Carotid guidelines recommend carotid endarterectomy (CEA) for patients with 60% to 99% asymptomatic carotid stenosis (ACS) provided the perioperative stroke/death rates are <3%. Several reports have noted that the average annual risk of ipsilateral any territory stroke among patients with asymptomatic moderate to severe internal carotid artery stenosis receiving medical therapy (MT) alone has now fallen to ≤1%. The decreased incidence of stroke has been attributed to modern MT and has made opinion leaders demand a revision of management strategies by either refraining from CEA or by identifying high-risk patients. Such high-risk patients should be offered prophylactic CEA in addition to MT to reduce the risk of a future stroke. It is therefore essential to develop methods to identify these ACS patients at high enough risk to warrant prophylactic intervention.

Several methods have been proposed for the identification of ACS patients at high risk for future stroke (Table). Namely: (1) the detection of microemboli by transcranial Doppler (TCD), (2) identification of the unstable carotid plaque using ultrasound, (3) reduced cerebral blood flow reserve, (4) intraplaque hemorrhage using magnetic resonance imaging (MRI) scans, (5) silent embolic infarcts on brain computed tomography (CT) or MRI, and (6) progression in the severity of ACS. A discussion of the involved mechanisms and the predictive value of each of these methods is presented.

Microemboli Detection on TCD

The predictive value of microemboli detection on TCD for the identification of ACS patients at high risk for stroke has been validated by 2 independent studies and is further supported by a meta-analysis. A small prospective, observational, cohort study failed to verify the association between TCD-detected emboli and higher stroke risk for ACS patients. A possible reason is that this study accepted 1 microembolus as positive although the test was repeated at 6 monthly intervals. Evidence suggests that ≥2 embolic signals detected in a recording lasting 1 hour improve the accuracy of the method. The detection of ≥2 embolic signals in a single 1-hour recording suggests a high-risk, unstable asymptomatic plaque or a plaque with a thrombus on its surface. In the most recent meta-analysis, microembolic signals were detected in 195 (17%) of a total of 1144 patients. At the end of the follow-up, this high-risk group with an average annual stroke risk of 8% contained 17 (57%) of the 30 strokes that occurred during follow-up. This means that TCD recording once for 1 hour may not be enough or many plaques may rupture and produce strokes without prior microemboli. It may be argued that TCD equipment or expertise may not be available in many hospitals. However, the cost of TCD equipment is low (approximately the cost of 3 CEAs), and training and certification for TCD embolus detection is not onerous. In view of the increasing use of TCD for neurovascular disorders, it could be argued that TCD embolus detection should be performed in all centers that perform CEA for ACS.

Identification of the Unstable Carotid Plaque Using Ultrasound

Recent reports from the largest prospective study on ACS patients undergoing medical intervention alone, the Asymptomatic Carotid Stenosis and Risk of Stroke (ACRSRS) study, demonstrated clearly that not all ACS patients carry the same stroke risk. In ACRSRS, 1121 patients with 50% to 99% ACS received MT and were followed up for 6 to 96 months (mean, 48 months).

As shown in ACRSRS, severity of stenosis, a history of contralateral transient ischemic attack (TIA) episodes and a number of plaque texture features at baseline could stratify patients into groups of varying annual stroke rate from <1% to >10%. In addition, the presence of a juxtaluminal black area of >8 mm2 in a plaque (indicating a thrombus or a thin or absent fibrous cap) identified a group of 245 patients (21% of the cohort) that had an average annual stroke rate of 4.1% and contained 42 (86%) of the strokes that occurred during follow-up. These results clearly show that not all ACS patients are...
### Table. Suggested Predictors of the Development of Stroke/Transient Ischemic Attack in Asymptomatic Carotid Patients

<table>
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- Spence et al<sup>8</sup> Patients with microemboli at baseline (n=32) were more likely to have a stroke during the first year of follow-up (15.6% [95% CI, 4.1–79] vs 1% [95% CI, 1.01–1.36]; P<0.0001)  
- Spence et al<sup>6</sup> In the first year, a stroke was recorded in 3 of 37 patients with vs 5 of 431 patients without microemboli (10.3% vs 1.4%, respectively; P=0.02).  
- In the second year, a stroke was recorded in 5 of 37 patients with vs 5 of 431 without microemboli (18.5% vs 1.8%, respectively; P=0.001)  
- Markus et al<sup>14</sup> Patients with embolic signals on TCD had a >2.5-fold higher 2-year stroke and TIA risk compared with patients without (HR, 2.54; 95% CI, 1.20–5.36; P=0.015)  
- For ipsilateral stroke alone, the HR was 5.57 (95% CI, 1.61–19.32; P=0.007)  
- The absolute ipsilateral stroke or TIA annual risk was 7.13% in patients with and 3.04% in patients without embolic signal  
- Topakian et al<sup>9</sup> Plaque echolucency (164 carotid plaques; 37.7%) was associated with an increased risk of ipsilateral stroke (HR, 6.43; 95% CI, 1.36–30.44; P=0.019)  
- Plaque echolucency in combination with TCD emboli was associated with a >10-fold higher ipsilateral stroke risk (HR, 10.61; 95% CI, 2.98–37.82; P=0.0003) |  
| **Identification of unstable carotid plaques using ultrasound** |  
- Kakkos et al<sup>11</sup> The mean annual stroke rate was 0.4% in 706 patients with a JBA <4 mm<sup>2</sup>, 1.4% in 171 patients with a JBA 4–8 mm<sup>2</sup>, 3.2% in 46 patients with a JBA 8–10 mm<sup>2</sup>, and 5% in 198 patients with a JBA >10 mm<sup>2</sup> (P<0.001)  
- Of the 59 ipsilateral ischemic strokes, 42 (71%) occurred in the 244 patients (22% of the cohort) who had a JBA ≥8 mm<sup>2</sup>  
- Reduced cerebral blood flow reserve  
- Gupta et al<sup>12</sup> A positive relationship was observed between baseline cerebrovascular reserve impairment and increased risk of stroke/TIA (summarized random effects OR, 3.96; 95% CI, 2.60–6.04)  
- Intraplaque hemorrhage using MRI  
- Singh et al<sup>13</sup> Of the 98 carotid arteries included, 36 had MRI-depicted intraplaque hemorrhage (36.6%)  
- MRI-depicted intraplaque hemorrhage was associated with a >3.5-fold higher risk of cerebrovascular events (HR, 3.59; 95% CI, 2.48–4.71; P<0.001)  
- Hellings et al<sup>14</sup> Patients with intraplaque hemorrhage had a >2-fold higher risk for the occurrence of stroke compared with patients without intraplaque hemorrhage (50 of 59 vs 9 of 227 or 8.4% vs 3.9%, respectively; HR, 2.1; 95% CI, 1.1–4.4)  
- van Lammeren et al<sup>15</sup> The carotid plaques from ACS patients (n=182) had less frequently intraplaque hemorrhage (21 of 182 vs 25 of 82 or 11.5% vs 30.5%, respectively; P=0.005) compared with patients with ipsilateral events >6 mo before CEA (n=82)  
- Qiao et al<sup>16</sup> The occurrence of cerebrovascular ischemic events was associated with the presence of intraplaque hemorrhage (OR, 10.18; 95% CI, 1.42–72.21; P=0.02)  
- Silent embolic infarcts on brain CT or MRI  
- Kakkos et al<sup>17</sup> In 462 patients with 60% to 99% ACS, the annual stroke rate was 3.6% vs 1.0% when embolic signals were present vs absent, respectively (HR, 3.0; 95% CI, 1.46–6.29; P=0.002)  
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- Progression in the severity of ACS  
- Balestrini et al<sup>19</sup> Progression of ACS was detected in 129 patients (24.7%). Of these, 35 patients (27.1%) had an ipsilateral stroke and 22 (17.0%) had a TIA  
- Progression of ACS was strongly associated with the risk of ipsilateral stroke (HR, 3.19; 95% CI, 9.83–103.91; P<0.001)  
- Kakkos et al<sup>20</sup> The 8-year cumulative ipsilateral cerebral ischemic stroke rate was 0% in patients with regression, 9% of the stenosis was unchanged, and 16% if there was progression (relative risk in patients with progression, 1.92; 95% CI, 1.14–3.25; P=0.05)  
- Conrad et al<sup>21</sup> Plaque progression occurred in 262 arteries and 36 (13.7%) of these developed symptoms  
- The symptomatic conversion rate in patients with plaque progression was almost twice that of those without plaque progression (13.7% vs 8.5%; P=0.02)  
- Plaque ulceration on 3D ultrasound  
- Madani et al<sup>22</sup> Patients with >3 ulcers had a 2-year stroke risk of 18.2% vs 1.7% in patients with <3 ulcers  

3D indicates 3-dimensional; ACS, asymptomatic carotid stenosis; CEA, carotid endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; IMT, intima-media thickness; JBA, juxtaluminal black area; MRI, magnetic resonance imaging; OR, odds ratio; SCI, silent cerebral infarction; TCD, transcranial Doppler; and TIA, transient ischemic attack.
the same. It therefore seems inappropriate to offer all asymptomatic individuals the same treatment. Furthermore, these results provide proof that multiple risk stratification parameters (4 independent predictors: baseline degree of stenosis, history of contralateral stroke or TIA, size of black juxtaluminal plaque area ≥8 mm² without a visible echogenic cap, and the presence of discrete white areas in a hypoechoic plaque) are better than single parameters for stroke risk stratification.13

A limitation of this technique is that ultrasonographers require special training in equipment settings and image capture during duplex scanning and in image analysis using commercially available software (info@lifeqmedical.com) on a laptop. In the ACSRS study,11 a 1-day course was adequate for each ultrasonographer from the 80 centers participating. Besides training, there are the issues of cost and also if these analyses could be readily and reliably performed in the community setting.

Reduced Cerebrovascular Reserve
Several studies have demonstrated that impairment in cerebral blood flow reserve is associated with the development of stroke in ACS patients.10–13 With increasing degree of carotid stenosis and an incomplete circle of Willis or contralateral occlusion, cerebral perfusion pressure is reduced. As a result of cerebrovascular autoregulation, cerebral arterioles dilate maximally to maintain a constant cerebral blood flow. However, when the arterioles are maximally dilated, further reduction in cerebral perfusion pressure (such as may occur during a hypotensive episode) is associated with a reduction in perfusion that may result in TIA or stroke.

Four studies have investigated the cerebrovascular reserve using TCD velocity measurements in response to acetazolamide or breathing 5% CO₂ in asymptomatic patients with severe stenosis or occlusion.13–18 Average follow-up was 24 months. Raw data are not available in 1.18 Impaired cerebrovascular reserve was present in 183 (75%) of the 244 included in the remaining three studies.18–20 This high-risk group had an average annual event rate (TIA or stroke) of 5.7% and contained 21 (75%) of the 28 events that occurred during follow-up.

A meta-analysis summarizing the association between cerebrovascular reserve impairment with stroke risk demonstrated an ≥4-fold higher stroke risk in asymptomatic patients with impaired cerebral blood flow.19 Reduced cerebrovascular flow reserve may therefore identify ACS patients at high risk for stroke. The cost, access, insurance coverage, and availability of trained technicians and physicians to perform and read the studies are possible limitations of this technique.

Identification of Intraplaque Hemorrhage Using MRI
Intraplaque hemorrhage is a marker of plaque instability and contributes to 2 features that synergistically increase the odds of plaque rupture, namely necrotic core size and plaque volume.14–18 A histological study of 264 excised carotid plaques has demonstrated that intraplaque hemorrhage and a large lipid core were associated with symptomatic patients.15 In an MRI study involving 47 patients having CEA demonstrated that intraplaque hemorrhage and adventitial enhancement indicating neovascularization were independently associated with previous events.16

In a study of 75 men with 50% to 70% ACS, MRI identified the presence of intraplaque hemorrhage in 36 (36.7%) of 98 carotid arteries.11 In this high-risk group, 2 strokes and 4 TIA s occurred during a 25-month follow-up. Strokes or TIA s did not develop in the patients without intraplaque hemorrhage.13

The evidence to date on the value of MRI in the cerebrovascular bed is not enough and has not been validated prospectively. Moreover, this is not covered by insurance.

Silent Embolic Infarcts on Brain CT or MRI
Earlier studies demonstrated that the presence of silent embolic infarcts on brain CT or MRI scans is associated with an increased risk of stroke in the general population.24–26 The prevalence of silent infarcts on brain CT scans in asymptomatic patients having CEA was 14% and 18% in 2 studies.27–28 The ability of such infarcts to predict the risk of future strokes was tested in the ACSRS study.17 Embolic infarcts were present in 61 (9.6%) of 633 patients with 60% to 99% stenosis in relation to the normal distal internal carotid. This high-risk group which had an average annual stroke rate of 3.5% contained 9 (24%) of the 38 strokes that occurred during follow-up.17 This means that 76% of the plaques that produce a stroke will be missed probably because many plaques rupture without giving off emboli that produce silent infarcts. This report,17 as well as an independent study,18 seem to support that ACS patients found to have prior infarcts should be referred for intervention.

Another factor to be considered is that brain CT scans are not sensitive in demonstrating small embolic infarcts. It is well known that brain CT scans may miss ≤50% of small infarcts shown on brain MRI scans. Future longitudinal studies need to investigate the value of silent infarcts using MRI.

Progression in the Severity of ACS
Several natural history studies in medically managed patients with ACS have investigated the association between stenosis progression and risk of ipsilateral cerebrovascular events.28–30 Most authors have concluded that progression to >80% stenosis in relation to the diameter of the distal internal carotid was associated with an increased risk of cerebrovascular events. However, these studies did not determine whether progression itself is a risk factor that is independent of the degree of stenosis and have not answered the question whether different degrees of stenosis are associated with different rates of progression.

In a recently published series involving 900 carotid arteries (794 patients) with 50% to 69% ACS, plaque progression occurred in 262 (29.1%) arteries during a mean follow-up of 3.6 years.21 This high-risk group (average annual stroke rate, 2.1%) contained 20 (38%) of the 52 strokes that occurred during follow-up (absolute values calculated from percentages given in the article). In the absence of progression the average annual stroke rate was 1.4%.21

In a second study involving 523 patients with 50% to 69% ACS, plaque progression occurred in 129 (24.7%) arteries during a mean follow-up of 3.5 years.19 This high-risk group (average annual stroke rate, 7.7%) contained 35 (92%) of the
38 strokes that occurred during follow-up. In the absence of progression the average annual stroke rate was 0.4%.19

In the most recently published study (ACRSRS) involving 1121 patients with 50% to 99% ACS in relation to the bulb, plaque regression occurred in 43 (3.8%), no change in stenosis in 856 (76.4%), and progression in 222 (19.8%) arteries during a mean follow-up of 4.0 years.20 This high-risk group (average annual stroke rate, 2.0%) contained 19 (32%) of the 59 strokes that occurred during follow-up. In the absence of progression the average annual stroke rate was 1.12%, whereas it was 0% in the presence of regression.20 For patients with 80% to 99% baseline stenosis (70%–99% in relation to the distal internal carotid), the average annual ipsilateral ischemic stroke rate was 1.7% in the absence and 3.1% in the presence of progression.20 In addition, this study demonstrated that the incidence of plaque progression is inversely proportional to the severity of baseline stenosis and that both baseline stenosis and progression were independent predictors of stroke risk.20

These data argue for continued screening and treatment by CEA of patients with progressive ACS even if they remain asymptomatic.

**Combination of Methods**

The combination of multiple risk stratification parameters, which are independent predictors (baseline degree of stenosis, history of contralateral stroke/TIA, size of black juxtaluminal plaque area ≥8 mm² without a visible echogenic cap and the presence of discrete white areas in a hypoechoic plaque), is better than single parameters when it comes to stroke risk stratification.11 Another example is the combination of gray scale median score with TCD microembolic signals.9 A low gray scale median score is an independent predictor for an increased risk of stroke during carotid intervention.41

**Conclusions**

Although intensive MT now reduces the overall risk of stroke below that of CEA in the majority of ACS patients, some patients with ACS may go on to have a stroke. It is therefore important to identify specific subgroups of ACS patients who despite MT are still at increased risk (>2%/y) and may require a carotid intervention. Identification of these high-risk ACS patients is crucial to target carotid revascularization procedures appropriately and to avoid excessive use of unnecessary interventions. Performing CEA or carotid artery stenting on those with >80% stenosis as currently practiced in many centers ignores the fact that many strokes occur in patients with moderate stenosis, which may be identified by the presence of TCD embolic signals or unstable plaques using ultrasound. Thus, the approach of selective intervention will lead to a refinement of the current indications for CEA and would also reduce costs spent on unnecessary or even harmful procedures. Current evidence suggests that certain ACS patients (ie, those with TCD-detected microemboli4,8–10,20 or silent embolic infarcts on brain CT/MRI scans17,18,34–37 those with reduced cerebrovascular reserve,12,26–33 ACS severity progression despite MT19–21 or history of contralateral stroke/TIA, size of black juxtaluminal plaque area ≥8 mm² without a visible echogenic cap)11 are at increased stroke risk and should be considered for prophylactic CEA or carotid artery stenting. Another modality that may be of use in the future is ulceration on 3-dimensional ultrasound.42

A limitation of practically all the studies reviewed above is that they have been performed during the era when MT was not optimal. Many of these studies need to be repeated in cohorts that are on what is currently considered optimal MT. Positive results from such studies are likely to make risk stratification methods accepted in routine medical practice.

**Disclosures**

Dr Nicolaides has >10000 or 5% stock or other ownership of LifeQ Ltd. Dr Spence received research grants from the Heart & Stroke Foundation of Canada (Ontario) that are pertinent to the topic of this article. The other authors report no conflicts.

**References**


**Key Words:** endarterectomy, carotid
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*Stroke*. 2014;45:3720-3724; originally published online October 30, 2014;
doi: 10.1161/STROKEAHA.114.006912

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Identifying Which Patients With Asymptomatic Carotid Stenosis Could Benefit From Intervention

Kosmas I. Paraskevas, MD; J. David Spence, MD, FRCPC; Frank J. Veith, MD; Andrew N. Nicolaides, MD, FRCS, PhD (Hon)

(Stroke.2014;45:3720-3724.)
초음파를 이용한 불안정성 경동맥뇌경화반의 규명

ACS 환자가 내과적 치료만 받은 경우에 대한 최대규모 전향적 연구인 Asymptomatic Carotid Stenosis and Risk of Stroke (ACRS) 연구(11,20,29)에서 최근 보고한 바에 따르면, 모든 ACS 환자<br>의 뇌졸중 위험률이 모두 같은 것은 아니라는 것은 분명히 확인되어<br>졌다. ACSRS 연구에서, 50%~99%의 협착을 보이는 ACS 환자에서<br>뇌졸중 위험률은 모두 같은 것은 아닌 것으로 확인되었다. 이는 모든 ACS 환자가<br>뇌졸중 위험성을 가지고 있음을 시사한다. ACSRS 연구의 64,788명의 ACS 환자<br>중에서 6개월 동안의 추적 관찰 후 1,121명이 약물치료를 받았고, 6개월에서 96개월의 기간 동안(평균 48개월) 추적하였다.

Table. Suggested Predictors of the Development of Stroke/Transient Ischemic Attack in Asymptomatic Carotid Patients

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경우)가 하나의 변수를 사용하는 것보다 더 좋은가에 대한 증명도 있다.  

이 방법의 제한점은 초음파 기사가 기구 설정 및 이중초음파 검사 중에 영상을 포착하는 것, 컴퓨터를 이용해서 시판 중인 소프트웨어(info@lifeqmedical.com)를 사용하여 영상을 분석하는 과정 등에 특별한 훈련이 필요하다는 점이다. ACSRS 연구에서는,  

연구에 참여하는 80개 센터의 음파기사들 대상 1일 코스의 훈련으로 충분했다. 훈련뿐 아니라, 비용 문제도 있으며 이 분석이 지역사회 상황에서도 쉽게, 믿을만한 수준으로 시행될 수 있지만 여부도 문제가 된다.

뇌혈류 예비력의 감소

여러 연구에서 뇌혈류 예비력의 손상이 ACS 환자에서 뇌졸중의 발생과 연관되어 있음을 보고하였다.  

뇌혈류 예비력이 감소한 것으로 야마도 뇌졸중의 위험군을 규명할 수 있을 것이다. 비용, 훈련 가능한 여부, 보험적용 문제, 검사를 시행하고 해석할 훈련된 기사 및 의사의 유무 등이 이 방법에서 제한점으로 작용할 수 있다.

뇌 콤폽터단층촬영이나 자기공명영상에서 관찰되는 무증상 색전성뇌경색

이전 연구들은 일반인에서 뇌 콤폽터단층촬영이나 자기공명영상에서 무증상 색전성뇌경색이 관찰될 경우 뇌졸중의 위험이 증가한다고 보고하였다.  

그중 일부 연구에서는 뇌 자기공명영상에서 관찰되는 색전성뇌경색이 뇌졸중의 위험을 예측하는 데 역할을 하며 보험적용 문제도 불립니다. 

뇌 자기공명영상의 가치 평가는 앞으로 추적연구가 필요하다.

자기공명영상 사용한 축성경화반내 출혈

축성경화반내 출혈은 축성경화반의 불안정성의 표시이며, 축성경화반 파열 현상으로 대시 혈관의 동맥투의 불안정성은, 축성경화반 내경동맥에 발생한 축성경화반 내경동맥의 264개를 조직학적으로 분석한 연구에서, 축성경화반내 출혈이 있는 것으로 보고되어 있다.  

ACSRs의 중증도의 진행

약물치료를 받은 ACS 환자의 자연 경과에 대한 이론 연구에서 혈청 정도의 진행과 같은 영역의 뇌혈관사건의 위험성 사이의 연관성을 조사하였다.  

또한 이들 연구는 혈청 정도의 진행을 위한 80% 이상의 경동맥 관찰을 위한 방법으로 사용할 수 있을 것으로 보아, ACS의 중증도의 진행은 축성경화반의 발생될 때부터 이미 진행하게emes. 이는 치료의 필요성을 의미한다.
50%에서 69%의 협착 정도를 보인 ACS 794명 환자의 900개 경동맥을 대상으로 최근 발표된 시리즈에서, 죽상경화반의 진행은 평균 3.6년의 추적기간 동안 262개의 경동맥(29.1%)에서 나타났다. 이 고위험군(평균 뇌졸중 발생률 2.1%)에는 추적기간 중 발생한 52례의 뇌졸중 중 20례(38%)의 뇌졸중이 포함되었다(논문에 발췌된 백분율에서 발생 증례 수를 계산함). 진행하지 않은 군에서는 평균 연간 뇌졸중 발생률이 0.4%이었다. 19

가장 최근에 발표된 연구(ACSRS)에서는 경동맥 팽대부 대비 50%에서 99%의 협착 정도를 보인 ACS 환자 523명을 대상으로 한 두 번째 연구에서는, 죽상경화반의 진행이 평균 3.5년의 추적기간 동안 129개의 혈관(24.7%)에서 나타났다. 이 고위험군(평균 연간 뇌졸중 발생률 7.7%)에는 추적기간 중 발생한 38례의 뇌졸중 중 35례(92%)가 포함되었다. 진행하지 않은 군에서는 평균 연간 뇌졸중 발생률 0.4%이었다. 19

결론

현재 임상적인 약물치료가 대부분의 ACS 환자에서 뇌졸중의 전반적인 위험도를 CEA를 받은 경우보다 낮을 수 있지만, 일부 ACS 환자에서는 뇌졸중이 발생할 수 있다. 그러나, 약물치료에 도 불구하고 위험성이 여전히 높은(>2% y) ACS 환자의 특정군을 규명하는 것이 중요하며, 이들에 이들은 경동맥시술을 필요로 할 것이다. 이 고위험 ACS 환자를 선택하는 것은 적절하게 경동맥중

Disclosures

Dr Nicolaides has >10000 or 5% stock or other ownership of LifeQ Ltd. Dr Spence received research grants from the Heart & Stroke Foundation of Canada (Ontario) that are pertinent to the topic of this article. The other authors report no conflicts.

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Key Word: endarterectomy, carotid