Carotid guidelines recommend carotid endarterectomy (CEA) for patients with 60% to 99% asymptomatic carotid stenosis (ACS) provided the perioperative stroke/death rates are <3%.1,2 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%.3–5 The decreased incidence of stroke has been attributed to modern MT and has made opinion leaders demand a revision of management strategies4 by either refraining from CEA6 or by identifying high-risk patients.7 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).6,8–22 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.6,8–10,23 A small prospective, observational, cohort study failed to verify the association between TCD-detected emboli and higher stroke risk for ACS patients.24 A possible reason is that this study accepted 1 microembolus as positive although the test was repeated at 6 monthly intervals.24 Evidence suggests that ≥2 embolic signals detected in a recording lasting 1 hour improve the accuracy of the method.25,26 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.26 In the most recent meta-analysis,10 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,27,28 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,11,20,29 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,11,20,29 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 juxtalaminal 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.11 These results clearly show that not all ACS patients are

**Comments and Opinions**

**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)

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microemboli detection on TCD</td>
<td>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&lt;0.0001)</td>
</tr>
<tr>
<td>Spence et al8</td>
<td>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)</td>
</tr>
<tr>
<td>Markus et al10</td>
<td>Patients with embolic signals on TCD had a &gt;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</td>
</tr>
<tr>
<td>Topakian et al9</td>
<td>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 &gt;10-fold higher ipsilateral stroke risk (HR, 10.61; 95% CI, 2.98–37.82; P=0.0003)</td>
</tr>
<tr>
<td>Identification of unstable carotid plaques using ultrasound</td>
<td>The mean annual stroke rate was 0.4% in 706 patients with a JBA &lt;4 mm², 1.4% in 171 patients with a JBA 4–8 mm², 3.2% in 46 patients with a JBA 8–10 mm², and 5% in 198 patients with a JBA &gt;10 mm² (P&lt;0.001) Of the 59 ipsilateral ischemic strokes, 42 (71%) occurred in the 244 patients (22% of the cohort) who had a JBA ≥8 mm²</td>
</tr>
<tr>
<td>Gupta et al12</td>
<td>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)</td>
</tr>
<tr>
<td>Intraplaque hemorrhage using MRI</td>
<td>Of the 98 carotid arteries included, 36 had MRI-depicted intraplaque hemorrhage (36.6%) MRI-depicted intraplaque hemorrhage was associated with a &gt;3.5-fold higher risk of cerebrovascular events (HR, 3.59; 95% CI, 2.46–4.71; P&lt;0.001)</td>
</tr>
<tr>
<td>Singh et al13</td>
<td>Patients with intraplaque hemorrhage had a &gt;2-fold higher risk for the occurrence of stroke compared with patients without intraplaque hemorrhage (50 of 591 vs 9 of 227 or 8.4% vs 3.9%, respectively; HR, 2.1; 95% CI, 1.1–4.4)</td>
</tr>
<tr>
<td>Hellings et al14</td>
<td>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 &gt;6 mo before CEA (n=82)</td>
</tr>
<tr>
<td>Qiao et al16</td>
<td>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)</td>
</tr>
<tr>
<td>Silent embolic infarcts on brain CT or MRI</td>
<td>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) In the subgroup of 216 patients with 60% to 79% ACS, the annual TIA and stroke rate was 4.4% vs 1.3% when embolic signals were present vs absent, respectively (P=0.005)</td>
</tr>
<tr>
<td>Miwa et al18</td>
<td>During an average follow-up of 4.1±2.0 y (range, 1–105 mo), the presence of SCI was associated with a &gt;8.5-fold higher risk for the development of stroke/TIA after adjustment for carotid IMT (HR, 8.56; 95% CI, 1.72–42.55; P=0.003)</td>
</tr>
<tr>
<td>Progression in the severity of ACS</td>
<td>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, 31.97; 95% CI, 9.83–103.91; P&lt;0.001)</td>
</tr>
<tr>
<td>Balestrini et al19</td>
<td>The 8-year cumulative ipsilateral cerebral ischemic stroke rate was 0% in patients with progression, 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)</td>
</tr>
<tr>
<td>Kakkos et al20</td>
<td>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)</td>
</tr>
<tr>
<td>Madani et al22</td>
<td>Patients with &gt;3 ulcers had a 2-year stroke risk of 18.2% vs 1.7% in patients with &lt;3 ulcers</td>
</tr>
</tbody>
</table>

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.11

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 Cerebral Blood Flow 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.30–33 Average follow-up was 24 months. Raw data are not available in 1.35 Impaired cerebrovascular reserve was present in 183 (75%) of the 244 included in the remaining three studies.30–33 This high-risk group 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.36–38 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

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.13–16 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 occurred during a 25-month follow-up. Strokes or TIA 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.34,35 The prevalence of silent infarcts on brain CT scans in asymptomatic patients having CEA was 14% and 18% in 2 studies.36,37 The ability of such infarcts to predict the risk of future strokes was tested in the ACSRS study.17 Embolic infaracts 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.
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 or TIA, size of black juxtaluminal plaque area ≥ 8 mm² without a visible ecchogenic 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 microemboli,4,8,10,20 or silent embolic infarcts on brain CT/MRI scans,17,18,34–37 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 ecchogenic 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.22

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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경 동맥질환에 관한 진료지침에는 60%~99%의 무증상 경동맥협착(asymptomatic carotid stenosis, ACS) 환자의 경우 수술로 인한 뇌졸중이나 사망 위험이 3% 미만인 경우에 경동맥내막절제술(carotid endarterectomy, CEA)을 권고한다.1,2 여러 연구에서 무증상인 중등도 이상의 내경동맥협착 환자에서 약물치료받은 경우에 혈관 내경동맥의 악영양 또는 전체 영역의 뇌졸중 발생 위험을 평가 관절 1% 정도까지 낮아지는 것을 언급했다.3-5 뇌졸중 발생률의 감소는 현재 약물 치료에 기인하며, 이로 인해 여러 학자들이 CEA를 검토하거나 또는 고위험군을 규명하는 등 현재의 치료전략을 보완한 것을 요구하게 되었다.7 고위험군의 환자는 미래의 뇌졸중의 위험을 줄이기 위해 약물치료뿐 아니라 예방적 CEA를 권장해야 한다. 그러므로, 예방적 시술을 요구하는 정도의 높은 위험을 가지는 ACS 환자는 CEA를 피해야 하는 것이 중요하다.

지금까지 미래의 뇌졸중 발생위험이 높은 ACS 환자를 규명하기 위한 여러 방법이 제안되어왔다(Table).6,8-10 다시 말하면, (1) 경두께초음파(transcranial doppler, TCD)을 통해 미세색전을 감지하는 방법, (2) 초음파를 이용해서 불안정한 경동맥확장반을 확인하는 방법, (3) 혈류 예비력이 감소했는지 여부, (4) 자기공명영상로 이용해서 축상경화반 내 출혈 여부를 확인하는 방법, (5) 뇌 컴퓨터단층촬영이나 자기공명영상으로서 대뇌증상성뇌경색 여부를 확인하는 것, (6) ACS의 정도가 진행하는지 여부 등이 다. 이들 각각의 방법의 배경이 되는 기전 및 예측 가치에 대해 기술하였다.

**TCD를 이용한 미세색전의 감지**

ACS 환자에서 뇌졸중의 위험이 높은지를 알아보기 위해 TCD를 이용해서 미세색전을 확인하는 방법의 예측 가치는 2개의 독립적인 연구에서 입증되었으며, 이후 메타분석에서 이를 뒷받침하는 결과가 보고되었다.6-10,23 소규모의 연령, 성별, 카테고리에 따라 연구에서 CEA에서 관찰된 색전과 ACS 환자의 뇌졸중 위험도 간의 연관관계를 규명하는데 실패하였다.24 그 이유로는 아마도 해당 연구에서 검사 전 6개월의 간격을 두고 반복되었을 때도 불구하고 한 개의 미세색전도 양성으로 해석한 것일 수 있다.24 한 시간 가량 지속해서 기록할 때 관찰되는 2개 이상의 색전 신호가 CEA 방법의 정확도를 개선시킨다는 근거가 있으며,25,26 1회 한 시간 검사 시 2개 이상의 색전 신호가 차단되는 경우 고위험군, 불안정성 무증상 축상경화반 또는 표면에 혈전을 동반한 축상경화반만 가능성을 시사한다.26 가장 최근의 메타분석에서도, 15,26,27 총 1,144명의 환자 중 195명(17%)에서 미세색전 신호가 관찰되었다. 추적판찰 기간이 완료된 시점에서, 30례의 뇌졸중에서 추적기간 동안 발생한 뇌졸중 중 17례(57%)를 포함하여 이들 고위험군의 평균 연간 뇌졸중 발생 위험은 8%였다. 이는 단지 한 시간 1회의 TCD 검사는 아마도 충분하지 않거나, 또는 많은 수의 축상경화반이 미세색전이 발생하게 되어 검사가 실패되거나, 뇌졸중을 일으킬 수 있다는 것을 의미하니, 그리고 많은 병원에서 TCD 기계가 없고 전문가가 없는 것도 결과의 여지가 될 수 있다. 그러나, TCD 기계 가격은 저렴하고(3건 CEA의 비용), TCD를 이용한 색전 확인 방법을 훈련하고 인증하는 것이 아주 힘들지 않으나, TCD를 이용한 색전 검사가 ACS 환자에서 CEA를 시행하는 모든 센터에서 시행되어야 한다고 주장할 수도 있다.

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**Identifying Which Patients With Asymptomatic Carotid Stenosis Could Benefit From Intervention**

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초음파를 이용한 불안정성 경동맥중족경화반의
규정

ACS 환자가 내과적 치료만 받은 경우에 대한 최대규모 전향적 연구인 Asymptomatic Carotid Stenosis and Risk of Stroke (ACRS) 연구에서는 최근 보고한 바에 따르면, 모든 ACS 환자 약 2년간 뇌졸중 위험도가 약 16%로 보고하였다. ACRS 연구에서는, ACS 환자 1,121명이 약물치료를 받았고, 6개월에서 96개월의 기간 동안(평균 48개월) 추적하였다. 연구에서는 ACS 환자의 뇌졸중 위험률이 대부분의 경우 약 4%였으며, 추적기간 중 42례의 뇌졸중이 발생하였습니다. 3D시각화를 이용한 연구에서는 ACS 환자 245명의 환자(코호트의 21%)에서 확인되었는데, 이러한 경우 평균 연간 뇌졸중 발생률이 4.1%였으며, 추적기간 중 42례의 뇌졸중이 발생하였다. 이는 ACS 환자 전반에 걸쳐서 발생할 수 있는 것으로 보인다.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Outcome</th>
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</thead>
<tbody>
<tr>
<td>Spence et al8</td>
<td>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=0.001)</td>
</tr>
<tr>
<td>Spence et al8</td>
<td>In the first year, a stroke was recorded in 3 of 37 patients with vs 5 of 431 patients without microemboli (15.3% vs 1.4%, respectively; P=0.02)</td>
</tr>
<tr>
<td>Markus et al9</td>
<td>Patients with embolic signals on TCD had a &gt;2.5-fold higher 3-year stroke and TIA risk compared with patients without (HR, 2.54; 95% CI, 1.20–5.36; P=0.015)</td>
</tr>
<tr>
<td>Topkian et al13</td>
<td>For ipsilateral stroke alone, the HR was 5.57 (95% CI, 1.61–19.32; P=0.007)</td>
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<td>The absolute ipsilateral stroke or TIA annual risk was 7.1% in patients with and 3.04% in patients without embolic signal</td>
</tr>
<tr>
<td>Identification of unstable carotid plaques using ultrasound</td>
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<tr>
<td>Kakkos et al11</td>
<td>The mean annual stroke rate was 0.4% in 706 patients with a JBA &lt;4 mm2, 1.4% in 171 patients with a JBA 4–8 mm2, 3.2% in 46 patients with a JBA 8–10 mm2, and 5% in 198 patients with a JBA &gt;10 mm2 (P&lt;0.001)</td>
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<tr>
<td></td>
<td>Of the 59 ipsilateral ischaemic strokes, 42 (71%) occurred in the 244 patients (22% of the cohort) who had a JBA 8 mm2</td>
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<tr>
<td>Reduced cerebral blood flow reserve</td>
<td></td>
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<tr>
<td>Gupta et al9</td>
<td>A positive relationship was observed between baseline cerebrovascular reserve impairment and increased risk of stroke/TIA (summarized random effects OR, 3.96; 95% CI, 2.69–6.04)</td>
</tr>
<tr>
<td>Intraplaque hemorrhage using MRI</td>
<td></td>
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<tr>
<td>Singh et al11</td>
<td>Of the 96 carotid arteries included, 36 had MRI-depicted intraplaque hemorrhage (36.6%)</td>
</tr>
<tr>
<td>Hellings et al14</td>
<td>Patients with intraplaque hemorrhage had a &gt;2-fold higher risk for the occurrence of stroke compared with patients without intraplaque hemorrhage (OR, 2.1; 95% CI, 1.1–4.4)</td>
</tr>
<tr>
<td>van Lammeren et al15</td>
<td>The carotid plaques from ACS patients (n=182) had less frequently intraplaque hemorrhage (21 of 182 vs 25 of 82 or 8.4% vs 3.9%, respectively; HR, 2.1; 95% CI, 1.1–4.4)</td>
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<tr>
<td>Silent embolic events on brain CT or MRI</td>
<td></td>
</tr>
<tr>
<td>Kakkos et al11</td>
<td>The mean annual stroke rate was 0.4% in 706 patients with a JBA &lt;4 mm2, 1.4% in 171 patients with a JBA 4–8 mm2, 3.2% in 46 patients with a JBA 8–10 mm2, and 5% in 198 patients with a JBA &gt;10 mm2 (P&lt;0.001)</td>
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<td>Of the 59 ipsilateral ischaemic strokes, 42 (71%) occurred in the 244 patients (22% of the cohort) who had a JBA 8 mm2</td>
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<tr>
<td>Plaque ulceration on 3D ultrasound</td>
<td></td>
</tr>
<tr>
<td>Topkian et al9</td>
<td>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)</td>
</tr>
<tr>
<td>Plaque echolucency in combination with TCD emboli was associated with a &gt;10-fold higher ipsilateral stroke risk (HR, 10.61; 95% CI, 2.39–47.82; P=0.003)</td>
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<tr>
<td>Progression in the severity of ACS</td>
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<tr>
<td>Balsevistri et al10</td>
<td>Progression of ACS was strongly associated with the risk of ipsilateral stroke (HR, 31.97; 95% CI, 9.83–103.91; P&lt;0.001)</td>
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<tr>
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<td>Higher risk for the development of stroke/TIA after adjustment for carotid IMT (HR, 8.56; 95% CI, 1.72–42.55; P=0.02)</td>
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<tr>
<td></td>
<td>P=0.05).</td>
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<td>When embolic signals were present vs absent, respectively (P=0.005)</td>
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<tr>
<td>Conrad et al11</td>
<td>Plaque progression occurred in 262 arteries and 36 (13.7%) of these developed symptoms of ipsilateral stroke and 22 (17.0%) had a TIA</td>
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<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Plaque ulceration on 3D ultrasound</td>
<td></td>
</tr>
<tr>
<td>Modan et al10</td>
<td>Patients with ≥3 atherosclerotic plaques (OR, 4.25; 95% CI, 1.19–15.07; P=0.02)</td>
</tr>
<tr>
<td></td>
<td>Progression of ACS was strongly associated with the risk of ipsilateral stroke (HR, 6.43; 95% CI, 1.36–30.44; P=0.019)</td>
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<td></td>
<td>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).</td>
</tr>
<tr>
<td>Study Study Outcome</td>
<td></td>
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</tbody>
</table>
| 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.
뇌혈류 예비력의 감소

여러 연구에서 뇌혈류 예비력의 손상이 ACS 환자에서 뇌졸중의 발생과 연관되어 있음을 보고하였다. 스트레스와의 관계로 혈관의 확장과 축소를 일으키는 대뇌혈관자동조절(cerebrovascular autoregulation)과 미생물, 염증의 조절, 혈전소의 증가 등이 이에 기여한다. 뇌혈류 예비력의 감소는, 혈관내경기저감소증(vessel enlargement), 혈관내경기저감소증증후군(vessel enlargement syndrome)의 특성을 보이며, 뇌혈류예비력의 감소는 뇌졸중 위험을 증가시킨다. ACS의 중증도의 진행

약물치료를 받은 ACS 환자와 자연 경과에 대한 여러 연구에서 혈관 장애의 진행과 같은 영역의 뇌혈관사건의 위험성 사이의 연관성을 조사하였다. ACS의 중증도의 진행

자기공명영상에 사용한 죽상경화반내 출혈 확인

자기공명영상(CA/CEA)을 시행한 47명의 환자를 포함한 자기공명영상 연구에서 죽상경화반내 출혈 여부와 신생혈관을 시사하는 혈관외막(adventitia)의 조영증강이 이전에 뇌졸중이 있던지 여부와 독립적인 연관성을 보였다. 50%~70%의 혈착 정도를 보이는 남성 ACS 환자 75명을 대상으로 한 연구에서는, 자기공명영상은 이화에서 98개의 뇌혈관내경기저감소증을 확인하였다. 이들 고위험군에서, 25개월의 추적기간 동안 2개의 뇌졸중과 4개의 일상성혈관적 출혈이 발생했다. 뇌졸중이나 일상성혈관적 출혈을 뇌혈관네경기저감소증에 증가된 경우 자기공명영상에서 뇌졸중의 위험을 확인할 수 있었다. 뇌혈관장애에 대한 자기공명영상의 가치와 관련하기는 지금까지의 근거로는 부족함이 있지만, 전향적으로 검증되지 않았다. 또한 이는 보험이 적용되지 않는다.
50%에서 69%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.

가장 최근에 발표된 연구(ACSRS)에서는 경동맥 팽대부 대비 50%에서 99%의 협착 정도를 보인 ACS 환자 1,121명의 환자를 대상으로 했는데, 추적관찰 기간 4년 동안 죽상경화반이 호전된 경우는 43개(3.8%), 변화가 없는 경우는 856개(76.4%), 진행은 222개(19.8%)로 나타났다.19 고위험군(평균 연간 뇌졸중 발생률 2.0%)에는 추적기간 중 발생한 59례의 뇌졸중 중 19례(32%)가 포함되었다. 진행하지 않은 군에서 평균 연간 뇌졸중 발생률은 1.12%였으며, 호전된 경우는 0% 이었다.20 첫 진단 당시 혈착 정도가 80%에서 99% 사이(원위부 내경동맥 기준으로 70%~99%)의 환자에서, 동측에 혈관내경 8 mm2를 넘는 검은색 음영이 있는 경우, 저에코죽상경화반 내에 분산된 흰색 병변이 존재하는 경우)11에서 뇌졸중 위험이 증가하며, 그러므로 예방적 CEA나 경동맥스텐트삽입술을 고려해야 한다는 것을 뒷받침한다. 앞으로 사용될 수 있을만한 다른 방법은 3차원 초음파에서 관찰되는 궤양이다.22

현실적으로 위에서 검토한 모든 연구의 제한점은 이들이 최적의 약물치료가 아닌 시대에 이루어진 연구라는 것이다. 이들 연구의 많은 수는 현재 최적의 약물치료라고 생각되는 상황에 있는 코호트에서의 반복 연구가 필요하다. 앞의 연구들의 긍정적인 연구 결과들은 일반적인 의료행위에서 위험도 계측 방법으로 받아들여질 만하다.

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