Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis

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Objectives: This study tested the hypothesis that silent embolic infarcts on computed tomography (CT) brain scans can predict ipsilateral neurologic events and stroke in patients with asymptomatic internal carotid artery stenosis. Methods: In a prospective multicenter natural history study, 821 patients with asymptomatic carotid stenosis graded with duplex scanning who had CT brain scans were monitored every 6 months for a maximum of 8 years. Duplex scans were reported centrally, and stenosis was expressed as a percentage in relation to the normal distal internal carotid criteria used by the North American Symptomatic Carotid Endarterectomy Trialists. CT brain scans were reported centrally by a neuroradiologist. In 146 patients (17.8%), 8 large cortical, 15 small cortical, 72 discrete subcortical, and 51 basal ganglia ipsilateral infarcts were present; these were considered likely to be embolic and were classified as such. Other infarct types, lacunes (n = 15), watershed (n = 9), and the presence of diffuse white matter changes (n = 95) were not considered to be embolic.

Results: During a mean follow-up of 44.6 months (range, 6 months-8 years), 102 ipsilateral hemispheric neurologic events (amaurosis fugax in 16, 38 transient ischemic attacks [TIAs], and 47 strokes) occurred, 138 patients died, and 24 were lost to follow-up. In 462 patients with 60% to 99% stenosis, the cumulative event-free rate at 8 years was 0.81 (2.4% annual event rate) when embolic infarcts were absent and 0.63 (4.6% annual event rate) when present (log-rank P = .032). In 359 patients with <60% stenosis, embolic infarcts were not associated with increased risk (log-rank P = .65).

In patients with 60% to 99% stenosis, the cumulative stroke-free rate was 0.92 (1.0% annual stroke rate) when embolic infarcts were absent and 0.71 (3.6% annual stroke rate) when present (log-rank P = .002). In the subgroup of 216 with moderate 60% to 79% stenosis, the cumulative TIA or stroke-free rate in the absence and presence of embolic infarcts was 0.90 (1.3% annual rate) and 0.65 (4.4% annual rate), respectively (log-rank P = .005).

Conclusion: The presence of silent embolic infarcts can identify a high-risk group for ipsilateral hemispheric neurologic events and stroke and may prove useful in the management of patients with moderate asymptomatic carotid stenosis.


Currently, the decision to perform prophylactic carotid endarterectomy (CEA) in asymptomatic patients is based mainly on the presence of a hemodynamically significant 60% to 99% internal carotid artery stenosis in relation to the normal lumen of the distal internal carotid artery. Compared with best medical treatment alone, this strategy reduces the risk of ipsilateral stroke, as shown by the Veterans Administration (VA) study, the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST). The midterm overall risk reduction is minimal, however; the ACAS reported that in patients with stenosis >60%, CEA reduced the annual risk of stroke from 2% to 1%, which implies that approximately 20 procedures need to be performed to prevent one stroke in 5 years.

For this reason, there is considerable debate on the appropriateness of this procedure in all patients with asymptomatic carotid stenosis, and restriction to patients who are at high risk of developing neurologic events might be more cost-effective. Previous studies in asymptomatic patients have associated severe carotid stenosis, echolucent and heterogeneous carotid plaques on ultrasound imaging, and carotid stenosis with contralateral carotid artery occlusion with an increased rate of ipsilateral neurologic events. In contrast, a more conservative approach would certainly be desired in very elderly patients, in settings where the operative stroke risk is high, or in patients with very low stroke risk without surgery, because CEA is less cost-effective in those circumstances.
The presence of silent brain infarction (SBI) on magnetic resonance imaging (MRI) or computed tomography (CT) scanning has been associated with an increased risk of stoke in the general population,14-16 in the perioperative period in patients having CEA,17 and during long-term follow-up after CEA.18 The aim of the present study was to test the hypothesis that silent embolic infarcts on CT brain scans can predict ipsilateral neurologic hemispheric events and stroke in patients with asymptomatic internal carotid artery stenosis.

METHODS

During a 5-year period, 1121 patients with asymptomatic carotid stenosis graded with duplex scanning were enrolled in the Asymptomatic Carotid Stenosis and Risk of Stroke (ACRS) prospective natural history study. CT brain scanning upon admission to the study was optional and performed in 821 patients who are the subjects of this report.

Aims of ACRS study. ACRS is an international multicenter study under the auspices of the International Union of Angiology aiming to study patients with asymptomatic 50% to 99% stenosis in relation to the carotid bulb diameter according to the European Carotid Stenosis Trial (ECST) method and to monitor them for at least 5 years to identify subgroups at high and low risk for future neurologic events.

The study protocol was approved by the Multicenter Research Ethics Committee (North Thames, London, United Kingdom), and local ethics committees and patients were admitted to the study after informed consent. The methodology used in the ACRS study, eligibility of participating centers, and quality control procedures have been published in detail previously.19 A brief outline of the methodology used in ACRS is presented.

Admission to the study. Patients with internal carotid artery diameter stenosis >50% (ECST method) on duplex scanning who had never had any ipsilateral hemispheric or retinal symptoms and did not have any neurologic abnormality on examination were eligible for admission to the study. Patients who had contralateral hemispheric symptoms were also included provided they had been asymptomatic for at least 6 months at the time of recruitment. The side with the more severe stenosis was considered to be the ipsilateral side for any patient with bilateral stenosis.

Risk factors. The presence of conventional atherosclerotic risk factors, their duration, and severity, including the presence of cardioembolic conditions (atrial fibrillation and history of myocardial infarction), was recorded.

Grading of ICA stenosis. Duplex scanning was performed on admission to the study and subsequently every 6 months to grade internal carotid artery stenosis. The team, which included a neurologist, reviewed each patient at all visits to provide clinical information. Doppler velocity recordings in the common and internal carotid arteries were obtained with the ultrasound beam as close as possible to an angle of 60° to the axis of flow. Velocity criteria used for grading the degree of stenosis in terms of the method used in the ECST (stenosis in relation to the carotid bulb diameter) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (percentage of diameter stenosis in relation to the normal distal internal carotid) have been previously published.20

Because absolute velocity measurements could underestimate stenosis (eg, in the presence of cardiac arrhythmia) or overestimate stenosis (eg, in the presence of severe contralateral disease), the ultrasonographers at each center were trained to use a combination of absolute intrastenotic peak systolic and diastolic velocity measurements and velocity ratios, using the prestenotic common carotid artery as reference point. For the purpose of the current study, the NASCET method was used to grade carotid artery stenosis and is reported as such throughout the current report.

In plaques that were not calcified, anatomic criteria (percentage diameter stenosis) using color flow or power Doppler imaging of the artery in transverse section was used to supplement velocity criteria. The entire duplex examination was recorded on videotape and reported centrally.

CT brain scanning. Noncontrast CT brain scan films were reported centrally by an experienced neuroradiologist (J. S.), and any ischemic damage was classified using the Stevens classification:21

1. Discrete subcortical were small, well-circumscribed hypodense lesions, usually only a little greater than 1 cm in size, adjacent to apparently noninvolved cerebral cortex in the anterior and middle cerebral artery territory.
2. Large cortical infarcts had cortical distribution occupying usually >50% of the entire anterior and middle cerebral artery territories.
3. Small cortical infarcts had cortical distribution occupying usually substantially <50% of the entire anterior and middle cerebral artery territories.
4. Basal ganglia infarcts were one or more circumscribed lesions in the basal ganglia or thalami, usually about 1 cm.
5. Watershed infarction involved cortical and subcortical regions at the periphery of the middle cerebral artery supply territory.
6. Diffuse white matter low-density changes were areas of poorly circumscribed low density in the cerebral white matter, usually bilaterally.
7. Lacunar state was multiple hypodensities in the basal ganglia and thalami, bilaterally.

Categories 1 through 4 were regarded as “embolic” (Fig 1) and categories 5 through 7 were classified as “nonembolic.” A normal CT brain scan or a scan showing unrelated pathology was considered as normal.

End points. Primary end points were (1) ipsilateral hemispheric ischemic stroke, including fatal stroke, defined as a hemispheric neurologic deficit lasting >24 hours; (2) any stroke; (3) ipsilateral hemispheric transient ischemic attacks (TIAs); (4) amaurosis fugax; and (5) death from cardiovascular causes other than stroke.19 A special form
was completed locally for reported strokes, and two members of the coordinating team, which included a neurologist, made the final classification. The local team made the diagnosis of TIA or amaurosis fugax. Patients were followed up every 6 months for a maximum of 8 years.

Exit points. Exit points are any of the above end points, death from any cause, ipsilateral CEA, stenting, or loss to follow-up. Thus, patients who died, had an ipsilateral CEA or stenting, or had an ipsilateral ischemic event were followed up to the event only. Apart from the ipsilateral fatal strokes, no overlap occurred between these events.

Quality control. Results of the quality control, already published,\textsuperscript{19} indicate that the goal of prospectively controlling quality in the ACSRS study has been achieved.

Statistical analysis. Data were analyzed using SPSS 11 statistical software (SPSS Inc., Chicago, Ill). The $\chi^2$ test and relative risk was used to test the significance of the incidence of neurologic event rates in relation to different types of plaque. Kaplan-Meier curves were used for cumulative stroke-free survival rates and the log-rank test for significance of difference between curves. Cox regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Logistic regression was used to identify independent predictors of neurologic events. The level of significance was considered as $P \leq .05$.

RESULTS

The study enrolled 328 women and 493 men with a median age of 71 years (interquartile range [IQR], 65-75 years). Stenosis severity distribution in relation to gender is summarized in Table I. On admission to the study, 8 large cortical, 15 small cortical, 72 discrete subcortical, and 51 basal ganglia ipsilateral infarcts were present in 146 patients. Other ipsilateral infarct types included 15 lacunes and 9 watershed infarcts, and diffuse white matter changes were also diagnosed in 95 patients. The distribution of embolic and nonembolic infarction in the ipsilateral and contralateral hemisphere is compiled in Table II. A signifi-

Table I. Stenosis severity distribution in relation to gender

<table>
<thead>
<tr>
<th>Stenosis severity</th>
<th>Gender, No. (%)</th>
<th>All patients (n = 821), No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n = 328)</td>
<td>Male (n = 493)</td>
</tr>
<tr>
<td>&lt;60%</td>
<td>137 (39.1)</td>
<td>213 (60.9)</td>
</tr>
<tr>
<td>60% to 79%</td>
<td>94 (41.4)</td>
<td>133 (58.6)</td>
</tr>
<tr>
<td>80% to 99%</td>
<td>97 (39.8)</td>
<td>147 (60.2)</td>
</tr>
</tbody>
</table>

*A uniform distribution was noted ($P = .86$).
Embolic subjects had had symptoms in the contralateral hemisphere before entering the study.

Distribution of embolic and nonembolic infarcts in the ipsilateral and contralateral brain hemispheres

<table>
<thead>
<tr>
<th>Infarct type</th>
<th>Brain hemisphere, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Embolic</td>
<td></td>
</tr>
<tr>
<td>Discrete subcortical</td>
<td>72</td>
</tr>
<tr>
<td>Large cortical</td>
<td>8</td>
</tr>
<tr>
<td>Small cortical</td>
<td>15</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>51</td>
</tr>
<tr>
<td>Nonembolic</td>
<td></td>
</tr>
<tr>
<td>Watershed</td>
<td>9</td>
</tr>
<tr>
<td>Diffuse white matter changes</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>59</td>
</tr>
<tr>
<td>Moderate</td>
<td>31</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
</tr>
<tr>
<td>Basal ganglia lacunar</td>
<td>15</td>
</tr>
</tbody>
</table>

*More infarcts were seen in the contralateral hemisphere. Note that some subjects had had symptoms in the contralateral hemisphere >6 months before entering the study.

Distribution of embolic and nonembolic infarcts in the ipsilateral and contralateral brain hemispheres was found; results are summarized in Table III.

Patients were monitored for a mean of 44.6 months (range, 6 months-8 years). During that time, 102 ipsilateral hemispheric neurologic events (amaurosis fugax in 16, TIA in 39, and stroke in 47) were observed, 138 patients died, and 24 were lost to follow-up. The ipsilateral hemispheric event rate in relation to the presence of embolic brain infarction was stratified by stenosis severity.

In 359 patients with <60% stenosis, the presence of embolic infarcts in 60 patients was not associated with increased risk (1.66% annual event rate) compared with patients where these were absent (2.38% annual event rate, log-rank \( P = .65; \) Cox regression HR, 1.14; 95% CI, 0.50-2.58). However, in 462 patients with 60% to 99% stenosis, the cumulative event-free rate at 8 years was 0.81 (2.4% annual event rate) in the absence of embolic infarcts and 0.63 (4.6% annual event rate) in the 86 patients where they were present (log-rank \( P = .032, \) Fig 2; Cox regression HR, 1.82; 95% CI, 1.05-3.14).

Subgroup analysis for stroke revealed similar findings. In patients with 60% to 99% stenosis, the cumulative stroke-free rate was 0.92 (1.0% annual stroke rate) in the absence of embolic infarcts and 0.71 (3.6% annual stroke rate) in their presence (log-rank \( P = .002, \) Fig 3; Cox regression HR, 3.0; 95% CI, 1.46-6.29). A similar association in <60% stenoses was not observed, where the presence of embolic infarcts was not associated with increased stroke risk (0.48% annual stroke rate) compared with patients in whom these were absent (1.1% annual stroke rate, log-rank \( P = .76; \) Cox regression HR, 0.72; 95% CI, 0.16-3.20).

Finally, in the subgroup of 216 patients with moderate, 60% to 79% stenosis, the cumulative TIA or stroke-free rate in the absence and presence of embolic infaracts was 0.90 (1.3% annual rate) and 0.65 (4.4% annual rate), respectively (log-rank \( P = .005; \) Fig 4). Compared with normal CT brain scans, the presence of nonembolic brain infarction (watershed, lacunes) or diffuse white matter changes had no effect on rates of ipsilateral neurologic events (\( P = .68 \)) or stroke (\( P = .67 \)); similar nonsignificant results were obtained from subgroup analysis by stenosis severity (Fig 5).

Multivariate logistic regression with ipsilateral embolic infarcts, degree of stenosis (<60%, 60% to 79%, 80% to 99%), age, gender, history of myocardial infarction, arrhythmia, and use of antiarrhythmic medications, antiplatelet use, and anticoagulant therapy as independent variables, identified embolic infarcts (relative risk, 2.0; 95% CI, 1.1-3.8; \( P = .033 \)) and degree of stenosis (relative risk, 1.6; 95% CI, 1.1-2.5; \( P = .019 \)) as independent predictors of ipsilateral neurologic events.

**DISCUSSION**

In ACSRS we demonstrated that the prevalence of silent embolic infarcts in the ipsilateral brain hemisphere in patients with moderate and severe asymptomatic carotid artery stenosis was associated with an increased risk of ipsilateral hemispheric neurologic events and stroke compared with patients without such infarcts. This difference may prove useful in the management of patients with asymptomatic carotid disease by identifying a high-risk group for neurologic events, including those with moderate carotid stenosis (60% to 79% range) who are poor surgical candidates (eg, positive stress echo) and in whom many surgeons are more conservative in treating with CEA or angioplasty and stenting.

The prevalence of SBIs on CT brain scanning in patients with asymptomatic carotid stenosis was 18% in our study; similar rates varying between 10% and 24% have been reported. Baseline SBIs in the ACAS was 15% and 72% were described as being small and deep. This is consistent with our study, where most patients had subcortical and basal ganglia infarcts.

The SBIs in ACAS were evenly distributed ipsilaterally and contralaterally to the study carotid artery. Neurologic examination factors such as abnormal gait and abnormal deep tendon reflexes or plantar responses were associated with SBI, but not the degree of carotid stenosis. In ACST the incidence of SBI on CT or MRI brain scanning in contralateral hemispheres that never had neurologic symptoms was 10% and 14%, respectively. Norris and Zhu reported a 19% incidence of SBI in asymptomatic carotid stenosis, whereas Cao reported a 24% incidence of SBI (15% lacunes, 9% nonlacunes) in patients with \( \geq 60 \) asymptomatic carotid artery stenosis undergoing CEA.

Direct comparison of these studies is difficult because of different SBI classification schemes. To overcome this potential problem, central reporting was performed in ACSRS.

The mechanism of SBI has been the subject of several studies. Most SBIs are embolic in nature (as defined in
Methods) and are due to cardiac disease or artery-to-artery embolism. Reports indicate the severity of asymptomatic carotid stenosis is associated with the appearance of SBIs.24,25 Like other studies,26 such an association was not found in our study, however, when stenoses were stratified using a 60% NASCET cutoff. Plaques that appear ulcerated on B-mode ultrasound imaging in asymptomatic patients were also closely related to the appearance of silent infarcts on MRI.25 Similarly, carotid plaques that are associated with nonlacunar SBIs on Table III. Distribution of contralateral embolic infarction and other infarct types in relation to “embolic” brain infarction on computed tomography scanning

<table>
<thead>
<tr>
<th>Type</th>
<th>Present (n = 146)</th>
<th>Absent (n = 675)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other infarct types, ipsilaterally</td>
<td>21 (14.4)</td>
<td>3 (0.4)</td>
<td>&lt;.001</td>
<td>37.6 (11.1-128.1)</td>
</tr>
<tr>
<td>Contralateral embolic infarction</td>
<td>81 (55.5)</td>
<td>91 (13.5)</td>
<td>&lt;.001</td>
<td>8.0 (5.4-11.9)</td>
</tr>
<tr>
<td>Other infarct types, contraterally</td>
<td>17 (11.6)</td>
<td>8 (1.2)</td>
<td>&lt;.001</td>
<td>11.0 (4.6-26.0)</td>
</tr>
</tbody>
</table>

CI, Confidence interval; OR, odds ratio.
These included watershed and basal ganglia lacunes in the ipsilateral or contralateral hemisphere.

Fig 2. Ipsilateral hemispheric neurologic event-free rate is shown in 462 patients with 60% to 99% carotid artery stenosis in relation to “embolic” infarction on computed tomography (CT) brain scanning. The number of patients at risk at each interval is shown at the bottom of the figure.

Fig 3. Stroke-free rate is shown in 462 patients with 60% to 99% carotid artery stenosis in relation to “embolic” infarction on computed tomography (CT) brain scanning. The number of patients at risk at each interval is shown at the bottom of the figure.

Fig 4. Ipsilateral hemispheric transient ischemic attack (TIA) and stroke-free rate are shown in 216 patients with moderate (60% to 79%) carotid artery stenosis in relation to “embolic” infarction on computed tomography (CT) brain scanning. The number of patients at risk at each interval is shown at the bottom of the figure.

Fig 5. Ipsilateral hemispheric event-free rate is shown in 462 patients with 60% to 99% carotid artery stenosis in relation to “embolic” infarction, “non-embolic” infarction, and normal findings on computed tomography (CT) brain scanning. No difference between the last two groups was found. The number of patients at risk at each interval is shown at the bottom of the figure.
CT are more hyperechoic than those associated with lacunar or no infarcts. These indicators of plaque instability, known to be associated with brain infarction in symptomatic patients, might be also responsible for embolic SBIs in asymptomatic carotid artery stenosis; obviously, some of the embolic SBIs in this patient population are of cardiac origin. This is supported by the associations between “embolic” and “nonembolic” SBIs that is summarized in Table III.

Several natural history studies have investigated the role of SBIs on predicting future stroke. Three reported on the prognostic role of MRI-detected SBIs, but unfortunately, the status of the carotid arteries was not investigated. In a study conducted in Japan, subcortical SBI on MRI was an independent risk factor for clinical stroke and associated with a 3.6% annual stroke risk. A similar association between silent MRI infarcts and the risk of future stroke were found in the cardiovascular health study. The incidence of stroke was much higher in participants with SBIs than without such a finding, at 18.7 vs 9.5/1000 person-years (HR, 1.5; 95% CI, 1.1-2.1), but again, the status of the carotid arteries was not reported.

SBIs found on MRI also increased stroke risk in the general population as shown by the Rotterdam Scan Study. The absolute stroke risk at 4 years in the presence and absence of SBI was 11.7% and 2.3%, respectively, and this absolute risk was five times higher for participants with one or more SBIs on MRI compared with those without. Regarding the significance of SBI detected on CT scanning, Cao reported a 10-year stroke risk of 18% in patients with SBI compared with 5% for absent SBI. Unlike the MRI studies, patients in this study had CEA previously and therefore the differential effect of carotid stenosis cannot be tested.

Our group has previously reported that the presence of embolic SBI on CT brain scanning was associated with an increased stroke risk, but because this was a mixed group of symptomatic and asymptomatic patients, the results cannot be extrapolated to the latter group of patients. The present study is therefore the first to report, to our knowledge, the prognostic role of embolic SBIs in patients with asymptomatic carotid stenosis. SBIs imply that the ICA stenosis may have caused emboli, without symptoms because they occurred in silent areas. Alternatively, they may have occurred during sleep or were misinterpreted.

The present study is also unique in the sense that we included patients across a wide spectrum of carotid disease severity; in patients with stenosis <60%, the presence of embolic infarcts was not associated with increased risk, probably because this subgroup was underpowered (both small sample size and event rate). However, in patients with coexisting hemodynamically significant stenosis, the annual ipsilateral event rate was nearly doubled in patients who had embolic infarcts (4.6%) compared with those that did not (2.4%). Results on this subject from the randomized ACST are awaited.

It is possible that SBIs render the brain susceptible to cumulative damage. This would be the reason SBI was a risk factor for stroke complicating CEA in a previous study, possibly in association with carotid artery clamping–related hypoperfusion. However, this association was not evident in an earlier study in which SBI in patients undergoing CEA for asymptomatic carotid stenosis was associated with a 1.8% annual stroke risk during long-term follow-up compared with 0.5% for those without SBI.

Diminished collateral reserve capacity on cerebral angiography in association with SBIs on CT brain scanning in patients with TIAs has also been demonstrated. Cerebral hypoperfusion in half of the patients with asymptomatic carotid stenosis, predominantly in patients with a hypoplastic ipsilateral A1 segment, has been described. Another study showed impaired cerebrovascular reserve capacity on xenon-CT imaging with acetazolamide in patients in whom new lesions developed on MRI during follow-up. The Rotterdam Scan Study showed that cardiovascular risk factors for SBIs, which included age, blood pressure, diabetes mellitus, cholesterol and homocysteine levels, intima-media thickness, carotid plaques, and smoking were associated with new SBIs in participants without prevalent infarcts, whereas a prevalent SBI strongly predicted a new SBI on the second MRI.

Another study highlighted that multiple mechanisms might be involved with SBI when it showed that coronary artery disease-atherosclerosis and hypertension were independently involved. In addition, SBI in patients with a first-ever stroke has been thought to be a marker of widespread vascular disease. The results of our study, which demonstrated that the risk for an event was largely increased only in patients with a hemodynamically significant stenosis, indicate a synergistic mechanism that involves an endogenously and exogenously susceptible brain due to the presence of infarction and significant carotid stenosis, respectively.

Among the study limitations are that CT scanning does not detect all SBIs. MRI detects a higher number of brain infarcts in patients with asymptomatic carotid artery stenosis—42% in one study. At the time the study was designed, most centers did not have MRI equipment, and therefore CT scanning was the method of choice. The role of brain MRI in stratifying patients with carotid stenosis is warranted.

In conclusion, our study indicates that the presence of silent “embolic” infarcts can identify a high-risk group for ipsilateral hemispheric neurologic events and stroke and may prove useful in the management of patients with moderate asymptomatic carotid stenosis.

AUTHOR CONTRIBUTIONS
Conception and design: JS, DT, AN
Analysis and interpretation: SK, MS, TT, JS, DT, GG, AN
Data collection: SK, MS, TT, JS, MG
Writing the article: SK, MS, TT, JS, DT, GG, AN
Critical revision of the article: SK, AN
Final approval of the article: SK, MS, TT, JS, DT, GG, AN
Statistical analysis: SK, AN
REFERENCES


