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)

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/anterior 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 strategies6 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 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.11 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

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<td>Intraplaque hemorrhage using MRI</td>
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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.10–11 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.30–31 Average follow-up was 24 months. Raw data are not available in 1.30 Impaired cerebrovascular reserve was present in 183 (75%) of the 244 included in the remaining three studies.30–32 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.

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 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.

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.38–40 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.13–14 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.
plaque area ≥ increased stroke risk and should be considered for prophylactic stratification. Another example is the combination of gray matter in a hypoechoic plaque), which are independent predictors of stroke risk. 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. 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.

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 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. Another example is the combination of gray scale median score with TCD microembolic signals. A low gray scale median score is an independent predictor for an increased risk of stroke during carotid intervention.

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 or silent embolic infarcts on brain CT/MRI scans, those with reduced cerebrovascular reserve, ACS severity progression despite MT history of contralateral stroke/TIA, size of black juxtaluminal plaque area ≥ 8 mm² without a visible echogenic cap) 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.

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.)
초음파를 이용한 불안정성 경동맥즉석증화반의
규명

ACS 환자가 내과학적 치료받은 경우에 대한 최대규모 전향적 연구인 Asymptomatic Carotid Stenosis and Risk of Stroke (ACRSRS) 연구[11,20,29]에서 최근 보고한 바에 따르면, 모든 ACS 환자
의 뇌졸중 위험률이 모두 같은 것은 아니라는 것을 분명히 확인하였다. ACSRS 연구에서는 50%~99%의 협착을 보이는 ACS 환자
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Reduced cerebral blood flow reserve

Gupta et al[16] | A positive relationship was observed between baseline cerebrovascular reserve impairment and increased risk of stroke/TIA (summarized random effects OR, 3.36; 95% CI, 2.60–6.04) |  |

Intraplaque hemorrhage using MRI

Singh et al[17] | 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, 3.39; 95% CI, 2.48–7.41; P<0.001) |  |

Heddins et al[18] | Patients with intraplaque hemorrhage had a >2-fold higher risk for the occurrence of stroke compared with patients without intraplaque hemorrhage (50 of 591 vs 257 of 227 or 8.4% vs 3.9%, respectively; HR, 2.1; 95% CI, 1.1–4.4) |  |

van Lammereen et al[19] | The carotid plaques from ACS patients (n=182) had less frequently intraplaque hemorrhage (21 of 182 vs 9 of 227 or 11.5% vs 30.5%, respectively; P=0.005) compared with patients with ipsilateral events >6 mo before CEA (n=82) |  |

Ishii et al[20] | 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[21] | 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) |  |

Miao et al[22] | During an average follow-up of 4.1±2.0 y (range, 1–105 mo), the presence of SCI was associated with a >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) |  |

Progression in the severity of ACS

Balestrini et al[23] | Progression of ACS was detected in 129 patients (24.7%). Of these, 35 patients (27.1%) had an ipsilateral stroke and 22 (17.1%) 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<0.001) |  |

Kakkos et al[24] | The 8-year cumulative ipsilateral cerebral ischemic stroke rate was 9% 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<0.005 |  |

Conrad et al[25] | 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

Modan et al[26] | 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. |  |
경우)가 하나의 변수를 사용하는 것보다 더 좋다는 것도 증명했다.\(^{11}\) 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,\(^{11}\) 연구에 참여하는 80개 센터의 음파기사들 대상 1일 코스의 훈련으로 충분했다. 훈련뿐 아니라, 비용 문제도 있으며 이 분석이 지역사회 상황에서도 쉽게, 믿을만한 수준으로 시행될 수 있음을 여부도 문제가 된다.

뇌혈류 예비력의 감소

여러 연구에서 뇌혈류 예비력의 손상이 ACS 환자에서 뇌졸중의 발생과 연관되어 있음을 보고하였다.\(^{30−33}\) 월리스와는 불안정하여 반대쪽의 폐색이 있는 경우 경동맥혈착의 정도가 증가함에 따라 뇌혈류 예비력이 감소한다.\(^{11}\) ACSRS 연구에서는,\(^{11}\) 연구에 참여하는 80개 센터의 음파기사들 대상 1일 코스의 훈련으로 충분했다. 훈련뿐 아니라, 비용 문제도 있으며 이 분석이 지역사회 상황에서도 쉽게, 믿을만한 수준으로 시행될 수 있음을 여부도 문제가 된다.

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뇌혈류 예비력의 감소와 뇌졸중 위험간의 연관성을 요약한 메타분석에서 뇌혈류 장애를 보인 무증상 환자에서 뇌졸중의 위험은 4배 가까이 증가하는 것으로 나타났다.\(^{12}\) 나이, 성별, 혈압, 혈당, 고혈압, 고지혈증 등의 위험인자를 고려한 상태에서 ACS 환자에서 뇌혈류 예비력의 손상이 뇌졸중의 위험을 증가시킨 것으로 보고되었다.\(^{30−33}\) ACS 연구에서는,\(^{11}\) 연구에 참여하는 80개 센터의 음파기사들 대상 1일 코스의 훈련으로 충분했다. 훈련뿐 아니라, 비용 문제도 있으며 이 분석이 지역사회 상황에서도 쉽게, 믿을만한 수준으로 시행될 수 있음을 여부도 문제가 된다.\(^{11}\)

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50%에서 69%의 협착 정도를 보인 ACS 523명 환자의 1,121개 경동맥을 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 발생률은 0.4%였으며, 호전된 경우는 0%이었다. 이 연구 결과는 특정 ACS 환자(즉, TCD에서 미세색전이 관찰되는 경우, 11,22,23 또는 뇌 컴퓨터단층촬영이나 자기공명영상에서 무증상 캔선성뇌경색이 있는 경우, 17,18,34–37 뇌혈관 예비력이 감소한 경우, 12,30–33 적절한 약물치료에도 불구하고 ACS의 진행이 진행하는 경우, 19–21 반대측의 뇌졸중이나 일과성허혈발작 병력이 있는 경우, 에코발생막이 보이지 않고 혈관내경 근접부위에 8 mm\(^2\)를 넘는 검은색 음영이 있는 경우)에서는 뇌졸중 위험이 증가하며, 그러므로 예방적 CEA나 경동맥스텐트삽입술을 고려해야 한다는 것을 뒷받침한다. 앞으로 사용될 수 있을만한 다른 방법은 3차원 초음파에서 관찰되는 궤양이다. 

현실적으로 위에서 검토한 모든 연구의 제한점은 이들이 최적의 약물치료가 아닌 시대에 이루어진 연구라는 것이다. 이들 연구의 많은 수는 현재 최적의 약물치료라고 생각되는 상황에서 이루어진 연구로, 이들 연구의 많은 수는 현재 최적의 약물치료라고 생각되는 상황에 있는 코호트에서의 반복 연구가 필요하다. 앞의 연구들의 균일성은 연구결과들은 일반적인 의료행위에서 위험도 계측 방법으로 받아들일만하다.

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