**Original Article:**

# Delays to surgery and procedural risks following carotid endarterectomy in the UK National Vascular Registry

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Running Head: Delays to, and risks following carotid endarterectomy

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## Abstract

**Objectives:** Guidelines recommend that patients suffering an ischaemic transient ischaemic attack (TIA) or stroke due to carotid artery stenosis should undergo carotid endarterectomy (CEA) within 14 days.

**Design:** We examined the degree to which UK vascular units met this standard and whether rapid interventions were associated with procedural risks.

**Methods:** The study analysed patients undergoing CEA between January 2009 and December 2014 from 100 UK NHS hospitals. Data were collected on patient characteristics, intervals of time from symptoms to surgery, and 30-day postoperative outcomes. The relationship between outcomes and time from symptom to surgery was evaluated using multilevel multivariable logistic regression.

**Results**: In 23,235 patients, the median time from TIA/stroke to CEA decreased over time, from 22 days (IQR 10-56) in 2009 to 12 days (IQR 7-26) in 2014. The proportion of patients treated within 14-days increased from 37% to 58%. This improvement was produced by shorter times across the care pathway: symptoms to referral, from medical review to being seen by a vascular surgeon, and then to surgery. The spread of the median time from symptom to surgery among NHS hospitals shrunk between 2009 and 2013 but then grew slightly. Low-, medium- and high-volume NHS hospitals all improved their performance similarly. Performing CEA within 48 hours of symptom onset was associated with a small increase in the 30-day stroke and death rate: 3.1% (0-2 days) compared with 2.0% (3-7 days); adjusted odds ratio 1.64 (95% CI 1.04-2.59) but not with longer delays.

**Conclusions**: The delay from symptom to CEA in symptomatic patients with ipsilateral 50-99% carotid stenoses has reduced substantially, although 42% of patients underwent CEA after the recommended 14-days. The risk of stroke after CEA was low, but there may be a small increase in risk during the first 48 hours after symptoms.



**Keywords:** carotid endarterectomy, stroke, symptomatic carotid artery stenosis, time to carotid endarterectomy, transient ischaemic attack

**What does this study/review add to the existing literature and how will it influence future clinical practice?**

This paper demonstrates that, on a national level, the pathway from initial symptom to surgery for patients with symptomatic carotid stenosis, can be shortened to maximise the benefit of intervention, without increased perioperative risk in the period from 3-14 days. There may be a slight increase in perioperative risk of stroke and death in the first 48 hours.

## Introduction

Stroke is the second largest cause of death in the world causing 6,700,000 deaths each year[1] and is the fourth largest cause of death in the UK.[2] There are more than 150,000 new strokes in the UK each year. Of these, one in eight are fatal within 30 days, while one in four are fatal within a year.[2] Approximately 15% of ischaemic strokes are preceded by a transient ischaemic attack (TIA).[2] Thromboembolism from an ipsilateral carotid artery stenosis is responsible for about 20% of all strokes.[2,3]

Two landmark randomised trials; the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[4] and the European Carotid Surgery Trial (ECST),[5] demonstrated the benefit of performing carotid endarterectomy (CEA) in symptomatic patients with a 50-99% internal carotid artery (ICA) stenosis. An individual patient meta-analysis of data from NASCET and ECST subsequently showed that maximum benefit was conferred if CEA was performed within 14 days of randomisation.[6] Based on these findings, international guidelines increasingly recommend that CEA be performed within 2 weeks of an ischaemic cerebrovascular event (TIA or minor stroke) in symptomatic patients with ipsilateral high- (70-99%) or moderate-degree (50-69%) carotid artery stenoses.[7-10]

In addition, there is growing evidence that the natural history risk of stroke in the first few days after TIA onset is much higher than previously thought in patients with 50-99% ICA stenoses. In a review of the published literature, eight natural history studies observed that the risk of stroke in the hyperacute period was 5-8% at 48 hours, 17% at 72 hours, 8-22% at 7 days and 11-25% at 14 days[11] again emphasizing the need for expedited CEA.

Several studies have evaluated the delay between onset of symptoms to undergoing CEA.[12-25] Most [12-21,23-25] have demonstrated that only a minority of symptomatic patients undergo CEA within the recommended 2-week period from the index event. The reasons for excess delays to CEA are multifactorial including: access to carotid imaging, long waiting times to theatre,[16,17] delays in speed of referral to vascular surgeons[13,14,16,25] and/or delays due to medical comorbidities (e.g. angina pectoris, cardiac workup, etc.).[15,16,18,21] In addition, some surgeons have raised concerns about incurring a higher perioperative risk of stroke and/or death if CEA is performed soon after the neurological event[26], especially in the first 48 hours[27]. Conversely, studies which have reported delays of 12 weeks or more in performing CEA have observed recurrent stroke rates as high as 32%.[28] Because of these very high rates of recurrent stroke, it has been suggested that vascular services with excessive delays in delivering CEA should probably not perform carotid revascularization procedures.[29]

In the UK, around 4000-5000 patients undergo CEA each year. The National Carotid Interventions Audit was established in 2005 to assess the quality of care delivered to UK patients undergoing CEA, and has published annual reports on the patterns and outcomes of care since 2008[30]. The aim of the study was to assess how the time period from onset of symptoms to undergoing CEA has changed between 2009 and 2014 in the United Kingdom. The results for data collected between December 2005 to September 2009 have been previously reported[3,13].

## Materials and Methods

The study is based on data extracted from the National Vascular Registry (NVR), a national clinical audit commissioned by the Healthcare Quality Improvement Partnership (HQIP) and which incorporated the previous national carotid interventions audit in January 2013. The Registry covers five major vascular procedures and receives data from 97% of eligible National Health System (NHS) acute hospitals (hospital organisations) in England, Northern Ireland, Scotland and Wales. The Registry supports the revalidation process for surgeons, and provides organisational level information for NHS hospitals to support the commissioning of vascular services.

The study cohort was defined to be patients undergoing CEA for symptomatic carotid disease between 1 January 2009 and 31 December 2014. Details on each patient, their treatment and postoperative outcomes are electronically entered by their supervising vascular surgeon or other hospital staff. Patient characteristics included: age, sex, and indication for surgery, degree of ipsilateral and contralateral carotid disease, comorbidities and the pre-operative Rankin score. Key dates were also collected to allow the time from occurrence of neurologic symptoms to undergoing CEA to be calculated, as well as for intervals along the care pathway. The 'index' symptom was defined as the symptom, which led the patient to seek medical advice. Defined time periods were: i) time from index symptom to first carotid imaging, ii) time from index symptom to date of referral to the medical team, iii) time from referral to the date first seen by the vascular surgical team and (iv) time from date seen by the surgical team to undergoing CEA. The NVR also collected data relating to the operation and complications occurring within 30 days of CEA including: death, bleeding, myocardial infarct, cranial nerve injury and stroke.

Temporal changes in the time between index symptom and undergoing CEA were calculated (annually) between January 2009 and December 2014. Figures were calculated for the UK as a whole and for acute NHS hospitals individually. We excluded data on a small number of NHS hospitals that did not perform at least one CEA for each year between 2009 and 2014, and we excluded patients missing one or more of the key dates. We also examined whether changes in the time from index symptom to undergoing CEA was related to the volume of CEA activity within acute NHS hospitals. To take account of NHS hospital mergers, we used only those hospitals that existed on 31 December 2014. Using the average annual volume for each organisation, the NHS hospitals were divided into low, medium and high volume categories such that the three CEA volume groups contained approximately equal numbers of patients. The range of annual activity covered by the three groups were: 34 or less (low volume), 35 to 54 procedures (medium volume) and 55 or more procedures (high volume).

Finally, we examined the rates of 30-day stroke and death for various time periods between symptom onset and undergoing CEA, stratifying the interval into five groups (0-2 days, 3-7 days, 8-14 days, 15-21 days and >21 days). Multilevel multivariable logistic regression was used to estimate the crude and adjusted effect of the time from symptom to surgery on the outcome variables. The adjusted odds ratios derived from each regression model took into account patient age, presenting symptom, pre-operative ranking score, presence of diabetes or ischemic heart disease, and year of operation. The NHS hospital of surgery was included as a random-intercept to account for any lack of independence in the data because of the clustering of patients within hospitals. All statistical tests were two-sided and the level of statistical significance was set at 0.05. All statistical calculations were performed in STATA version 14.1 (StataCorp, College Station, TX, USA).

**Results**

A total of 33,194 CEA procedures were performed in 124 NHS hospitals between 1 January 2009 and 31 December 2014. Limiting analyses to include only those NHS hospitals that performed CEA over the entire five-year period removed 24 NHS hospitals (1,806 patients). In the remaining 31,388 patients, there were 4,268 patients who underwent CEA for asymptomatic disease (13.6%) and these were also excluded. Finally, it was necessary to exclude a further 3,885 patients from analyses because there was incomplete data regarding date of the index symptom, referral date and treatment date for each patient.

The characteristics of the 23,235 remaining patients are summarised in **Table 1**. The median age was 73 years and the majority were men. Comorbidities were common, with 21% having diabetes and 27% having a history of ischaemic heart disease. Previous ipsilateral carotid surgery was recorded for only 250 patients (1.1%). The most common presenting symptom was a TIA (47.5%), followed by stroke (35.4%). The proportion of patients with 90-99% ipsilateral stenoses remained constant over the years at around 29%, but the proportion of patients with 50-69% ipsilateral stenoses increased from 17.4% in 2009 to 25.4% in 2014, with a corresponding fall in the prevalence of 70-90% stenoses.

The median delay from index symptom to undergoing CEA reduced from 22 days (IQR 10-56) in 2009 to 12 days (IQR 7-26) days by 2014 (**Figure 1**). The proportion of patients who were treated within 14-days rose from 37% to 58%. There was a sustained improvement from 2009 to 2013, though there was a slight increase in delays in 2014. This improvement was achieved by a systematic reduction in the time through each stage of the patient pathway, including symptom to first medical referral, from first medical referral to being seen by the vascular team, and from being seen by a vascular surgeon to undergoing CEA (**Table 2**). The longer times in 2014 appear to occur in the stage between the referral and medical review. The time from onset of symptoms to undergoing carotid imaging was also significantly reduced from a median of 5 days (IQR 2-15) in 2009 to 3 days (IQR 1-8) in 2014.

**Figure 2** shows the temporal changes in median delays from symptom onset to undergoing CEA for every UK NHS hospital performing CEA, stratified by year of the procedure. The graph shows a distinct reduction in the spread of median delays across the NHS hospitals over time, both in terms of the tail of longer median values and the central 50% of NHS hospitals, whose position is marked by the horizontal lines. In 2009, this central group of NHS hospitals had median delays that ranged from 15 to 40 days. By 2014, the central group of NHS hospitals had median delays that ranged from 9 to 18 days. There was also no evidence that the degree of improvement achieved by the NHS hospitals was related to the volume of CEA performed (Figure 3).

The overall postoperative 30-day stroke and death rates after CEA were 1.85% (95% CI 1.67 to 2.02) and 0.83% (95% CI 0.71 to 0.94). The combined 30-day stroke and death rate was 2.31% (95% CI 2.11 to 2.50). The rates remained stable throughout the 6-year time period. Table 3 shows the relationship between the time from symptom to surgery and these three outcomes. There is no evidence that the risk of death is associated with the length of delay, but there is evidence of an increased risk of stroke within 30-days for CEA performed in the

first 2 days after the index symptoms compared to operations performed between 3 and 7 days after. There is no evidence that longer intervals from index symptom to surgery are associated with the rate of these three outcomes.

## Discussion

Following publication of ECST and NASCET, the 1995 American Heart Association (AHA) Guidelines advised that CEA was an appropriate intervention in recently symptomatic patients (defined as symptoms within the preceding 6 months) who had an ipsilateral 50-99% carotid stenosis, provided 30-day rates of death/stroke were <6%[32]. In 2008, NICE recommended that CEA should be performed within 14 days of symptom onset[10], followed in 2009 by the European Society of Vascular Surgery[33]. The reason for this major change in practice was that a meta-analysis of the pooled randomised trial data by the Carotid Endarterectomy Trialists Collaboration (CETC) had revealed that CEA conferred maximum benefit if performed within 14 days[6].

Based on the CETC meta-analysis, CEA conferred a 30% absolute risk reduction in stroke at five years when CEA was performed within 2 weeks in patients with a 70-99% symptomatic carotid stenosis.[6] This benefit almost halved (ARR 17%) when CEA was performed between 2-4 weeks and was reduced to nearly a third (ARR 11%) when CEA was delayed by more than four weeks.[6] In addition, a review of 8 natural history studies has now shown that the early risk of stroke may be even higher than previously thought, with some studies reporting recurrent stroke rates of 5-8% at 48 hours, 17% at 72 hours, 8-22% at 7 days and 11-25% at 14 days[11].

However, there have been concerns that performing CEA in the early time period after onset of symptoms may be associated with a significant increase in the procedural risk, which might then offset any benefit accruing to the patient[26]. These concerns appeared to be corroborated by one of the first national audits of practice. In the 2012 Swedish Vascular Audit (SwedVasc), only 6% of patients underwent CEA within 48 hours of symptom, but they incurred a 11.5% risk of death/stroke at 30-days[27]. Overall 63% underwent CEA within 14 days of symptom onset. After 48 hours had elapsed, procedural risks after CEA ranged between 3-5%[27].

The current study, therefore, is only the second national audit to report on outcomes, stratified for delays to CEA and a number of key findings are worthy of comment. First; the time from onset of the index symptom to undergoing CEA has continued to decrease (year on

year) from 2009 to 2014. CEA was performed within 2 weeks of index symptom onset in only 37% in 2009, but had increased to 58% in 2014.

Second, while there was a small but significant increase in the procedural risk when CEA was performed within 48 hours of the index symptom ((OR 1.63 (95%CI 1.05-2.54), a 4.1% peri-operative risk is perfectly acceptable. Interestingly, a multi-regression analysis found no other clinical factors to be associated with an increase in the risk of perioperative stroke.

Third, more than 40% of all symptomatic patients undergoing CEA in the UK in 2014 did not undergo their operation within 14 days. This is disappointing and requires further analysis. Somewhat disappointingly, the main three reasons neither changed in ranking, nor in their magnitude over the three-year time period[30,34]. The commonest reason was a delay in referral to the vascular surgeon. The second commonest was a delay in the patient seeking medical advice, while the third commonest were delays in accessing carotid imaging. In short, in addition to improving patient awareness about seeking urgent medical advice after symptom onset, Commissioners, Administrators and Clinicians in both primary and secondary care must work together to reconfigure referral, imaging and treatment pathways to ensure that patients can access CEA more rapidly. Evidence suggests that this can lead to significant reductions in the time from symptom onset to undergoing CEA[22].

Fourth, this audit has shown that the time from symptom onset to undergoing CEA does not seem to be affected by the volume of CEAs performed in the hospital.

Previous reports have suggested that there may be an under provision of CEA in the UK.[3,13] These reports have determined that at least 10,000 patients who suffer a TIA or a minor stroke in the UK each year could potentially benefit from CEA. Despite this, the number of CEAs performed for symptomatic carotid stenosis represents half this number. The data from the current NVR report, therefore, supports the conclusions reached in previous reports[3,13] If all 10,000 patients were to undergo CEA within 2 weeks of symptom onset, about 1,100 ipsilateral ischaemic strokes would be prevented at 5 years.[6]

This study does have potentially important limitations. Firstly, it only includes symptomatic patients who eventually underwent CEA. Symptomatic patients deemed to be at 'high surgical risk' and who were not offered surgery were not included. Secondly, a small percentage of patients undergoing CEA during this time period may not have been registered in the UK National CEA Clinical Audit. Thirdly, a significant minority of patients did not have complete data relating to all the time points in the patient pathway entered onto the

NVR. Finally, the reasons for not performing CEA within 14 days of symptom onset were provided by vascular surgeons and (for the most part) surgeons were also responsible for reporting death/stroke rates at 30-days.

In conclusion, the NVR has reported sustained national improvements in the delivery of CEA to 23,235 patients with recently symptomatic carotid stenosis, registered prospectively in the UK National CEA Clinical Audit from January 1, 2009 until December 31, 2014. The reduction in time from symptom to surgery has been achieved through a national quality improvement programme. Operating in the first 48 hours after symptom onset was associated with a small but significant increase in procedural risk, but this was still within accepted risk thresholds. Although the time to CEA has improved considerably in the last 5 years, more than half of all symptomatic patients still did not undergo CEA within 2 weeks of symptom onset. The commonest reasons for these delays have been identified and should be addressed in individual hospitals where delays consistently extend beyond 14 days.

**Conflicts of Interest:** None

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**Table 1: Characteristics of patients undergoing CEA for symptomatic disease between January 2009 and December 2014 in UK NHS trusts**

| | | n=23,235 | |
|---|---|---|---|
| Age at surgery (years), Median (IQR) | | 73 | (66 to 79) |
| Male, n (%) | | 15,510 | (66.8) |
| Co-morbid conditions, n (%) | | | |
| Diabetes | | 4,830 | (20.8) |
| Ischaemic heart disease | | 6,334 | (27.3) |
| Pre-op drugs prior to surgery, n (%) | | | |
| Antiplatelet/antithrombotic treatment | | 22,136 | (95.3) |
| Statin therapy | | 20,320 | (87.5) |
| Index event among symptomatic patients, n (%) | | | |
| TIA | | 11,029 | (47.5) |
| Amaurosis fugax | | 3,553 | (15.3) |
| Stroke | | 8,229 | (35.4) |
| Other | | 424 | (1.8) |
| Rankin score prior to surgery, n (%) | 0 | 9,299 | (40.1) |
| (missing = 31) | 1 | 7,135 | (30.7) |
| | 2 | 4,627 | (19.9) |
| | 3-5 | 2,143 | (9.2) |
| Grade of ipsilateral carotid stenosis, n (%) | <50% | 244 | (1.1) |
| (missing =176) | 50-69% | 5,532 | (24.0) |
| | 70-89% | 10,531 | (45.7) |
| | 90-99% | 6,629 | (28.7) |
| | Occluded | 123 | (0.5) |

**Table 2: Temporal changes in the time from index symptom to carotid surgery between 2009 and 2014, stratified by: index symptom to first medical review, medical review to first seen by vascular surgeon, surgeon to undergoing CEA**

| Year of surgery | Number of CEA | Symptom to medical review | | | Medical review to vasc. surgeon | | | Vascular surgeon to CEA | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Median | IQR | P5 - P95 | Median | IQR | P5 - P95 | Median | IQR | P5 - P95 |
| 2009 | 2811 | 7 | (3-20) | (0-73) | 1 | (0-7) | (0-31) | 8 | (3-20) | (1-74) |
| 2010 | 3483 | 5 | (2-16) | (0-64) | 1 | (0-6) | (0-26) | 6 | (3-15) | (1-61) |
| 2011 | 4119 | 4 | (2-12) | (0-58) | 1 | (0-5) | (0-22) | 5 | (2-11) | (1-50) |
| 2012 | 4286 | 4 | (2-10) | (0-50) | 1 | (0-4) | (0-18) | 5 | (2-10) | (1-48) |
| 2013 | 4242 | 4 | (1- 9) | (0-41) | 1 | (0-3) | (0-16) | 5 | (2- 9) | (1-39) |
| 2014 | 4294 | 4 | (2-11) | (0-58) | 1 | (0-3) | (0-15) | 5 | (2- 9) | (1-36) |

KEY: IQR = interquartile range. P5 and P95 = $5^{th}$ and $95^{th}$ percentile

* For the three stages of the care pathway (symptom to medical review, review to vascular surgeon assessment, assessment to CEA), data were missing for 23, 77 and 63 patients, respectively.

**Table 3: Postoperative 30-day stroke and death rates after CEA stratified for delay from onset of index symptom to undergoing CEA**

| Delay | Operations | Crude rate (%) | Crude odds ratio | Adjusted odds ratio | 95% CI |
|---|---|---|---|---|---|
| *Stroke within 30 days* | | | | | |
| 0 to 2 | 780 | 3.1 | 1.58 | 1.64 | 1.04 - 2.59 |
| 3 to 7 | 5,126 | 2.0 | 1 | 1 | |
| 7 to 14 | 6,292 | 1.7 | 0.84 | 0.85 | 0.64 - 1.12 |
| 15 to 21 | 2,765 | 2.1 | 1.05 | 1.09 | 0.78 - 1.52 |
| 22 plus | 8,272 | 1.7 | 0.88 | 0.94 | 0.72 - 1.23 |
| *Death within 30 days* | | | | | |
| 0 to 2 | 780 | 1.0 | 1.12 | 1.21 | 0.57 - 2.58 |
| 3 to 7 | 5126 | 0.9 | 1 | 1 | |
| 7 to 14 | 6292 | 0.7 | 0.81 | 0.81 | 0.54 - 1.21 |
| 15 to 21 | 2765 | 1.1 | 1.19 | 1.24 | 0.78 - 1.97 |
| 22 plus | 8272 | 0.7 | 0.80 | 0.96 | 0.65 - 1.43 |
| *Stroke or Death within 30 days* | | | | | |
| 0 to 2 | 780 | 3.7 | 1.52 | 1.59 | 1.05 - 2.41 |
| 3 to 7 | 5126 | 2.5 | 1 | 1 | |
| 7 to 14 | 6292 | 2.1 | 0.84 | 0.84 | 0.65 - 1.08 |
| 15 to 21 | 2765 | 2.6 | 1.06 | 1.10 | 0.82 - 1.49 |
| 22 plus | 8272 | 2.2 | 0.89 | 0.98 | 0.77 - 1.25 |

Figure 1: Distribution time from index symptom to carotid surgery by year of procedure. Boxes shows interquartile limits with median line. Whisker limits set to 5th and 95th percentiles.

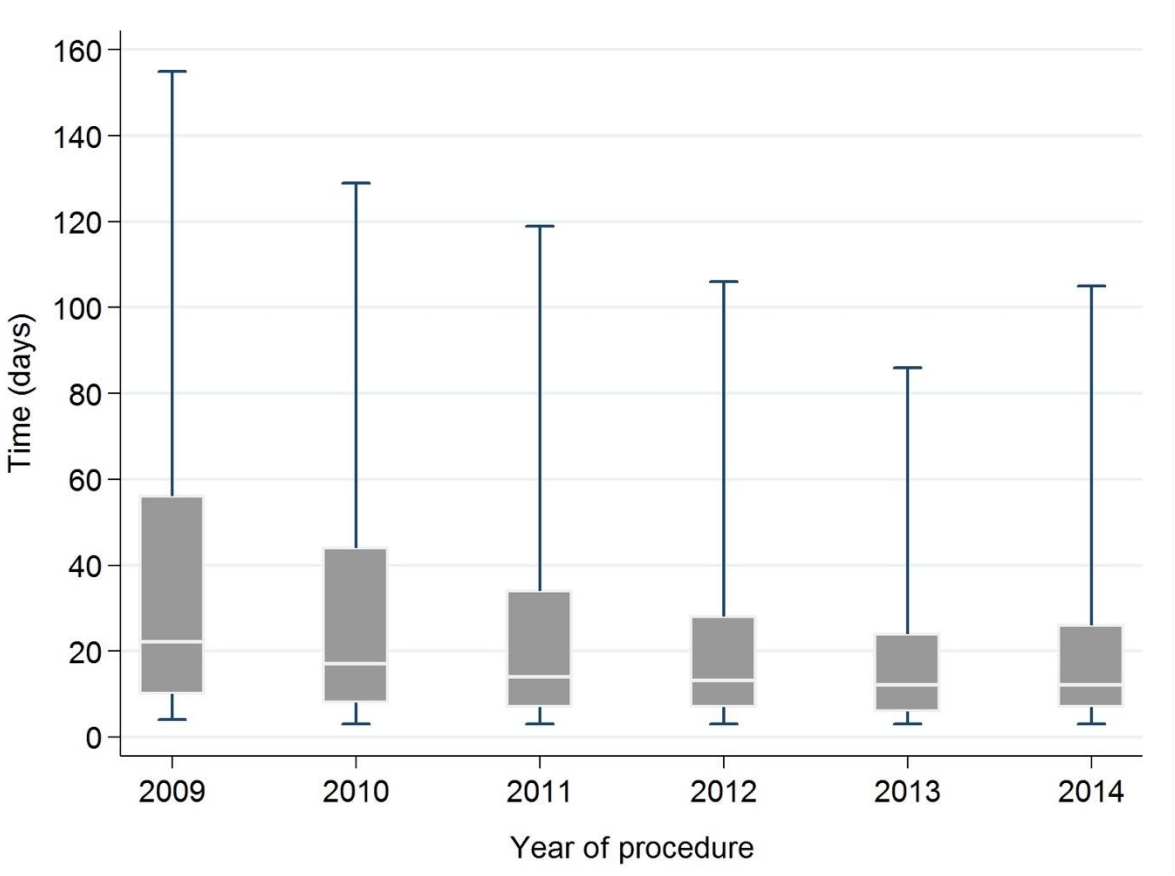
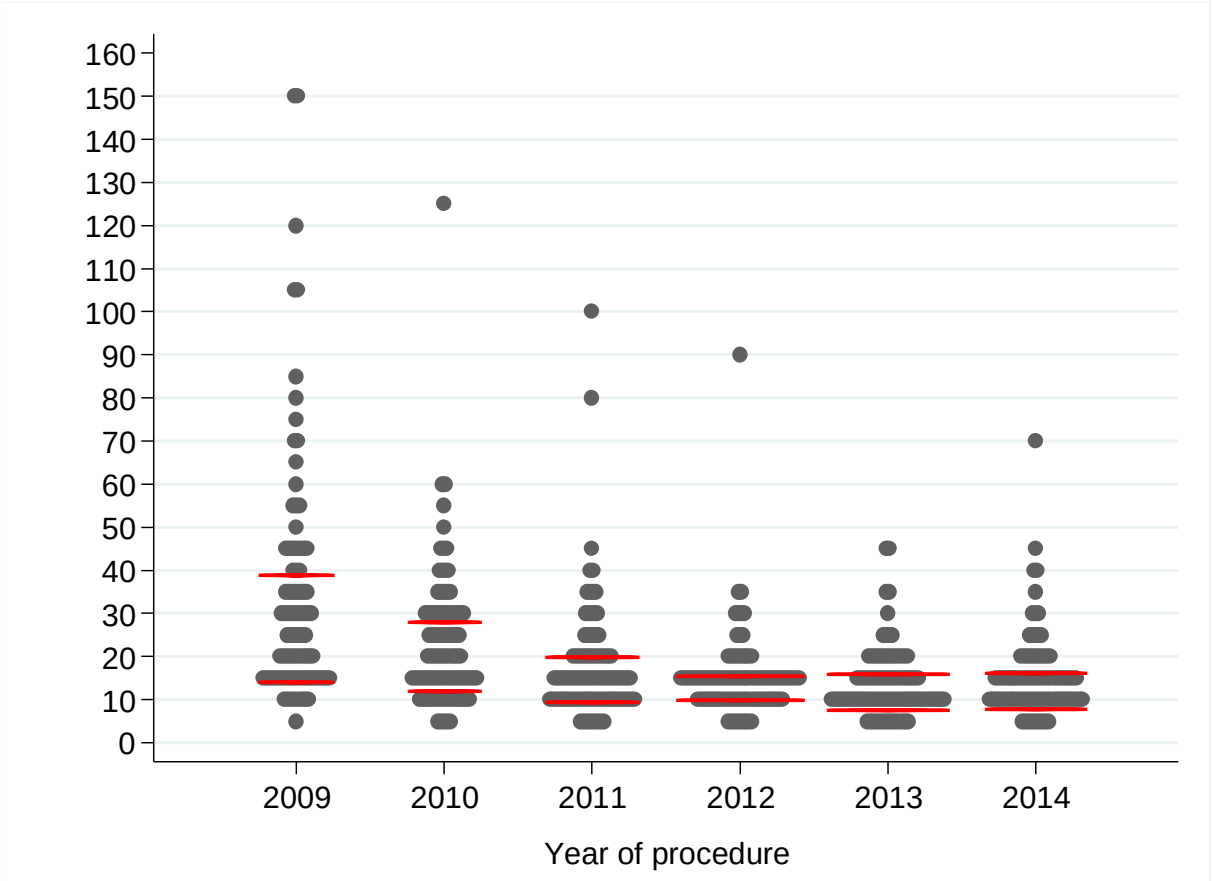


Figure 2: Dot plot of the median time from index symptom to carotid surgery for each NHS trusts by year of procedures*. Red lines show the 25th and 75th percentile within the distribution of NHS trust medians.




* Two highest values (179 and 207) in 2009 were winzorised to 150 days to reduce their effect on the scale of the vertical axis.

Figure 3: Changes in the proportion of patients whose time from index symptom to surgery exceeded 14 days among NHS trusts that were categorised by annual surgical volume as low (≤34 pa), medium (35-54 pa) or high volume (≥55 pa).