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Carotid artery procedures and the volume-outcome relationship in Europe: a systematic review

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Category: review article

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Abstract

Background: Hospitals that conduct more procedures on the carotid arteries may achieve better outcomes. In the context of on-going reconfiguration of UK vascular services this systematic review was conducted to evaluate the relationship between the volume of carotid procedures and outcomes including mortality and stroke.

Methods: Searches of electronic databases identified studies that reported the effect of hospital or clinician volume on outcomes. Reference and citation searches were also performed. Inclusion was restricted to European populations on the basis that the model of healthcare delivery is similar across Europe but differs from the US and elsewhere. Analyses of hospital and clinician volume, and carotid endarterectomy (CEA) and carotid artery stenting (CAS) were conducted separately.

Results: Eleven eligible studies were identified (217 593 participants); from the UK (n=5), Sweden (n=2) and one each from Germany, Finland and Italy and a combined German, Austrian and Swiss population, all studies were observational. Two large studies (n=179 736) suggested an inverse relationship between hospital volume and mortality (NNT as low as 165) and combined mortality and stroke following CEA (NNT as low as 93). The evidence is less clear for CAS where multiple analyses in three studies did not identify convincing evidence of an association. Limited data is available on the relationship between clinician volume and outcome in CAS; in CEA an inverse relationship was identified by two of three small studies.

Conclusion:

The evidence from the largest and highest quality studies included in this review supports the centralisation of carotid endarterectomy.
Introduction

Atherosclerosis of the extra cranial carotid arteries is a major cause of mortality and morbidity; treatment options include carotid artery stenting (CAS) and carotid endarterectomy (CEA). When treatment is necessary the favoured form of intervention in the UK is CEA with a minority of procedures being performed via endovascular routes. The combined death and stroke rate at 30 days following CEA in the UK is 2% though outcomes vary between individual clinicians (0 - 13.4%) and institutions (0 – 7%). These variations fall within the range that might be expected as a result of chance, though some of the variation is likely to be related to factors such as case mix, hospital policy, healthcare infrastructure and the institutional and individual resources of hospitals and clinicians. The volume of procedures conducted is one measurable variable that could explain some of the differences in outcomes attributed to different surgeons and institutions’ and can be used as a proxy for quality; though attributing causation is inherently difficult when available research is restricted to observational methods for practical and ethical reasons.

Preliminary searches identified four systematic reviews that addressed this relationship; all investigated the relationship between hospital volume and carotid procedures. Three additionally looked at the relationship between clinician volume and outcome. The evidence of a volume outcome relationship in these reviews was apparent at the hospital level but less clear at the clinician level. The included studies used data mainly from the USA; differences between US and European models of organisation and delivery of healthcare mean that the results of these reviews are of potentially limited relevance to European settings as selective referral to hospital or clinician may play a more substantial role in the market driven
US healthcare sector. Additionally these reviews were relatively old suggesting the need for a new review.

The primary aim of this systematic review was to evaluate the relationship between the volume of carotid procedures undertaken by hospitals and outcomes in Europe and additionally to investigate the relationship between clinician volume and outcome in Europe.

**Methods**

This systematic review is reported using the Preferred Reporting Outcomes for Systematic Reviews and Meta-analysis (PRISMA) statement. It was conducted according to a publicly available and pre-registered protocol.

Electronic databases including MEDLINE, EMBASE, the Cochrane Library, Science Citation Index and CINAHL were searched in two stages between December 2014 and March 2015, with searches updated in June 2016 and subsequent hand searches of key journals. Conference proceedings, citation and reference list searches (of included studies and relevant systematic reviews) were also conducted. (See appendix 1 for details of the search strategy).

The title and abstract of studies identified by the searches were sifted by a single reviewer and checked by a second reviewer. All potential full text papers were retrieved and read independently by two reviewers. A study specific data extraction form was used for data extraction and quality assessment of papers that met the inclusion criteria. Data extracted included details of the clinical and procedural populations, types of analysis, volume measurement, study design and results. Quality assessment was conducted using ACROBAT NRSI, a tool developed by the Cochrane collaboration for use with non-randomised studies.
We included studies of adults in Europe undergoing procedures to the extra cranial carotid arteries that reported the effect of hospital or surgeon volume (number of procedures in a fixed period) on outcomes. Outcomes were expected to include mortality, stroke, length of stay and complications. An intended meta-analysis was judged inappropriate due to the high risk of bias and the methodological and clinical heterogeneity amongst the included studies so a narrative synthesis supported by tabulation of results was conducted.

Results
From a total of 17 284 citations, 12 papers reporting 11 studies (see Table I) were eligible for inclusion in this review; they addressed the volume outcome relationship in 217 593 patients undergoing extra cranial carotid procedures. A summary of the study selection process is shown in the PRISMA flow chart (appendix 2). Studies were excluded for a variety of reasons, most commonly because they included the wrong population (geographical or clinical) or did not report a volume outcome relationship.

Five studies reported the relationship using UK data sources\(^{11, 15, 16, 18, 19, 21}\) two used data from Sweden\(^{13, 17}\), with lone studies from Finland\(^{12}\), Germany\(^{14}\) and Italy\(^{20}\); and one conducted in a combined populations from Germany, Austria and Switzerland\(^{22}\). Nine studies\(^{11-17, 20-22}\) reported data on the hospital volume outcome relationship and five\(^{12, 15-17, 21, 22}\) on clinician volume and outcome. Eight\(^{11-16, 18, 19, 21}\) reported on CEA and four\(^{14, 17, 20, 22}\) reported on CAS. One study used data from a single centre\(^{19}\), while Nine\(^{12-19, 21, 22}\) used data from clinical registries with only one study\(^{11}\) conducting analysis of data collected as part of an administrative database.

Insert Table I here
**Quality assessment:** the quality assessment of included studies is available in appendix 3.

All studies were judged at high risk of selection bias as randomisation was not used for practical and ethical reasons and it is possible that there were systematic differences between patients undergoing treatment in low or high volume situations. A low risk of bias due to volume measurement was assigned when volume data had been analysed as continuous data, i.e. without categorisation, as it was felt that categorisation was potentially arbitrary in the absence of empirical evidence to justify quantile divisions and thresholds. Risk of attrition bias was judged as low in studies using population based compulsory clinical and administrative data as there seemed little likelihood that there was a differential loss to follow up in these studies. The likely influence of attrition bias was less clear in the case of the voluntary vascular databases. Bias related to the measurement of outcome was judged low for analyses of mortality, but analyses of outcomes of combined stroke and mortality or complications were considered to be at a higher risk due to the potential variation in definition and diagnosis of these outcomes. A wide range of confounders were identified and adjusted for in included papers including; demographics, comorbidities, physiological factors, treatment and surgeon or hospital caseload. Studies that used adjustment for some confounders were judged at medium risk of bias. If all possible confounders were adjusted for a low risk of bias was to be assigned, though none of the included studies achieved this. The majority of studies were judged at high risk of reporting bias due to a lack of a priori statements of planned outcomes and analyses.

Results from studies are presented in four categories according to the procedural groups in which analyses were conducted (CEA or CAS) and whether the exposure considered was the hospital or clinician volume of procedures undertaken.
**CEA and hospital volume**, details of the results and analysis for CEA hospital volume and outcome are shown in Table II.

Insert Table II here

**Mortality: hospital volume and CEA**

Two large studies (Kuehnl et al\(^ {14}\) and Holt et al\(^ {11}\)) analysed this relationship. Adjusted odds ratios ranged from \(1.07 – 1.36\) with the high volume quintile as the reference group in a whole population study conducted in Germany\(^ {14}\) (\(n=161488\) that included an estimated 99.1% of the population undergoing CEA in the study period). Confidence intervals and \(p\) values were calculated but found to be non-significant though the relevance of these statistical tests is questionable in the context of a whole population study. Conversion of odds ratios to absolute measures suggests up to 3.7 fewer deaths per 1000 when procedures are conducted at higher volume hospitals (numbers needed to treat (NNT) in the range 273 to 1106, for details of calculations see appendix 4).

In the smaller UK study\(^ {11}\) (\(n=18248\)) when hospital mortality in the four higher volume quantiles was compared to the lowest volume group for elective and emergency patients separately a relationship between volume and outcome is apparent. This was most obvious for elective patients, with odds ratios ranged from 0.58 to 0.74 with the low volume quantile as reference. Conversion to absolute measures suggests numbers needed to treat in the range of 165 to 247 confidence intervals and \(p\) values are not reported for the odds ratios. When multiple logistic regressions were performed (adjusted for age and gender), a statistically significant effect was identified in the case of the relationship between hospital volume and mortality for elective surgery, odds ratio (OR) 0.898 (95% CI 0.808-0.999, \(p=0.047\)) though not for emergency surgery, OR 0.975 (0.798-1.191 \(p=0.8026\)).
**Combined mortality and stroke: hospital volume**

The largest and most contemporary analyses of this relationship used data from the Germany\textsuperscript{14} and UK\textsuperscript{11} (Table 2 for details). Multiple analyses suggested that unadjusted and adjusted, combined in hospital stroke (any) and death rates, and combined in hospital (major) stroke and death rates were inversely associated with volume when analyses were conducted with volume as a categorical variable. This relationship was still evident in exploratory analysis of the relationship as a continuous variable\textsuperscript{14}. Conversion of the adjusted odds ratios to NNT for rates of in-hospital stroke (any) or death, and in-hospital stroke (major) or death suggest that performance in the highest volume hospitals of 93 and 96 procedures respectively will result in one less event in comparison to the lowest volume hospitals.

Evidence of a statistically significant relationship was also identified using simple linear regression\textsuperscript{21} (p=0.004). This relationship was maintained in additional analyses comparing high versus low volume institutions with a threshold set at 50 CEA's per year (mortality/ morbidity rates 1.9 versus 3.0\% - above and below 50 CEA per year respectively, p=0.032). When a requirement for a minimum of six vascular surgeons per hospital was introduced into the analysis the relationship maintained borderline statistical significance p=0.053.

Three studies (n=3752)\textsuperscript{12,13,15,16} conducted analyses using data from national vascular registries using a variety of statistical techniques and levels of adjustment and found no statistically significant evidence of a relationship, these studies were smaller and older.

**CEA and complications: hospital volume**

A single study\textsuperscript{11} found no evidence of a relationship between the hospital volume of elective or emergency CEA undertaken and complication rates (renal, respiratory,
infection, shock, local complications, thrombotic or embolic events, cardiac, and disseminated intra-vascular coagulation or transfusion reactions) using multiple logistic regression adjusted for age and gender, (p=0.275 elective CEA, p=0.181 emergency CEA).

**CEA and length of stay: hospital volume**
Two analyses conducted by Holt et al\(^\text{11}\) found statistically significant evidence of an association between increased hospital volume of CEA and reduced length of hospital stay using multiple logistic regression adjusted for age and gender (p<0.0001 for both elective and emergency CEA). The evidence from a large German vascular database (Kuehnl) suggested a slight trend towards reduced inpatient length of stay in higher volume hospitals.

**Elapsed time between symptoms and CEA: hospital volume**
Analysis of 23235 procedures in the UK\(^\text{18}\) found no evidence of a relationship between the time from onset of symptoms to performance of CEA; over the five-year period of the study all hospitals improved their performance.

**CEA and clinician volume, detail of results and analyses for CEA clinician volume and outcome are shown in Table III.**

*Insert Table III here*

**CEA and combined stroke and mortality: surgeon volume**
Unadjusted analyses in two studies\(^\text{12,21}\) found evidence of a statistically significant association between CEA volume and combined stroke and mortality. This relationship was maintained when patient related factors and hospital volume were also adjusted for\(^\text{12}\), though his effect was not evident when adjustment for total vascular caseload was included in the analysis. Kuhan\(^\text{15,16}\) conducted analyses using
regression modelling which included only four surgeons and found no evidence of a statistically significant relationship.

**CEA and complications: surgeon volume**

McCollum\(^{19}\) found no evidence of a relationship between individual surgeon’s volume and 30-day stroke in CEA patients, though scant details of the analysis were provided.

**CAS and Hospital Volume**, detail of the results and analysis for CAS hospital volume and outcome are shown in Table IV.

**CAS and mortality: hospital volume**

No significant evidence of effect was identified in two studies looking at this relationship. Odds ratios ranged between 0.90-1.54 when CAS volume was analysed in quintiles in relation to in-hospital mortality in a large whole population study\(^{14}\). A smaller study\(^{17}\) used Fishers exact test to assess differences in 30 day mortality between the single, largest volume provider of CAS in Sweden (mortality rate 1% (2/208)) and the other centres in Sweden (n=9) that conduct CAS (mortality rate 2.3% (6/258)). The p value was unspecified but reported as non-significant.

**CAS and combined stroke/death: hospital volume**

No convincing evidence of a significant relationship between CAS volume and combined stroke/mortality rates was found. Kuehnl et al\(^{14}\) conducted a range of adjusted and unadjusted analyses and found no association (Table 5). Two smaller studies \(^{17, 22}\) found evidence of a statistically significant relationship between CAS volume and combined mortality and stroke in unadjusted analyses. These positive correlations were not replicated in multi-variate analysis adjusted for temporal trends, patient and operative factors and cumulative institutional experience (distinct from a caseload count in a fixed period) \(^{22}\). Lindstrom et al\(^{17}\) found a statistically significant
relationship between CAS volume and combined stroke or death (p=0.04). This relationship was maintained when the outcome measure was broadened to include acute myocardial infarction in the composite outcome (p=0.01). When patients were stratified into high or average risk groupings the statistically significant effect was no longer evident. When stratification was conducted according to symptoms, a statistically significant relationship was apparent in asymptomatic patients but not symptomatic patients.

**CAS and complications: hospital volume**

Lindstrom\textsuperscript{17} found no statistically significant evidence of a relationship between hospital CAS volume and stroke and between hospital CAS volume and acute myocardial infarction.

**CAS and Length of stay**

No clinically relevant volume related trends were identified for this relationship\textsuperscript{14}.

**CAS and Clinician volume**

**CAS mortality and combined mortality/stroke and stroke alone: surgeon volume**

There is very little data regarding the relationship between clinician volume and any outcomes following CAS procedures. The only results came from a single study\textsuperscript{20} in which volume is a cumulative total over the period 2006-2012. Towards the end of this period the ‘low volume’ surgeons conducted an increasing ratio of all operations (up to 81\% in one year) and so the results should be viewed with caution. No evidence of a statistically significant relationship was found between surgeon volume and mortality, combined mortality and stroke or complications.

**Discussion**

The results from the studies included in this review suggest an inverse relationship between CEA hospital volume and mortality, and CEA hospital volume and combined
stroke and mortality. The large population based studies from Germany\textsuperscript{14} and the
UK\textsuperscript{11} were judged as a low risk of bias as a result of recruitment into the study though
the risks associated with selection to exposure (high or low volume hospitals)
remained high. To some extent this was addressed by adjustment for confounding and
this was particularly robust in the German study and further enhanced by their use of
clinical data. The German Quality Assurance Database is a compulsory clinical
database and the data is 99.1\% complete for the population undergoing CEA and CAS
in Germany in the study period. The data is prospectively gathered and based on
clinical examination rather than administrative coding. The detailed data collected in a
clinical database such as this allows for the development of sophisticated models of
the volume outcome relationship.

This contrasts with a reliance on administrative data in the UK study\textsuperscript{11}, potentially
weakening the strength of the evidence both in terms of the accuracy of data collected
and the range of adjustment for potential confounders, though the consistency of
results over the two data sets is reassuring and there is evidence of relatively good
agreement between the two types of database (clinical and administrative) when used
to predict risk\textsuperscript{23}. Recognition of the relatively low quality of administrative data
available through Hospital Episode Statistics (HES) in the UK encouraged Holt et al\textsuperscript{11}
to use in hospital mortality as the primary outcome measure (rather than combined
mortality and stroke or stroke alone) because of the difficulties of differentiating
between pre and post procedure complications when using data from administrative
databases.

Data used in other studies came from voluntary clinical registries, which has
advantages related to the use of clinical data but shortcomings\textsuperscript{24} related to the possible
selective inclusion of subjects and outcomes onto databases in terms of which
clinicians and hospitals choose to participate and in terms of the potential for selectively entering details from individual patients.

There was an unclear risk of bias related to the inclusion of outcomes that were measured ‘in-hospital’. A reduced length of stay was correlated with high volume hospitals\textsuperscript{11,14} and this could feasibly have been responsible for some of the reduced in-hospital mortality in these hospitals though Kuehnl et al\textsuperscript{14} suggest that the risk of this is low. Notwithstanding this suggestion a more robust measurement could be achieved by the use of mortality linked to post discharge data, such as ONS (Office of National Statistics) statistics in the UK, to give 30 day, 1 year or longer term outcomes. Such an approach has been taken in volume outcome studies in other disease areas\textsuperscript{25}. This would improve the quality of the study and also add to the value of the results.

The limited evidence of relationships between CAS hospital volume and outcomes is affected by the factors discussed above in relation to CEA; additionally the number of CAS, in comparison to CEA, procedures carried out is relatively low and could account for the absence of evidence of effect.

The evidence of a relationship between clinician volume and outcomes in CEA is limited by the small scale of the studies, age and low quality and is therefore inconclusive. This review includes only European data and a case can be made for the inclusion of worldwide data in analyses of this relationship though it might be that referral patterns to individual clinicians are differentially influenced by factors such as patient, referring clinician or insurer preference, a future review including worldwide data could perform sensitivity analyses according to factors such as model of healthcare organisation and delivery.
Many of the limitations of this review are related to the limitations imposed by the reliance on observational studies in this review, which affects the overall strength of any recommendations that can be made. The quality of the review is also potentially affected by the restriction to English language papers as a result of available resources for translation and interpretation. The restriction of inclusion criteria to European populations however is not seen as a limitation but a reflection of the different models of healthcare worldwide. If as suggested \(^{26,27}\) selective referral and ‘practice make perfect’ can independently influence the volume outcome relationship, it is probable that the nature of the relationship differs between Europe and the US, with selective referral having more influence in the market driven context of the US than in the public sector dominated UK.

**Conclusion**

The results from this review suggest the existence of a relationship between the hospital volume of elective CEA and mortality in European populations.

Centralisation of arterial vascular surgery is on-going in the UK \(^{28}\) with the movement of complex arterial procedures to higher volume ‘hubs’. This appears to be justified for CEA on the basis of the evidence presented here with caveats regarding the observational, rather than experimental, nature of the included studies.

Further research could include a larger review that includes studies from the rest of the world, though it is likely that the results would then be ‘overwhelmed’ by the inclusion of US data.

An alternative approach could be a UK or European study using both administrative and clinical registry data linked with ONS data providing short and long-term mortality data from low and high volume hospitals. Such analyses are planned as part of the project of which this review is a component. More detailed clinical information
from the Vascular Surgical Quality improvement programme\textsuperscript{29} could also be used to analyse hospital and surgeon level data with cross validation adding to the credibility of results. In the context of on-going reorganisation of vascular services these analyses could explore the effects of reorganisation over time and between geographical locations allowing exploration of the effects of the variables that are components of ‘volume’.
References


27 Luft HS, Hunt SS, Maerki SC. The Volume Outcome relationship: practice makes perfect or selective referral patterns? Health Serv Res. 1987; 22 (2):157


Table I: table of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Data collection dates</th>
<th>Country</th>
<th>Study design</th>
<th>Data source</th>
<th>Study sample</th>
<th>Average age</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holt (2007) (^{11})</td>
<td>2000-05</td>
<td>UK</td>
<td>Retrospective analysis</td>
<td>HES</td>
<td>18248 CEA patients (16759 elective and 1489 emergencies)</td>
<td>70.2 (elective) and 70.4 (emergency)</td>
<td>In hospital mortality and length of hospital stay</td>
</tr>
<tr>
<td>Kantonen (1998) (^{12})</td>
<td>1991-95</td>
<td>Finland</td>
<td>Retrospective analysis</td>
<td>FINNVASC</td>
<td>1600 CEA patients</td>
<td>63.7</td>
<td>30 day stroke or death</td>
</tr>
<tr>
<td>Kragsterman (2004) (^{13})</td>
<td>1994-96</td>
<td>Sweden</td>
<td>Retrospective analysis</td>
<td>SWEDVASC</td>
<td>1411 CEA patients</td>
<td>68.8</td>
<td>Complication rates (death, stroke, TIA or amaurosis fugax).</td>
</tr>
<tr>
<td>Kuehnl (2016) (^{14})</td>
<td>2009-14</td>
<td>Germany</td>
<td>Retrospective analysis</td>
<td>German Quality Assurance Database</td>
<td>161488 CEA patients and 1757 CAS patients</td>
<td>CEA 70.7 CAS69.1</td>
<td>Any in-hospital stroke or death, major in-hospital stroke or death, death, length of stay,</td>
</tr>
<tr>
<td>Kuhn (2001) (^{15}) (2002) (^{16})</td>
<td>1992-99</td>
<td>UK</td>
<td>Retrospective analysis</td>
<td>UK vascular database</td>
<td>741 CEA patients</td>
<td>68</td>
<td>30 day stroke or death</td>
</tr>
<tr>
<td>Lindstrom (2012) (^{17})</td>
<td>2004-11</td>
<td>Sweden</td>
<td>Retrospective analysis</td>
<td>SWEDVASC and single centre registry</td>
<td>466 CAS patients</td>
<td>71 (HV centres) 69 (LV centres)</td>
<td>Stroke alone, mortality alone, combined stroke or death, combined stroke, death or AMI</td>
</tr>
<tr>
<td>Loftus (2016) (^{18})</td>
<td>2009-2014</td>
<td>UK</td>
<td>Retrospective analysis</td>
<td>National Vascular registry</td>
<td>23235 symptomatic CEA patients</td>
<td>73</td>
<td>Time from symptom to CEA</td>
</tr>
<tr>
<td>McCollum (1997) (^{19})</td>
<td>March-August 2004</td>
<td>UK</td>
<td>Retrospective analysis</td>
<td>VSGBI</td>
<td>590 CEA patients</td>
<td>66.8</td>
<td>Stroke alone</td>
</tr>
<tr>
<td>Parlani (2012) (^{20})</td>
<td>2006-12</td>
<td>Italy</td>
<td>Retrospective analysis</td>
<td>Single centre registry</td>
<td>1026 CAS patients</td>
<td>71.7</td>
<td>30 day combined stroke or death</td>
</tr>
<tr>
<td>Sidloff (2014) (^{21})</td>
<td>2009-12</td>
<td>UK</td>
<td>Retrospective analysis</td>
<td>National Vascular registry</td>
<td>1571 CEA patients</td>
<td>NS</td>
<td>30 day combined stroke or death</td>
</tr>
<tr>
<td>Theiss (2008) (^{22})</td>
<td>1995-2005</td>
<td>Germany, Austria, Switzerland</td>
<td>Retrospective analysis</td>
<td>Prospective Registry</td>
<td>5341 CEA patients</td>
<td>70</td>
<td>Peri-procedural stroke or death</td>
</tr>
</tbody>
</table>

Table II: Results and outcomes by analysis of CEA procedure volume by hospital

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reference</th>
<th>Analysis and adjustment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds ratios (OR) range 0.58-0.74, with low volume quantile as reference, are suggestive of a relationship between volume and outcome, 95% confidence intervals and p values are not reported.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A statistically significant effect was identified OR 0.898 (95% CI 0.808-0.999, p=0.047).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>There was no evidence of a statistically significant effect OR 0.975 (0.798-1.191, p=0.8026).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted for carotid surgery, co-morbidities, and surgeon’s caseload and hospital volume. <em>No statistically significant association was found between volume and outcome in adjusted or unadjusted analyses.</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>There was no significant correlation between the annual caseload of the centre and complication rates (Spearman’s correlation r =0.03; p = 0.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The crude rate of stroke or death decreased monotonically from 4.2% in the first quintile to 2.1% in the 5th (p&lt;0.001 for trend)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR range 0.91-1.36 with high volume quintile as reference suggesting a relationship between volume and in-hospital mortality; p values and confidence intervals were calculated but found to be non-significant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR range 0.99-1.50 with high volume quintile as reference suggesting a relationship between volume and in-hospital mortality; there was a statistically significant relationship between the lowest and highest volume groupings.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR range 0.99-1.50 with high volume quintile as reference suggesting a relationship between volume and in-hospital mortality; there was a statistically significant relationship between the two lowest quantiles and highest volume groupings.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>hospital volume as a continuous variable plotted against outcome suggests evidence of a statistically significant effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The differences between the two units (n=435 and n=306) were not statistically significant (p=0.695).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trusts performing a minimum of 50 CEAs per year had significantly lower perioperative mortality/morbidity rates (1.9 versus 3.0 per cent; P =0.032), a statistically significant relationship was also evident with linear regression (R2 =0.07, P =0.004).</td>
</tr>
</tbody>
</table>

**Note:** For CEA groups, the results are presented using the following quantiles:
- Quantile 1: 1-9.4
- Quantile 2: 9.5-17.2
- Quantile 3: 17.3-34.6
- Quantile 4: 34.7-52.2
- Quantile 5: 52.3-95.6
| Complications | Holt\textsuperscript{11}  
| CEA (elective)  
| (n=16759) | Complication rates (renal, respiratory, infection, shock, local complications, thrombotic or embolic events, cardiac, and DIC or transfusion reactions) Multiple logistic regression adjusted for age and gender | No evidence of a statistically significant relationship p=0.275 |
| Holt\textsuperscript{11}  
| CEA (emergency)  
| (n=1489) | As above | No evidence of a statistically significant relationship p=0.181 |
| **Length of hospital stay** | Holt\textsuperscript{11}  
| CEA (elective)  
| (n=16759) | Complication rates (renal, respiratory, infection, shock, local complications, thrombotic or embolic events, cardiac, and DIC or transfusion reactions) Multiple logistic regression adjusted for age and gender | An increasing annual hospital volume was associated with a decreased length of hospital stay for elective (p < 0.0001) |
| Holt\textsuperscript{11}  
| CEA (emergency)  
| (n=16759) | As above | An increasing annual hospital volume was associated with a decreased length of hospital stay for emergency procedures (p< 0.0001). |
| Kuehnl\textsuperscript{14}  
| (n=161488) | Length of stay plotted against volume quintiles | ‘Slight trend toward a shorter hospital stay when volume increases - median 1-2 days’ no statistical tests presented. |
| **Time from symptoms to CEA** | Loftus\textsuperscript{18}  
| (n=23235) | Graphical representation (unadjusted) showing the relationship between hospital volume (tertiles) and time from symptom onset to CEA:  
| CEA pa: Low volume <35  
| Medium volume 35-54  
| High volume >54 | No evidence of a relationship between hospital volume and time between 1st symptom and CEA and over the 5 year span of the analysis all hospitals (low, medium and high) improved their performance (reduced time from symptom to CEA) similarly. |

ASA - American Society of Anesthesiologists, CAS – carotid artery stenting, CEA – carotid endarterectomy, CI – confidence interval, DIC – disseminated intravascular coagulation, OR - odds ratio, TIA – transient ischaemic attack

**Adjusted for age, sex, ASA grade, neurological status on admission, degree of stenosis, periprocedural anti platelet therapy, formal neurological assessment, intra procedural neuro physiological monitoring; additionally for CEA surgical technique, type of anaesthesia, shunt use, intra operative completion study and clamping time; Additionally for CAS use of protection system, stent type and stent cell design. The hospital site specific code was also entered. The variables entered into the model were selected a priori according to a pre specified analysis plan with reference to the literature and theoretical considerations.
Table III: Results of analyses of CEA procedure volume by clinician and combined mortality and stroke

<table>
<thead>
<tr>
<th>Reference*</th>
<th>Analysis and adjustment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantonen 12 (n=1600)</td>
<td>Analysis by LOWESS curve (unadjusted), and multiple logistic regression adjusted for indication for carotid surgery, age, co-morbidity, surgeon caseload and hospital volume</td>
<td>An inverse association between the surgeon's carotid case load and the combined mortality and morbidity rate was found, as there was a trend towards better results after 10 carotid operations per year (p&lt;0.005) (LOWESS curve). An inverse association was also found (between the surgeons carotid caseload and combined mortality and morbidity rate) when surgeon's case load was added to the multivariate analysis though when the surgeons total vascular caseload was included in analysis this effect disappeared.</td>
</tr>
<tr>
<td>Kuhan 15 (n=741)</td>
<td>Log odds calculated with the high-volume surgeon (337 procedures) as reference. Analysis adjusted for age, sex, co-morbidities, internal carotid artery occlusion, respiratory disease, side of operation, shunt, patch, ASA grade, surgeon and vascular unit</td>
<td>Surgeon 1 (n=225) log odds 0.168, P=0.711</td>
</tr>
<tr>
<td>Kuhan 16 (n=741)</td>
<td>Bayesian regression modelling, adjusted for age, sex, co-morbidities internal carotid artery occlusion, respiratory disease, side of operation, shunt, patch, ASA grade, surgeon and vascular unit</td>
<td>This secondary analysis of Kuhan (2001) finds no significant differences between surgeons. ‘Focussing now on this distribution, there was little variability in outcome after adjustment for significant risk factors between the four surgeons studied’</td>
</tr>
<tr>
<td>Sidloff 21 (n=1571)</td>
<td>Linear regression unadjusted</td>
<td>A significant association was shown between number of CEA procedures performed by each consultant vascular surgeon in the UK (R2=0.21, P&lt;0.001) with unadjusted in-hospital stroke and/or mortality rates</td>
</tr>
<tr>
<td>Outcome</td>
<td>Reference and data source</td>
<td>Analysis and adjustment</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td>30 day mortality analysed between a single high volume provider and amalgamated lower volume providers using Fishers exact test</td>
</tr>
<tr>
<td>Kuehn [14]</td>
<td>(n=17905)</td>
<td>Adjusted in hospital mortality; regression modelling with volume as a categorical variable with high volume group as reference CEA pa: quantile (1) 1-2 quantile (2) 3-6 quantile (3) 7-12 quantile (4) 13-26 quantile (5) 27-240</td>
</tr>
<tr>
<td><strong>Combined Mortality and Stroke</strong></td>
<td></td>
<td>Combined stroke and death Fishers exact test comparison of single high volume centre with the remaining Swedish hospitals</td>
</tr>
<tr>
<td>Theiss [22]</td>
<td>(n=5341)</td>
<td>Peri-procedural stroke or death univariate and multivariate analysis adjusted for temporal trends, age, gender, symptomatic status, interval between symptoms and CAS, type of lesion, contralateral stenosis and operative factors</td>
</tr>
<tr>
<td>Kuehn [14]</td>
<td>(n=17905)</td>
<td>Unadjusted in hospital stroke (any) or death rates by volume groupings: CEA pa: quantile (1) 1-2 quantile (2) 3-6 quantile (3) 7-12 quantile (4) 13-26 quantile (5) 27-240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In hospital stroke (any) or death adjusted regression modelling with volume as a categorical variable with high volume group as reference (quantiles as above).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In hospital major stroke or death adjusted regression modelling with volume as a categorical variable with high volume group as reference (quantiles as above).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In hospital stroke (any) or death adjusted regression modelling with volume as a continuous variable</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Lindstrom 2012 [17]</td>
<td>AMI alone - Fishers exact test</td>
</tr>
<tr>
<td></td>
<td>(n=466)</td>
<td>Stroke alone - Fishers exact test</td>
</tr>
<tr>
<td><strong>Length of stay</strong></td>
<td>Kuehn [14]</td>
<td>Length of stay plotted against volume quintiles</td>
</tr>
</tbody>
</table>
Appendix 1

Data Sources

Data Sources Scoping Search

<table>
<thead>
<tr>
<th>Source</th>
</tr>
</thead>
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<tr>
<td>Medline and Medline in Process via Ovid</td>
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<tr>
<td>Embase via Ovid</td>
</tr>
<tr>
<td>The Cochrane library of systematic reviews via Wiley</td>
</tr>
<tr>
<td>Database of Abstracts of Effects (DARE) via Wiley</td>
</tr>
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</table>

Data Sources Primary Studies Search

<table>
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</tr>
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<tr>
<td>Medline and Medline in Process via Ovid</td>
</tr>
<tr>
<td>Embase via Ovid</td>
</tr>
<tr>
<td>The Cochrane library (all databases) via Wiley</td>
</tr>
<tr>
<td>Science Citation Index/ Book Citation Index - Science and Conference Proceedings Citation Index - Science via Thomson Reuters</td>
</tr>
<tr>
<td>CINAHL via EBSCO</td>
</tr>
</tbody>
</table>

Data Sources Surgery/Outcomes Search

As for primary studies search

Data Sources Conference Proceedings Search

The websites for the following conferences were scanned for outputs (posters or oral presentations) with any relevance to the topics of volume of vascular surgery and patient outcomes:

UK Vascular Society  
[http://www.vascularsociety.org.uk](http://www.vascularsociety.org.uk)

European Vascular Society  
[http://www.esvs.org](http://www.esvs.org)

BSIR (British Society of Interventional Radiology)  
[http://www.bsir.org](http://www.bsir.org)

ISVS (International Society for Vascular Surgery)  
[http://www.isvs.com](http://www.isvs.com)

SVS (Society for Vascular Surgery)  
[http://www.vascularweb.org/educationandmeetings/2015vam/Pages/home.aspx](http://www.vascularweb.org/educationandmeetings/2015vam/Pages/home.aspx)
Data Sources Citation Search

Science Citation Index (Web of Science) via Thomson Reuters
Scopus via Elsevier (where results not found in WoS)

Search Strategies

Scoping Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

--------------------------------------------------------------------------------
1     exp Vascular Surgical Procedures/ut [Utilization] (1806)
2     vascular surg$.mp. (33992)
3     exp Endarterectomy/ut (176)
4     Peripheral Arterial Disease/ (2447)
5     exp Peripheral Vascular Diseases/ (45653)
6     Intermittent Claudication/ (7157)
7     Amputation/ (16658)
8     (Peripheral arterial disease$ or peripheral vascular disease$).mp. (23163)
9     intermittent claudication.mp. (8577)
10    (Aortic aneurysm or triple A or true aneurysm).mp. (43979)
11    Aortic Aneurysm/ (18847)
12    Aortic Aneurysm, Abdominal/ (14281)
13    (carotid disease or carotid angioplasty or carotid surgery).mp. (3114)
14    exp Carotid Artery Diseases/ (38964)
15    exp Carotid arteries/ (51386)
16    (transient isch?emic attack or TIA or stroke).mp. (196320)
17    exp Stroke/ (91854)
18 Cerebrovascular Disorders/ (44229)
19 exp Brain Ischemia/ (85599)
20 (venous insufficiency or varicose vein$ or venous leg ulcer$).mp. (20286)
21 exp Venous Insufficiency/ (6093)
22 exp Varicose Veins/ (15810)
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or
18 or 19 or 20 or 21 or 22 (485513)
24 (surgeon volume or case volume or hospital Volume or workload).mp. (30063)
25 (surgery and (volume or outcome)).ti. (6182)
26 (surgery adj5 (volume or outcome)).ab. (13415)
27 exp Physician's Practice Patterns/ (43633)
28 exp Health services misuse/ (7557)
29 exp Utilization review/ (10730)
30 (surgery adj3 (utilisation or utilization)).ti,ab. (252)
31 24 or 25 or 26 or 27 or 28 or 29 or 30 (106459)
32 23 and 31 (4107)
33 Meta-Analysis as Topic/ (14509)
34 meta analy$.tw. (71100)
35 metaanaly$.tw. (1422)
36 Meta-Analysis/ (53861)
37 (systematic adj (review$1 or overview$1)).tw. (60909)
38 exp Review Literature as Topic/ (8068)
39 or/33-38 (136655)
40 cochrane.ab. (34565)
41 embase.ab. (33513)
42 (psychlit or psyclit).ab. (932)
43 (psychinfo or psycinfo).ab. (14233)
44 (cinahl or cinhal).ab. (11624)
45  science citation index.ab. (2193)
46  bids.ab. (388)
47  cancerlit.ab. (606)
48  or/40-47 (59856)
49  reference list$.ab. (10939)
50  bibliograph$.ab. (12608)
51  hand-search$.ab. (4356)
52  relevant journals.ab. (799)
53  manual search$.ab. (2606)
54  or/49-53 (27997)
55  selection criteria.ab. (21640)
56  data extraction.ab. (11276)
57  55 or 56 (31152)
58  Review/ (1969448)
59  57 and 58 (20616)
60  Comment/ (620891)
61  Letter/ (877156)
62  Editorial/ (373781)
63  animal/ (5531985)
64  human/ (14013133)
65  63 not (63 and 64) (3985649)
66  or/60-62,65 (5328963)
67  39 or 48 or 54 or 59 (171961)
68  67 not 66 (161249)
69  32 and 68 (100)

********************
Primary Studies Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

--------------------------------------------------------------------------------

1 exp Vascular Surgical Procedures/ut [Utilization] (1816)
2 vascular surg$.mp. (34473)
3 exp Endarterectomy/ (13415)
4 Peripheral Arterial Disease/ (2520)
5 exp Peripheral Vascular Diseases/ (45855)
6 Intermittent Claudication/ (7171)
7 Amputation/ (16863)
8 (Peripheral arterial disease$ or peripheral vascular disease$).mp. (23380)
9 intermittent claudication.mp. (8603)
10 (Aortic aneurysm or triple A or true aneurysm).mp. (44255)
11 Aortic Aneurysm/ (18915)
12 Aortic Aneurysm, Abdominal/ (14335)
13 (carotid disease or carotid angioplasty or carotid endarterectomy or carotid surgery).mp. (10408)
14 exp Carotid Artery Diseases/ (39195)
15 carotid stenosis/ (12586)
16 (venous insufficiency or varicose vein$ or venous leg ulcer$).mp. (20408)
17 exp Venous Insufficiency/ (6132)
18 exp Varicose Veins/ (15867)
19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 13 or 14 or 15 or 16 or 17 or 18 (170939)
20 (surgeon volume or case volume or hospital Volume or workload).mp. (30386)
21 ((surgery or surgeon$ or surgical$) and (volume or outcome)).ti. (10958)
22 ((surgery or surgeon$ or surgical$) adj5 (volume or outcome)).ab. (29362)
23 exp Physician's Practice Patterns/ (44152)
24 exp Health services misuse/ (7624)
25 exp Utilization review/ (10888)
26 (surgery adj3 (utilisation or utilization)).ti,ab. (261)
27 20 or 21 or 22 or 23 or 24 or 25 or 26 (125387)
28 19 and 27 (2535)
29 10 or 11 or 12 (44255)
30 27 and 29 (763)
31 limit 30 to yr="2004 -Current" (487)
32 28 or 31 (2796)

***************************

Surgery/Outcomes Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

--------------------------------------------------------------------------------
1 (Profundaplasty or carotid endarterectomy or amputation or aortic aneurysm repair or aorto-bifemoral bypass or femoro-popliteal bypass or femoro-distal bypass or endovascular aneurysm repair or EVAR or (carotid adj2 stent$) or CAS or angioplasty or balloon dilation or revascularisation or ((vascular or endovascular) adj2 (procedure or repair)) or (carotid adj2 (operation$ or surgery or procedure$)) or ((lower limb or arterial) adj2 (operation$ or surgery or procedure$)) or (arterial adj2 (operation$ or surgery or procedure$ or bypass or repair))).ti,ab. (101073)
2 exp *Vascular Surgical Procedures/ (140406)
3 1 or 2 (204334)
4 (re-admission or readmission or re admission or re-do or redo or re do or re-operation or reoperation or re operation or limb salvage or wound heal$ or length of stay).ti,ab. (104217)
((post-operative or post operative or postoperative) adj2 complication$) or mortality rate or hospital mortality or adverse outcome$ or survival rate or treatment outcome or stroke rate or fatal outcome or case fatality rate or outcome or outcome assessment or process assessment or complication or surgical mortality monitoring or ((clinical or surgical) adj2 performance) or ((amputation or morbidity or infection) adj2 rate)).ti,ab. (978814)

*postoperative complications/ or *hospital mortality/ or *survival rate/ or *treatment outcome/ (129746)

4 or 5 or 6 (1142018)

3 and 7 (52014)

(practice pattern$ or caseload or volume or clinical competence or surgical speciality).ti,ab. (426993)

*Physician's Practice Patterns/ or *Specialities, Surgical/ (25900)

9 or 10 (450589)

8 and 11 (1945)
## Appendix 3: Assessment of bias in included studies

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Selection</th>
<th>Volume measurement</th>
<th>Attrition</th>
<th>Outcome</th>
<th>Confounding</th>
<th>Reporting</th>
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<tbody>
<tr>
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<td>H</td>
<td>H/UC*</td>
<td>L</td>
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<td>H</td>
<td>H/M*</td>
<td>H</td>
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<td>H</td>
<td>UC</td>
<td>UC</td>
<td>M</td>
<td>UC</td>
</tr>
</tbody>
</table>

**Notes:** H-high, L-low, M-medium, U-unclear risk of bias. Risk of bias was assessed using a modified version of ACROBAT-NRSI. *Different conclusions for the risk of bias for included studies were found in relation to some domains of bias when alternative outcomes or analyses were considered.
Appendix 2 – Example calculations

Calculations performed based on the Cochrane handbook for systematic reviews of interventions (section 12.5.4.3) computing absolute risk reduction or NNT from an odds ratio.

Formula for calculating absolute risk reduction:

\[ \text{Number fewer per 1000} = 1000 \times \left( \frac{\text{ACR} - \frac{\text{OR} \times \text{ACR}}{1 - \text{ACR} + \text{OR} \times \text{ACR}}}{1} \right) \]

- OR – odds ratio
- ACR assumed control risk

We have used the event rate for the lowest quantile from each study as the assumed control risk (ACR).

Kuehnl 2016 calculations

Hospital volume of CEA and mortality – adjusted odds ratios ranged from 1.07 to 1.36 with high volume quintile as reference group, i.e., higher odds of death in the low volume groupings. Therefore the reciprocal of the odds ratio were used for the calculation

\[
\begin{align*}
1/1.07 &= 0.934579439 \\
1/1.36 &= 0.735294117
\end{align*}
\]

Mortality rate in the low volume quintile is 1.4%; rate = 0.014

\[ \text{Number fewer per 1000} = 1000 \times \left( \frac{\text{ACR} - \frac{\text{OR} \times \text{ACR}}{1 - \text{ACR} + \text{OR} \times \text{ACR}}}{1} \right) \]

\[
\begin{align*}
1000 \times (0.014 - & \frac{0.934579439 \times 0.014}{1 - 0.014 + 0.934579439 \times 0.014}) \\
& = 0.000903894
\end{align*}
\]

Number of deaths fewer per 1000 = 0.903894

\begin{align*}
\text{NNT} &= 1106
\end{align*}

The same calculation was performed for odds ratio 0.735294117

\[
\begin{align*}
\text{Number of deaths fewer per 1000} &= 3.667593
\end{align*}
\]
NNT = 273

Hospital volume of CEA and in-hospital stroke (any) or mortality
ACR = 0.042
OR = 1.36 reciprocal = 0.735294117
NNT = 93

Hospital volume of CEA and in-hospital stroke (major) or mortality
ACR = 0.032
OR = 1.50 reciprocal = 0.66666666
NNT = 96

**Holt 2007 calculation**

- The unadjusted odds ratio for in hospital mortality range from 0.58 to 0.74 in the four higher volume quantiles with the low volume quantile as the reference group.
- The mortality rate in the lowest volume quantile is 1.46%, therefore the ACR = 0.0146

- Calculation for OR 0.74:

\[
\text{Number fewer per 1000} = 1000 \times \left( \frac{0.0146 - 0.74 \times 0.0146}{1 - 0.0146 + 0.74 \times 0.0146} \right)
\]

\[
\text{Number fewer per 1000} = 1000 \times \left( \frac{0.0146 - 0.010804}{1 - 0.0146 + 0.010804} \right)
\]

\[
\text{Number fewer per 1000} = 1000 \times \left( \frac{0.0146 - 0.010845168}{0.996204} \right)
\]

\[
\text{Number fewer per 1000} = 1000 \times (0.0146 - 0.010845168)
\]

\[
\text{Number fewer per 1000} = 1000 \times 0.003754832
\]

\[
\text{Number fewer per 1000} = 3.754832
\]

That is approximately 4 fewer deaths per 1000 operations conducted – however it must be borne in mind that this is based on an odds ratio that is reported without confidence intervals and p values.

Numbers needed to treat (NNT) can also be calculated, NNT = 267, suggesting that for every 267 patients treated at the high volume hospitals there will be one less in hospital death.
• Calculation for OR 0.58:

Number fewer per 1000 = 1000 x \( \frac{0.0146 - 0.58 \times 0.0146}{1 - 0.0146 + 0.58 \times 0.0146} \)

Number fewer per 1000 = 1000 x \( \frac{0.0146 - 0.008468}{1 - 0.0146 + 0.008468} \)

Number fewer per 1000 = 1000 x \( \frac{0.0146 - 0.008468}{0.993868} \)

Number fewer per 1000 = 1000 x \( 0.0146 - 0.008520246 \)

Number fewer per 1000 = 1000 x 0.006079754

Number fewer per 1000 = 6.079754

That is approximately 6 fewer deaths per 1000 operations conducted – however it must be borne in mind that this is based on an odds ratio that is reported without confidence intervals and p values.

Numbers needed to treat (NNT) can also be calculated, NNT = 165, suggesting that for every 165 patients treated at the high volume hospitals there will be one less in hospital death.

References