventing dementia. European guidelines[10] will continue to consider whether particular groups of asymptomatic patients, such as those with prior symptoms, cerebral infarction, or impaired cerebrovascular reserve, might benefit from carotid intervention, but a large, long term randomised study will be necessary to determine this.

CONFLICTS OF INTEREST

None.

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DATA SHARING STATEMENT

Requests for access to the data reported in this paper will be considered by the corresponding author.

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Eur J Vasc Endovasc Surg (2022) 63, 545

COUP D'OEIL

Hybrid Repair of Large Radial Artery Pseudo-Aneurysm

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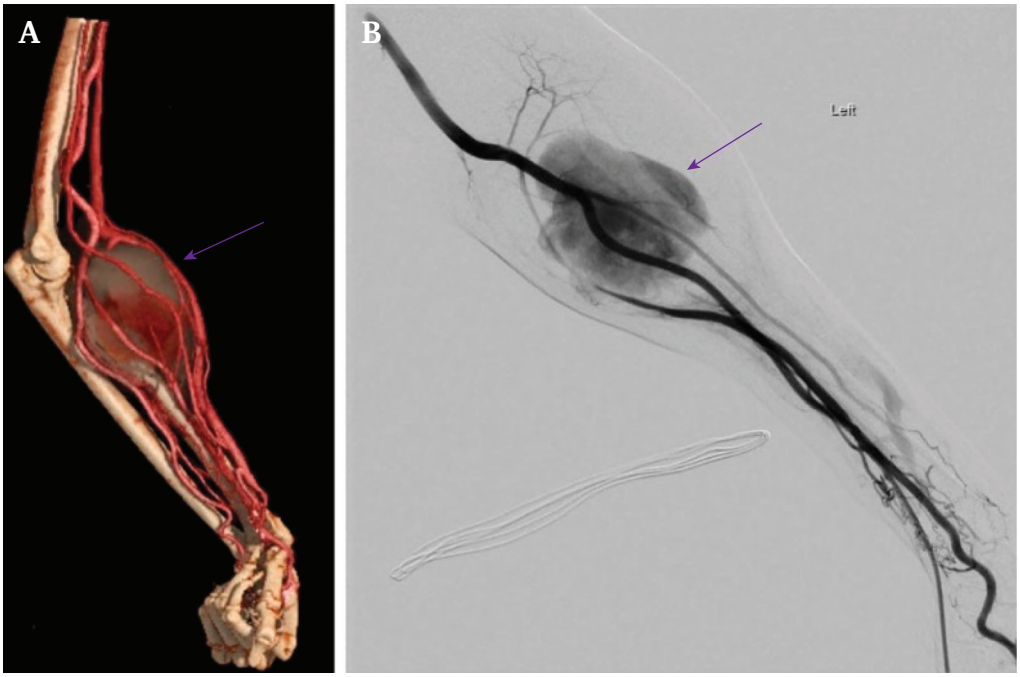

A 56 year old female presented with a two month history of worsening left arm swelling after radiocephalic fistula cannulation. (A) Computed tomography angiography demonstrated a 6 cm pseudo-aneurysm (arrow) in the middle third of her left radial artery. Under general anaesthetic, ultrasound guided retrograde micro-puncture of the left radial artery was performed at the wrist, with angiography confirming a large radial pseudo-aneurysm (B). A 4 × 40 mm balloon was inflated across the defect, the pseudoaneurysm entered, radial artery clamped, and defect primarily repaired with a 6-0 Prolene suture. Digital pressure was applied to the puncture site on sheath removal.

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