Doppler Embolic Signals in Cerebrovascular Disease and Prediction of Stroke Risk
A Systematic Review and Meta-Analysis

Alice King, BSc (Hons); Hugh S. Markus, DM, FRCP

Background and Purpose—Asymptomatic embolic signals (ES) detected using transcranial Doppler have been reported in patients with potential cerebral embolic sources. They may be useful in risk stratification and in assessing therapies. First, it is essential to show whether they predict stroke risk.

Methods—A systematic review and meta-analysis was performed to determine the prognostic value of ES in different potential cerebral embolic sources. Studies were identified that used transcranial Doppler to detect ES and included prospective stroke/TIA follow-up. Numbers of ES-positive and ES-negative patients were extracted with stroke/TIA and stroke alone outcomes.

Results—ES are most frequent in large artery disease, less frequent in cardioembolic stroke, and infrequent in lacunar stroke. Data relating ES to future stroke risk were available for acute stroke, large artery disease, and the perioperative period of carotid endarterectomy. For symptomatic carotid stenosis, ES predicted stroke alone (OR, 9.57; 95% CI, 1.54 to 59.38; \( P = 0.02 \)) and stroke/TIA (OR, 6.36; 95% CI, 2.90–13.96; \( P < 0.00001 \)). For asymptomatic carotid stenosis, ES predicted stroke alone (OR, 7.46; 95% CI, 2.24–24.89; \( P = 0.001 \)) and stroke/TIA (OR, 12.00; 95% CI, 2.43–59.34; \( P = 0.002 \)) but with heterogeneity (\( P = 0.004 \)). In acute stroke ES predicted stroke alone (OR, 2.44; 95% CI, 1.17–5.08; \( P = 0.02 \)) and stroke/TIA (OR, 3.71; 95% CI, 1.64–8.38; \( P = 0.002 \)). A high frequency of ES immediately after carotid endarterectomy predicted stroke alone (OR, 24.54; 95% CI, 7.88–76.43; \( P < 0.00001 \)) and stroke/TIA (OR, 32.04; 95% CI, 11.36–90.39; \( P < 0.00001 \)).

Conclusion—ES predict stroke risk in acute stroke, symptomatic carotid stenosis, and postoperatively after carotid endarterectomy; in asymptomatic carotid stenosis, data are less robust. In these conditions ES may be useful in risk stratification and in assessing therapeutic efficacy. For other embolic sources, further prospective data are required. (Stroke. 2009; 40:3711-3717.)

Key Words: carotid stenosis ● cerebrovascular disease ● embolism ● ultrasound

Diagnosis of embolic stroke is usually made by identifying a potential embolic source in a patient with stroke, ie, by guilt by association. Only occasionally can emboli be seen either in the retina or on brain imaging. Using transcranial Doppler, it is possible to detect asymptomatic circulating cerebral emboli. This technique has potential applications in diagnosis, localization of the embolic source, and most importantly, in prediction of risk. Emboli back scatter and reflect more of ultrasound than surrounding red blood cells. They appear as high-intensity signals, which are of short duration as they rapidly pass through the sample volume. Studies in animal and laboratory models have shown the technique has a high sensitivity and specificity for detection of a variety of embolic materials including thrombus, platelet aggregates, and atheroma.1–3 Embolic signals (ES) have been detected in patients with a wide variety of potential embolic sources (Table). TIA is a strong predictor of recurrent stroke risk and is usually believed to be caused by emboli. By analogy one might expect asymptomatic ES to predict risk. This has led to the technique being increasingly used to direct patient management, and as a surrogate marker of antithrombotic drug efficacy.4 However, before this it is essential to show that ES do predict future stroke risk. This needs to be demonstrated individually for different potential embolic sources; it is possible that the presence of ES may have different clinical significance in different conditions.

We performed a systematic review and meta-analysis to identify whether ES are independent predictors of future stroke and TIA risk for different potential cerebral embolic sources.

Materials and Methods

Studies containing information on the relationship between ES and future stroke and TIA risk were identified by a defined search strategy. Only prospective studies were included.
Search Strategy
MEDLINE, EMBASE, and PubMed were searched between January 1, 1990 and July 15, 2009. Limits were articles on humans and in English. Search terms were “transcranial Doppler” or “transcranial Doppler” or “ultrasound” or “ultrasonography” and “embolic signals” or “HITS” or “emboli” or “cerebral embolism” or “embolic particles” or “MES” or “microembolic signals” and “stroke” or “transient ischemic attack” or “transient ischaemic attack” or “amaurosis fugax” or “death.” Reference lists of articles fulfilling the inclusion criteria and reviews were hand-searched.

Articles were excluded if they:
1. Did not provide data on future stroke/TIA events
2. Used transcranial Doppler-detected ES to guide administration/dosage of drugs to reduce ES
3. Were retrospective
4. Provided insufficient data to construct 2×2 contingency tables
5. Were case reports or series including <5 subjects

Data Extraction and Management
Studies meeting the inclusion criteria were assessed by 2 researchers. In the event of divergent analysis, a consensus was achieved by discussion. If appropriate data were available for a subset of patients in an article, this subset was included. For duplicate data, the article with the greatest number of subjects was included.

Studies were split into subgroups according to potential embolic source. The numbers of ES-positive and ES-negative patients were extracted for 2 outcomes, stroke or TIA and stroke alone. For patients after CEA, when ES frequency can be very high, analysis was also performed according to high vs low rates of ES. When

<table>
<thead>
<tr>
<th>Group</th>
<th>List of Conditions</th>
<th>ES Detected</th>
<th>Prospective Follow-Up</th>
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<tbody>
<tr>
<td>Acute stroke/TIA</td>
<td>Acute stroke/TIA</td>
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<td>Large vessel disease</td>
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<td>Extracranial</td>
<td>Symptomatic carotid stenosis</td>
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<td>Asymptomatic carotid stenosis</td>
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<td>Carotid occlusion</td>
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<td>Symptomatic vertebral stenosis</td>
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<td>Cervical artery dissection</td>
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<td>Takayasu arteritis</td>
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<td>Aortic atherosclerosis</td>
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<td>Intracranial stenosis</td>
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<td>Basilar artery fibromuscular dysplasia</td>
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<td>Carotid intervention</td>
<td>Carotid endarterectomy</td>
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<td>Carotid stenting</td>
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<td>Angiography</td>
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<td>Nonvalvular atrial fibrillation</td>
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<td>Myocardial infarction</td>
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<td>Patent foramen ovale</td>
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<td>Mechanical/prosthetic heart valves</td>
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<td>Bacterial endocarditis</td>
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<td>Native heart valvular disease</td>
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<td>Pulmonary vein antrum isolation</td>
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<td>Cardiac catheterization</td>
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<td>Cardiopulmonary bypass</td>
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<td>Coronary artery bypass grafting</td>
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<td></td>
<td>Aortic valve replacement</td>
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<td></td>
<td>Transcatheter closure of patent foramen ovale</td>
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<td>Aneurysmal subarachnoid hemorrhage</td>
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<td>Systemic lupus erythematosus</td>
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<td>Polycythemia rubra vera</td>
<td>+</td>
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<tr>
<td>Orthopaedic</td>
<td>Fat embolism after long-bone fracture</td>
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<td>Hip arthroplasty</td>
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++ indicates data from >1 study; +, data from 1 study; –, no data reported.
stroke alone data were not specified, corresponding authors were contacted.

**Data Synthesis and Statistical Analysis**

Subgroup analysis and investigation of heterogeneity was performed. RevMan 5 (http://www.cc-ims.net/revman) was used to generate a pooled estimate for each subgroup. A random effects model by DerSimonian and Laird (supplemental ref s1, available online at http://stroke.ahajournals.org/) was used to calculate odds ratios with 95% CI and Mantel-Haenszel weights. Heterogeneity was present between studies even within subgroups; therefore, a random effects model was used.

**Findings**

The prespecified search strategy retrieved 1674 abstract articles from PubMed (1133), Medline (278), and EMBASE (263). Sixty studies were identified on abstract screening and, after reading full-text articles, 30 of these studies met all inclusion criteria and were included in the meta-analysis.

Studies reported the detection of ES in patients with a wide variety of potential embolic sources (Table). However, for many conditions data were only from cross-sectional studies, and prospective studies relating the presence of ES to future risk were available in only a number of conditions, namely acute stroke and TIA, symptomatic carotid stenosis, asymptomatic carotid stenosis, and CEAs. Forest plots summarizing the meta-analyses for these conditions are shown in Figures 1 and 2.

**Results**

**Acute Stroke and TIA**

ES have been detected in between 9.3% and 71% of patients in the acute phase after TIA and stroke (and supplemental refs s2–s10). Studies have consistently shown they are most frequent in patients with large artery disease, less frequent in those with cardioembolic stroke, and infrequent or absent in patients with lacunar stroke (and supplemental refs s5–s8, s11–s13).

Eight studies (n = 737) were identified for the acute stroke subgroup. Monitoring was performed from the middle cerebral artery for 20 minutes in 2 studies, 30 minutes in 2, and 60 minutes in 4. Six of the studies limited themselves to anterior circulation stroke alone, whereas 2 included all ischemic stroke.

The presence of ES predicted risk of both stroke alone (OR, 2.44; 95% CI, 1.17–5.08; P = 0.02; heterogeneity 0.25) and the combined end point of stroke/TIA (OR, 3.71; 95% CI, 1.64–8.38; P = 0.002; heterogeneity P = 0.07).

**Large Vessel Disease**

**Symptomatic Carotid Stenosis**

Many studies have detected ES in patients with symptomatic carotid stenosis; ES has been detected in ~40% of patients if recordings are made for 1 hour. Their presence correlates with known markers of increased risk including: recent symptoms (and supplemental refs s14–s17), ulcerated plaques (supplemental refs s16, s18–s20, and stenosis (and supplemental refs s2, s20–s23), and is reduced in cases of near occlusion with distal collapse (supplemental ref s23).

Four studies (n = 270) were identified that met the inclusion criteria. The presence of ES predicted risk of both stroke alone (OR, 9.57; 95% CI, 1.54–59.3; P = 0.02; heterogeneity P = 0.78) and the combined end point of stroke/TIA (OR, 6.36; 95% CI, 2.90–13.96; P < 0.00001; heterogeneity P = 0.83).

**Asymptomatic Carotid Stenosis**

ES are less frequent in asymptomatic than symptomatic carotid stenosis (and supplemental refs s1, s17–s18, s22, s24). Five prospective studies (n = 677) were identified meeting inclusion criteria. The presence of ES predicted stroke alone (OR, 7.46; 95% CI, 2.24–24.89; P = 0.001; heterogeneity P = 0.23). It also predicted the combined end point of stroke/TIA (OR, 12.00; 95% CI, 2.43–59.34; P = 0.002), but there was significant heterogeneity (P = 0.004). There were 2 larger studies examining this relationship and they produced divergent results, 1 negative and 1 positive.

**Other Large Artery Disease**

A single study (n = 114) in middle cerebral artery stenosis found the presence of ES (detected in 22%) during a single hour, recordings predicted future stroke/TIA (OR, 8.45; 95% CI, 1.69–42.22; P = 0.01).

**Cervical Artery Dissection**

A single small study in 28 subjects suggested ES (detected in 46%) may be predictive of early ischemic recurrence in acute internal carotid artery dissection.

**Perioperative Period During CEA**

ES have been detected at all stages during CEA. It is unclear whether those occurring after arterial opening and before vessel closure are attributable to air emboli accidentally introduced or attributable to solid emboli. The former, although having lesser clinical significance, produce more intense signals because of greater reflection and backscattering of ultrasound at the air–blood interface. However, ES occurring during the dissection phase (ie, before arterial opening) and after skin closure are believed to be attributable to solid ES and have been suggested as potential risk markers.

Five studies (n = 779) were identified that correlated outcome with monitoring during the dissection phase. An analysis using the outcome stroke/TIA was not used because identifying TIA during general anesthesia is not possible. Very high rates of ES have been reported in this setting and a further analysis of the predictive value of very frequent ES was performed (supplemental ref s25). A high frequency of ES during the dissection phase predicted stroke alone (OR, 14.79; 95% CI, 5.15–42.47; P < 0.00001; heterogeneity P = 0.56).

Six studies (n = 649) monitoring in the immediate period after CEA were identified. For 5 of these, data on the end point stroke alone was available. The presence of ES did not predict postoperative stroke risk (OR, 2.53; 95% CI, 0.83–7.74; P = 0.10; heterogeneity P = 0.99). Data for the end point of stroke or TIA were available for all 6 studies; the presence of ES predicted stroke/TIA (OR, 3.56; 95% CI, 1.37–9.22; P = 0.009; heterogeneity P = 0.97). ES rates are often high; therefore, a second analysis was performed comparing high vs low ES. The cut-off used to identify high ES in the original studies were used and varied between >10 ES min−1 and >0.25 ES min−1. A high frequency of ES after CEA predicted stroke alone (OR, 24.54; 95% CI, 7.88–76.43; P < 0.00001; heteroge-
Cardioembolic Sources

ES have been reported in patients with a wide variety of cardioembolic sources. With the exception of mechanical prosthetic valves their frequency is lower than in those in patients with symptomatic large artery disease\(^3\) (and supplemental refs s8, s11, s13).

Only 2 studies were identified that met criteria for cardioembolic stroke (supplemental refs s26, s27). The first study was of myocardial infarction, the second was of patients with

Figure 1. The presence of ES and the combined end point of future stroke/TIA. Forest plots (A) of random effects meta-analysis showing odds ratios for ES-positive vs ES-negative patients and stroke/TIA outcome separated by potential embolic source. Relationship (B) between high ES count and the combined end point of future stroke/TIA. Forest plots of random effects meta-analysis showing odds ratios for high ES rate vs low ES rate and stroke/TIA outcome.
Figure 2. The presence of ES and future stroke alone risk. Forest plots (A) of random effects meta-analysis showing odds ratios for ES-positive vs ES-negative patients and stroke outcome separated by potential embolic source. Relationship (B) between high ES count and the future stroke alone. Forest plots of random effects meta-analysis showing odds ratios for high ES rate vs low ES rate and stroke outcome.
The lack of large, multicenter, prospective studies determining prognostic significance, the expertise required to analyze and interpret recordings, and the lack of reliable automated systems for ES detection.

In asymptomatic carotid stenosis, meta-analysis demonstrated an association but with heterogeneity in the analysis of future stroke/TIA risk. This reflects conflicting results of the 2 large studies in this area. These studies had important methodological differences, including one with a single baseline recording, whereas the second repeated recordings at 6 monthly intervals. Further studies are required in this area, and the International Asymptomatic Carotid Emboli Study, which has recruited 482 patients, will finish follow-up in late 2009 and results are expected in 2010.

Transcranial Doppler is widely used to detect ES during and immediately after CEA. After arterial opening, air is introduced. Small air bubbles, despite resulting in high-intensity ES, have limited clinical significance, but are impossible to differentiate from potentially more serious solid ES using current transcranial Doppler systems. Not surprisingly, associations have only been detected in situations when gaseous ES are not present, namely the dissection phase (before arterial opening) and the postoperative phase (after arterial closure). During both phases a high rate of ES predicted stroke risk and was more strongly associated than the presence or absence of ES. These data support the use of ES monitoring in this clinical setting.

In contrast to the data relating large artery disease to future risk, there are limited data in cardioembolic stroke but that data available suggest ES are less frequent. In atrial fibrillation, ES were only detected in 10% of patients (supplemental ref s35), there was variability between results of recordings performed on different days, although ES did appear less frequent in patients treated with anticoagulation (supplemental ref s36).

One cardioembolic source in which high ES frequencies have been reported is mechanical cardiac valves, with frequencies as high as >100 per hour (supplemental ref s34). The parallel between this high ES frequency and the high clinical stroke risk suggested a possible prognostic value. However, ES were found to be more intense than expected from thrombus (supplemental ref s12), and ES frequency was not altered by anticoagulation, (and supplemental refs s11, s13, s28, s37), suggesting that they might not represent thromboembolic material. Further studies showed ES frequency was reduced by altering atmospheric pressure in a barometric chamber (supplemental refs s38, s39), or by increasing inspired oxygen concentration (supplemental refs s29, s40–s42), consistent with this representing gaseous bubbles, perhaps resulting from cavitation at the valve surface. This emphasizes the fact that ES may have different implications in patients with different embolic sources. A recent study (supplemental ref s43) used a novel method of trying to separate solid from gaseous ES and suggested “solid” ES might predict risk in this group, although most recurrent events were TIA and there was only 1 stroke during follow-up. Furthermore, it has been suggested that the technique used for differentiation of solid ES is not reliable.

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Emboli resulting from different embolic sources have different composition and respond differently to treatment. For example, anticoagulants are more effective for cardioembolic stroke, whereas antiplatelet agents appear more effective for emboli from large artery atherosclerotic plaques. For this reason, it is important that the prognostic significance of ES is determined separately for different potential embolic sources. This review found data consistent with ES in different conditions having differing clinical significance.

ES have been consistently detected in some patients with acute ischemic stroke, and in this group are more frequent in the large artery stroke subtype, less frequent in cardioembolic stroke, and absent or rare in lacunar stroke. On meta-analysis significant associations were found with both future stroke and stroke/TIA. This association appeared to be largely attributable to the relationship within the subgroup of patients with large vessel stroke.

In symptomatic carotid stenosis, studies have consistently shown an association between ES and future stroke and TIA risk. Meta-analysis confirmed a highly significant association, although the majority of patients (more than two-thirds) were obtained from 1 study. Further evidence supporting this association comes from the multicenter CARESS trial in which an association was found between baseline ES frequency and 7-day stroke/TIA risk. Patients were only included if they had ES at baseline; therefore, these results could not be incorporated in our meta-analysis. Another intervention study provided further evidence for a causal relationship with stroke risk. ES-positive patients, who then become ES-negative after treatment with aspirin, had a similarly low risk compared to patients who were ES-negative at baseline (supplemental ref s32). Therefore, there is considerable evidence of ES to predict stroke risk. Importantly, it has been shown on multivariate analysis that ES independently predict risk to a greater degree than conventional markers, such as time from symptoms and stenosis, (and supplemental ref s32). Associations have been examined on different days, although ES did appear less frequent. In atrial fibrillation, ES were only detected in 10% of patients (supplemental ref s35), there was variability between results of recordings performed on different days, although ES did appear less frequent in patients treated with anticoagulation (supplemental ref s36).

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In summary, this review provides strong evidence that ES predicts future ipsilateral stroke risk in patients with large artery disease, particularly symptomatic carotid stenosis. A high frequency also is a strong risk predictor in the immediate postoperative period after CEA and during the dissection phase of CEA. Data are promising in asymptomatic carotid stenosis, although further studies are required. In other conditions, further prospective data are required.

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None.

References
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