# The Efficacy of Carotid Surgery by Subgroups: The Concept of Stroke Prevention Potential☆

**Ellinoora Aro** [a], **Petra Ijäs** [b,c], **Leena Vikatmaa** [d], **Lauri Soinne** [b,c], **Reijo Sund** [e,f], **Maarit Venermo** [a], **Pirkka Vikatmaa** [a,*]

[a] Department of Vascular Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[b] Department of Neurology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[c] Department of Neurosciences, University of Helsinki, Helsinki, Finland
[d] Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[e] Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[f] Centre for Research Methods, Faculty of Social Sciences, University of Helsinki, Helsinki, Finland

**WHAT THIS PAPER ADDS**

Patient selection should be a key component of carotid surgery reports. A calculator was created where the presence and recentness of symptoms, sex, increasing stenosis severity, and complication rates could all be combined into a single figure. The calculator was tested on real life material and some theoretical inclusion scenarios. Single hospital treatment development over time and benchmarking between hospitals can be monitored when registered data includes these parameters, ultimately leading to improved patient selection.

**Objective:** Considering carotid endarterectomy (CEA), reporting treatment delay, symptom status, and surgical complication rates separately gives an incomplete picture of efficacy; therefore, the aim was to combine these factors and develop a reporting standard that better describes the number of potentially prevented strokes. With a real life cohort and theoretical inclusion scenarios, the aim was to explore the stroke prevention potential of different carotid practices.

**Methods:** Landmark studies for symptomatic and asymptomatic patients were revisited. By using published estimates of treatment effect, a simplified calculator was designed to assess the five year stroke prevention rate per 1000 CEAs (stroke prevention potential [SPP], range 0–478), including the presence and recentness of symptoms, sex, increasing stenosis severity, and complication rates. Patients operated on for carotid stenosis at Helsinki University Hospital (HUH) between 2008 and 2016 were collected from a vascular registry (HUSVASC) and categorised according to the model. The local annual complication rate was re-evaluated and added to the model. The HUH patient cohort was incorporated into the SPP model, and changes over time analysed. Finally, theoretical changes in patient selection were compared in order to explore the theoretical impact of patient selection and shortening of the delay.

**Results:** Fifteen hundred and five symptomatic and 356 asymptomatic carotid stenoses were operated on with stroke plus death rates of 3.6% and 0.3%, respectively. The proportion of CEAs performed within two weeks of the index event increased over the follow up period, being 77% in 2016. The SPP increased from 123 in 2008 to 229 in 2016. Theoretically, 350 ischaemic strokes were prevented in the period 2008–16, with 1861 CEAs.

**Conclusions:** National and international comparison of different CEA series is irrelevant if the inclusion criteria are not considered. A calculator that is easy to apply to large scale high quality registered data was developed and tested. SPP was found to increase over time, which is a probable sign of improved patient selection and an increased number of strokes prevented by the CEAs performed.

**Keywords:** Benchmarking, Carotid endarterectomy, Registries, Secondary prevention, Stroke, Treatment outcome, Vascular diseases
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## INTRODUCTION

Carotid endarterectomy (CEA) has been the subject of several qualified randomised controlled trials (RCTs) and an extensive number of post-hoc analyses.[1–10] However, although the information from these studies is readily available, it is interpreted very diversely in different countries and guidelines.[11–15]

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* Corresponding author. Helsinki University Hospital (HUH), P.O. Box 340, 00029 HUS, Helsinki, Finland.
*E-mail address:* pirkka.vikatmaa@hus.fi (Pirkka Vikatmaa).

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Patient selection is mainly based on symptom status and the grade of carotid artery stenosis. High grade (70—99%) symptomatic stenosis is the most evident indication for ipsilateral CEA. Operating on symptomatic patients within two weeks of the event confers maximum benefit from the procedure. However, in subgroup analysis, the impact of timing has been least apparent in symptomatic men with high grade stenosis.[16,17]

Recommendations for treating asymptomatic patients are more controversial. The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) have underpinned the practise guidelines, although with diverse interpretations. The proportion of asymptomatic patients varies from 0% to 90% between countries and from 0% to100% between individual centres.[14,18,19]

Traditionally, reporting includes the number of symptomatic/asymptomatic patients treated and the annual complication rates. Since 2004 the importance of operating promptly has been appreciated increasingly and short delay is considered to be an independent indicator of good carotid practice. To date, five European countries have published national data on treatment delay from symptom to CEA. The median delay is seven days in Sweden (Swedvasc annual report 2018), nine in Germany, 12 in the UK, and 14 in Norway.[20—22] In the Netherlands 75% of the symptomatic patients are operated on within two weeks.[23]

Post-hoc analyses of large RCTs (The Carotid Endarterectomy Trialists Collaboration [CETC]) allows estimation of the number of strokes prevented per 1000 CEAs at five years in relation to selected clinical subgroups.[16,17,24] By using the earlier published theoretical absolute risk

Symptomatic patients — Number of strokes prevented at five years by 1000 CEAs

| Stenosis | Sex | Delay – wks <2 | 2–4 | 4–12 | >12 |
|---|---|---|---|---|---|
| 50–69% | Female | 138 | 0 | 0 | 0 |
| | Male | 152 | 68 | 50 | 63 |
| 70–99% | Female | 418 | 66 | 0 | 0 |
| | Male | 235 | 238 | 183 | 204 |

Asymptomatic patients — Number of strokes prevented at five years by 1000 CEAs

| Stenosis | Sex | |
|---|---|---|
| 60–69% | Female | 0 |
| | Male | 51.5 |

**Figure 1.** Developing the grid. The multiplier in each cell is generated from the number of strokes prevented per 1000 operations over five years of follow up, extracted from the published figures from the major randomised controlled trials divided according to symptomatology, grade of stenosis, sex, and delay.[16,17,24—26] In order to respect the individual decision making by the professionals, the choice was to use zero, when the reported figure was negative. The cells are colour coded: green indicates the number needed to treat was <7, yellow indicates the number needed to treat was 8—20, and orange indicates no strokes prevented (or some strokes caused). CEA = carotid endarterectomy.

reduction (ARR) for sex, delay, grade of stenosis, and symptom status (asymptomatic/symptomatic), and by adding the effect of local complication rate, a calculator was designed that takes into account all these parameters and counts the theoretical number of strokes prevented by a given carotid service. This concept is launched here as the "stroke preventing potential" (SPP). Investigation of the evolution of the above mentioned parameters at the authors' institution from 2008 to 2016 was carried out. Lastly, theoretical proportions of asymptomatic patients, delays, and complication rates were included in order to show their impact on SPP.

## MATERIALS AND METHODS

The results of benchmark RCTs that randomised symptomatic (North American Symptomatic Carotid Endarterectomy Trial [NASCET], European Carotid Surgery Trial [ECST])[1,2] or asymptomatic (ACAS, ACST)[3,4] patients to either conservative or operative arms were revisited. By using their published estimates of efficacy for selected clinical subgroups (Fig. 1), a calculator was designed that estimates the five year stroke prevention rate per 1000 CEAs performed (SPP).[16,17,24—26] Firstly, patients were divided into subgroups by their symptom status (symptomatic/asymptomatic) and by sex. Secondly, symptomatic patients were further subgrouped by degree of stenosis d (50—69% and 70—99%) and treatment delay (0—2 weeks, 2—4 weeks, 4—12 weeks, and >12 weeks). In line with the ACST and ACAS trial results, degree of asymptomatic stenosis subcategories were not introduced. It was assumed that no asymptomatic patients with <60% stenosis or symptomatic patients with <50% stenosis were operated on. Borderline cases were analysed in the moderate stenosis group. With these specifications every patient could be placed in a group representing the potential for stroke prevention (strokes prevented at five years by performing 1000 CEAs). By calculating the number of patients in each cell an absolute and proportional number of strokes prevented could be calculated and a single SPP figure defined for the whole cohort.

All CEAs performed at Helsinki University Hospital (HUH) between January 2008 and December 2016 were identified from a prospectively collected validated vascular surgery registry (HUSVASC).[27] In order to further improve the quality of the data and decrease the number of missing data, the following parameters were double checked from the hospital electronic patient database or recalculated from images when inaccurate: symptom status (symptomatic/asymptomatic); grade of ipsilateral carotid artery stenosis (percentage); and delay from index symptom to surgery.

Index symptom was defined as the event leading to consultation and surgery. The grade of stenosis was assessed by computed tomography angiography (CTA) or magnetic resonance imaging (MRI) according to the NASCET method.[1] Carotid stenosis was classified as symptomatic if the patient had experienced a preceding ipsilateral hemispheric or retinal stroke, transient ischaemic attack (TIA), or amaurosis fugax in the six months prior to surgery. Patients with no clear underlying ipsilateral ischaemic retinal or hemispheric symptoms were defined as asymptomatic. Also, patients with uncertain symptoms such as suspicion of hypoperfusion were classified as asymptomatic. The perioperative events (any stroke or death within 30 days after surgery) have been evaluated annually as part of the quality control system at HUH. Each complication was re-assessed retrospectively from the patient records by a stroke neurologist and a vascular surgeon. It was not always possible to determine the delay and these patients were excluded from the relevant analyses (Table 1).

The template of the figures used in the calculations is shown in Fig 1. By using the SPP calculator, the theoretical efficacy of the carotid service at HUH for the period 2008—16 was defined. For comparison, SPP was also calculated for different theoretical patient selection policies. The effect of complication rates were calculated as follows: the 30 day complication figures of 6% for symptomatic and 3% for asymptomatic patients were considered to be the basis for the figures in Fig 1. By increasing the effectiveness for each cell with the number of fewer perioperative 30 day complications, a novel table for fewer or zero complication calculations was produced. In case of zero effect in the original table the figure was kept at zero and no negative figures were used. This was in order to respect the individual decision making in less evident indications.

Data handling, calculations, and figures were carried out with SPSS Statistics 22.0 (IBM, Armonk, NY, USA) and the SPP calculator in Excel v16.0 (Microsoft, Redmond, WA, USA).

## RESULTS

In total, 1861 CEAs were performed at HUH between 1 January 2008 and 31 December 2016. Over this time period the annual number of CEAs increased by 32%. The operated stenosis was symptomatic in 1505 (81%) patients and

**Table 1. Carotid endarterectomy patients operated on at Helsinki University Hospital from 2008 to 2016, divided into relevant subgroups**

| Characteristic | Total (*n*) | Symptomatic | Asymptomatic |
|---|---|---|---|
| No. of CEAs | 1861 | 1505 (81) | 356 (19) |
| *Sex* | | | |
| Male | 1260 (68) | 967 (64) | 293 (82) |
| Female | 601 (32) | 538 (36) | 63 (18) |
| *Mean age ± SD − y* | 70.2 ± 8.5 | 70.8 ± 8.7 | 67.3 ± 6.7 |
| < 75 | 1263 (68) | 958 (64) | 305 (86) |
| ≥ 75 | 598 (32) | 547 (36) | 51 (14) |
| *Degree of stenosis − %* | | | |
| 50–69 | 480 (26) | 406 (27) | |
| 70–99 | 1381 (74) | 1099 (73) | |
| *Delay − wks* | | | |
| < 2 | | 791 (53) | |
| 2–4 | | 285 (19) | |
| > 4–12 | | 225 (15) | |
| >12 | | 66 (4) | |
| Index date unreliable | | 138 (9) | |

Data are *n* (%) unless otherwise stated. CEA = carotid endarterectomy.

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asymptomatic in 356 patients (19%). The annual proportion of asymptomatic patients ranged from 11% to 31%, with no significant trend (Fig. 2).

The mean ± SD age of the patients was 70.2 ± 8.5 years; 68% were male. Asymptomatic patients were younger and more often male. In symptomatic patients, the degree of stenosis was severe (70—99%, according to the NASCET method)[1] in 73% of the cases (Table 1). Regarding the index event in symptomatic patients, most common was minor stroke (42%) or TIA (35%). With four exceptions calculated to have a 55% stenosis, all operated asymptomatic stenoses were >60%.

The time from index event to surgery was reliably obtainable for 1367 (91%) symptomatic patients. Median time from index event to surgery was 12 days (interquartile range 7—24 days). The detailed distribution of patients to different categories is shown in Table 1. In 2008, 18% underwent CEA within the two weeks, while in 2016 this proportion had increased to 77% (Fig. 3).

For symptomatic patients, the combined 30 day stroke and death rate was 3.6% ($n$ = 54; yearly range 2.0—6.7%) (Fig. 4). Forty-three suffered a non-fatal ischaemic or haemorrhagic stroke. Of the 11 deaths, all of which occurred after discharge, two were classified to have been caused by an ischaemic stroke and one by a haemorrhagic stroke, four had cardiac causes, and in four patients the reason remained unknown. Of all asymptomatic patients, the combined stroke and death rate was 0.3% ($n$ = 1); one patient with a contralateral occlusion developed a hyperperfusion syndrome and was treated for low blood pressure in a stroke unit but eventually died of a haemorrhagic stroke.

The SPP for the period 2008—16 at HUH was 188 (strokes potentially prevented by performing 1000 operations in five years of follow up) when all patients and the actual complication rates were taken into consideration. The development of the SPP index during the study period is illustrated in Fig. 5. If theoretically no complications would have occurred, the SPP would have increased to 215, and with the 6% complication rate as in NASCET/ECST for symptomatic and 3% as in ACST for asymptomatic patients, the SPP would have been 166 (Fig. 5). By excluding asymptomatic patients, but keeping the characteristics of symptomatic patients at HUH in the calculation, the SPP would have been 220. If the annual proportions of asymptomatic patients were 50% or 90%, the SPP would have been 141 and 78, respectively (Fig. 6A). The effect of theoretical time delays is demonstrated in Fig. 6B. If all the symptomatic patients in the HUH 2008—16 CEA cohort were operated on within two weeks, keeping the same sex distribution and proportions of high and moderate grade stenosis, the SPP would have been 2.2 times higher than if the operations were carried out after 12 weeks' delay (SPPs of 239 and 109, respectively).

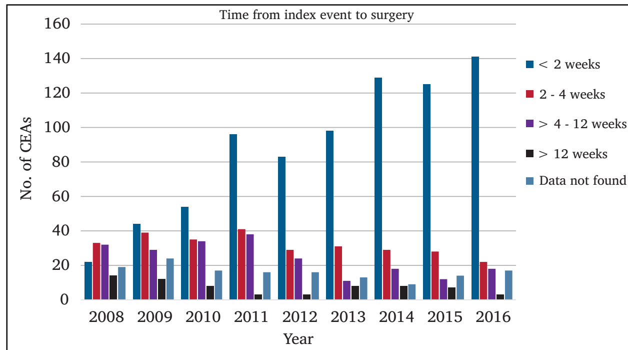


**Figure 3.** Time from index event to surgery. Distribution of symptomatic patients into the following delay groups (from index event to carotid endarterectomy) < 2, 2—4, 4—12, and >12 weeks from 2008 to 2016. CEA = carotid endarterectomy.

## DISCUSSION

SPP includes symptom status (symptomatic/asymptomatic), grade of ipsilateral carotid stenosis, sex, delay from index symptom to surgery, and local complication

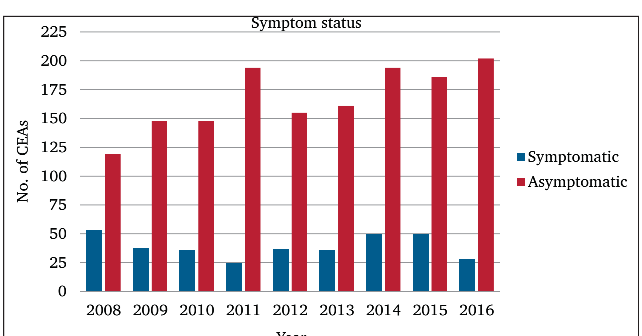


**Figure 2.** The annual number of symptomatic and asymptomatic patients operated on for carotid stenosis between 2008 and 2016. In 19% the indication for surgery was an asymptomatic stenosis. CEA = carotid endarterectomy.

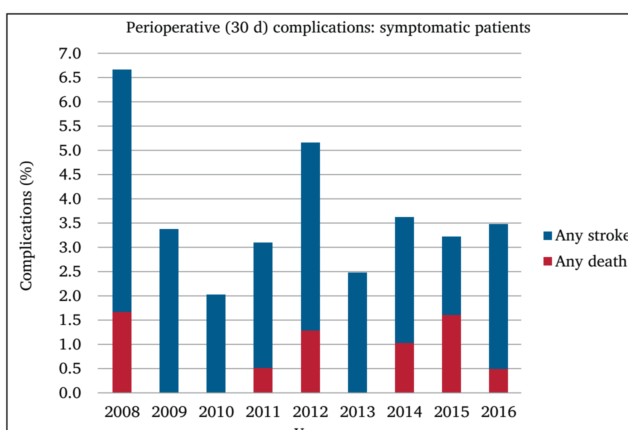


**Figure 4.** Annual rates of stroke/death for symptomatic patients within 30 days. There were no strokes and one post-operative death (0.3%) in the asymptomatic group.

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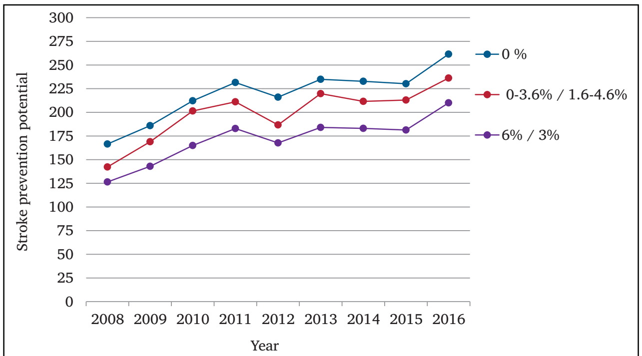


**Figure 5.** The development of stroke prevention potential at Helsinki University Hospital (HUH). The three lines represent different possible complication levels, calculated separately for symptomatic and asymptomatic patients. The three different complication levels (asymptomatic/symptomatic) were 0%/0%, actual annual HUH levels, and for 3%/6%, respectively.

rate. These factors are mostly well documented, unambiguous, easily collected, and incorporated into vascular registries. Thus, SPP could be a relatively simple method when assessing the institutional carotid service and when comparing national and international data.

## *Delay and sex*

According to the analyses by CETC, operating on symptomatic patients within two weeks of the event results in 18.5% absolute risk reduction (ARR) in the stroke rate at five years, while after 12 weeks the ARR is only 0.8%.[16] Women were shown to benefit most when CEA was carried out within two weeks, with a rapid decline in benefit with the passage of time since the event. However, in men, particularly those with high grade stenosis, the efficacy of CEA in preventing strokes was clearly evident even after longer delays.[17] The index event is the one that got the patient to seek medical advice and this event is recorded prospectively into the HUSVASC register.[28]

CECT calculations are based on old RCTs that randomised the patients two decades ago; however, even in the era of modern medical treatment the incidence of recurrent events remains high. In a combined analysis of two vascular registries and one population based study, including symptomatic patients awaiting CEA on modern stroke prevention medication, the risk of ipsilateral stroke or retinal artery occlusion was 2.7% (1 day), 5.3% (3 days), 11.5% (14 days), and 18.8% (90 days).[29] In a series of operations after thrombolysis, seven of 128 (5.5%) patients had a recurrent stroke prior to surgery a median of four days (interquartile range 0—8 days) after the thrombolysis, whereas the 30 day peri-/post-operative stroke rate was six of 128 (4.7%).[30] This means that operating promptly remains important, despite improved medication.

At HUH, continuous efforts in decreasing the delay to surgery have resulted in more rapid access to carotid surgery. The median delay over the study period was 12 days, bears international comparison, and improved over time.

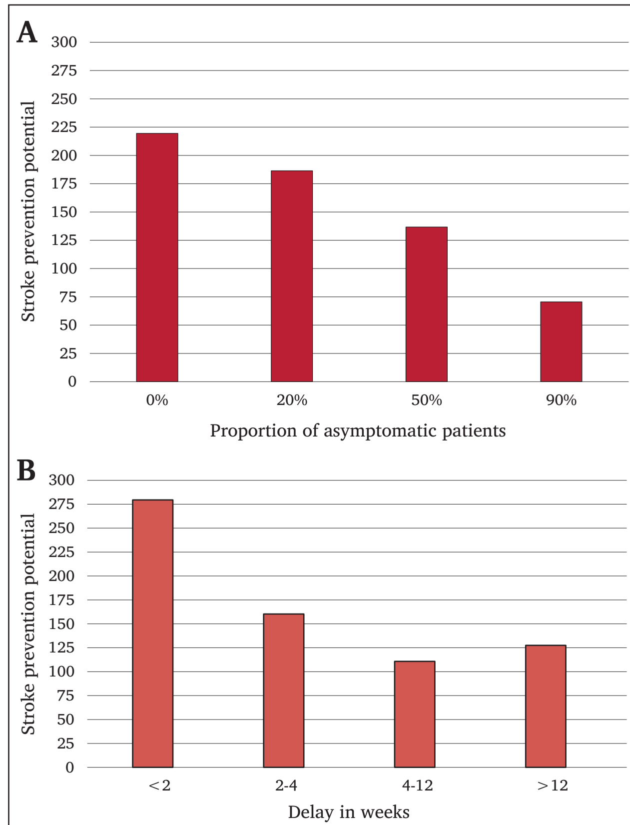


**Figure 6.** Two theoretical exercises on how patient selection changes the number of potentially prevented strokes. The (A) proportion of asymptomatic patients and (B) delay from symptom to surgery have a paramount impact on the stroke prevention potential (SPP). The effect of delay in (B) is calculated using the symptomatic patients operated on at Helsinki University Hospital with actual sex distribution and proportions of high and moderate grade stenosis. The higher SPP for longest delay is explained by the high proportion of men. SPP = stroke prevention potential, strokes prevented at 5 years by performing 1000 carotid endarterectomies.

Yet, in 2016, 23% of symptomatic patients did still not receive surgical treatment in time. This was mostly as a result of the lack of patient awareness in seeking urgent medical advice, but delay in the diagnostics still occur.[28,31] The two week recommendation is obtained from post-hoc analysis and has not been evaluated in RCTs.

## *Grade of stenosis and plaque characteristics*

Symptomatic patients with high grade stenosis (70—99%) benefit more from the CEA than those with moderate (50—69%) stenosis.[24] In asymptomatic patients, the risk reduction becomes evident in stenosis $\geq$60%, but no further benefit is gained with increasing degree of stenosis.[3,4] In the original RCTs for symptomatic patients the stenosis severity was measured from digital subtraction angiography, while ACST accepted diagnosis by duplex ultrasound (DUS) alone. Today, the measurement and decision making mostly rely on CTA and/or magnetic resonance angiography imaging.[32,33] Other imaging features, such as plaque area on computerised plaque analyses,[34] intraplaque haemorrhage

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on MRI[35] and plaque lucency on DUS,[36] may identify subgroups of patients that are at increased risk of stroke. So far, these characteristics are too elusive to be incorporated into a calculator.

## *Asymptomatic stenosis*

ACST reported an overall five year risk of recurrent stroke of 6.4% in the surgical group vs. 11.8% in medical group, with women having a lower ARR than men (4.1% vs. 8.2%, respectively).[4] A meta-analysis of data from ACAS and ACST showed a benefit of CEA for men but not for women or for any patient older than 75 years regarding five year risk of any stroke or peri-operative death.[25,26] When the ACST continued follow up until 10 years an ARR of 4.6% was observed in both sexes, which can be reported as 46 prevented strokes per 1000 patients operated on.[5] Stroke rates among asymptomatic patients on modern best medical treatment have declined since the original RCTs, and common criticism questions the validity of the results today.[15] In order to maintain coherence, the decision was made to use the ARRs derived from the five year follow up for both symptomatic and asymptomatic patients. This compromise may underestimate the efficacy of operating asymptomatic women.

## *Complications*

When assessing the quality of the carotid service, the local complication rate should be proportional to patient selection and delays. Operating on low risk patients with minimal complications provides tidy statistics, but more strokes are

Symptomatic patients

Patients (%) operated on at HUH

Delay – wks

| Stenosis | | < 2 | 2–4 | 4–12 | > 12 | NA |
|---|---|---|---|---|---|---|
| 50–69% | Female | 85(6) | 25(2) | 14(0.1) | 1 (0) | 7 (0) |
| | Male | 142 (9) | 48 (3) | 45 (3) | 16 (1) | 23 (2) |
| 70–99% | | < 2 | 2–4 | 4–12 | > 12 | NA |
| | Female | 203 (13) | 85 (5) | 61 (4) | 18 (4) | 42 (3) |
| | Male | 361 (24) | 130 (9) | 105 (7) | 31 (2) | 66 (4) |

20

Asymptomatic patients

Patients (%) operated on at HUH

| Stenosis | | |
|---|---|---|
| 60–69% | Female | 63 (18) |
| | Male | 293 (82) |

**Figure 7. Patients ($n = 1861$) who had a carotid endarterectomy done at Helsinki University Hospital between 2008 and 2016.** In order to get a stroke preventing potential figure for the population, each patient was designated their own potential prevention number. This number could then be manipulated according to the general complication rate. HUH = Helsinki University Hospital; NA = delay not available. SPP = stroke prevention potential, strokes prevented at 5 years by performing 1000 carotid endarterectomies.

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prevented when focusing the operations on high risk symptomatic patients. This is highlighted by the fact that, in the present study, 0.3% and 3.6% of asymptomatic and symptomatic patients, respectively, suffered a stroke or died.

### *Vascular registries and risk calculators*

Modern quality control requires hospitals to maintain proper registries of the operations performed. Standardised and validated vascular registries enable national and international comparison and fair benchmarking. In the future, SPP or a related efficacy index should be incorporated into registry reporting. A model to estimate the five year stroke risk for each individual patient with a symptomatic carotid stenosis has been developed (www.ndcn.ox.ac.uk). The model is beneficial in daily decision making but not applicable to large scale registry data.

### *Limitations*

The SPP concept has some limitations. Firstly, the model is based on relatively old RCT data, which may not be fully valid today. The predictive value of the individual variables may be updated to the model as soon as ongoing RCTs (e.g., Carotid Revascularisation Endarterectomy vs. Stenting Trial-2 [CREST-2], ECST-2, and ACST-2) are finalised and results published. For example, if the effect of surgery is halved the SPP number may simply also be halved in order to get a more accurate estimate. Secondly, the model comprises only some variables and fails to take into account well known plaque and patient related details like the nature of the symptom, possibly causing a significant problem in case mix.[11] However, when dealing with large registry data, simplification could be regarded as a strength rather than a weakness of the model.

Thirdly, a high SPP number should not be interpreted directly as a sign of effective and recommendable carotid practice. For example, the highest SPP (478) would be obtained by operating only on symptomatic females within two weeks of the index event with no complications, which would lead to exclusion of the largest group of patients, males with a high grade stenosis (46% in the present series). The minimum was set to zero, but patients operated on outside the recommended indications should always be reported (Fig. 7). The authors chose to exclude carotid stenting because it is rarely performed in the authors' unit owing to the fact that large scale RCT data has demonstrated CEA superiority in the most important subgroup, symptomatic patients with a short delay.

Some statistical issues remain in the SPP calculator. In principle, SPP is only a justified weighted average based on available data and extracted evidence from RCTs. For the actual comparisons it would be beneficial to provide some confidence intervals or other measure of uncertainty. Some assumptions had to be made to keep the calculator simple and because of the limited information available in published RCTs. Most importantly, it was assumed that the subgroups are independent of each other. For example the grade of stenosis should not have had any systematic impact on delay in the original publications, because otherwise some part of the benefit may be accounted for twice. This needs to be acknowledged, but it does not invalidate the SPP calculations. Another assumption that had to be made was that there were no censored observations in published cumulative complication rates. This may have a minor impact on the recalculations of the impact of different local complication proportions. This error was estimated to be $<1\%$.

SPP seems a promising tool for benchmarking. Owing to the fact that the original calculations are based on post-hoc analysis, the SPP result should not be seen as an absolute figure, but rather as a tool for assessing the quality of the carotid service over time and between units.

## CONCLUSIONS AND RELEVANCE

The SPP summarises the main findings of the RCTs that have given a solid basis for CEA practice guidelines today. The SPP figure (a summary of symptom, delay, sex, grade of stenosis, and complications representing strokes prevented per 1000 operations over five years of follow up) serves as a comparison tool over time and between hospitals, regions, and countries, providing that reliable data are registered. It is hoped that, in the future, inclusion criteria reporting could be a requirement when CEA results are reported. Ideally, SPP should be implemented in all vascular registries in order to make benchmarking more accurate.

## CONFLICT OF INTEREST

None.

## ACKNOWLEDGEMENTS

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.04.003.

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