Clomethiazole Acute Stroke Study (CLASS)

Results of a Randomized, Controlled Trial of Clomethiazole Versus Placebo in 1360 Acute Stroke Patients

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Background and Purpose—The efficacy and safety of the neuroprotective drug clomethiazole was tested in a double blind placebo controlled trial in patients with a clinical diagnosis of acute hemispheric stroke.

Methods—Patients with symptom onset of ≤12 hours before the start of treatment were included in the study. Clomethiazole (75 mg/kg) or placebo was given as an intravenous infusion over a 24-hour period. Patients were followed up for 90 days. The primary efficacy variable was the proportion of patients reaching relative functional independence (≥60 points on the Barthel Index) at 90 days.

Results—A total of 1360 patients were included. In the main efficacy analysis (n=1353), 56.1% of patients taking clomethiazole and 54.8% of placebo patients reached relative functional independence. The difference was not statistically significant. An analysis of the effect of time since onset of symptoms showed no difference between the treatment groups. Clomethiazole was generally well tolerated and appeared safe in the population studied. Sedation was the most common adverse event, leading to treatment withdrawal that occurred in 15.6% of clomethiazole-treated patients compared with 4.2% of placebo-treated patients. In a subgroup classified before randomization as having total anterior circulation syndrome (TACS) (n=545, or 40% of all randomized patients), the percentage of those reaching relative functional independence was 40.8% on clomethiazole and 29.8% on placebo, a difference of approximately 11 percentage units. TACS patients have clinical symptoms suggesting a “large” stroke.

Conclusions—Clomethiazole had no adverse or beneficial effect on long-term outcome for all patients but produced sedation. The hypothesis that clomethiazole is effective in patients with large strokes will be tested in a further study.


Key Words: cerebral ischemia ■ clinical trials ■ clomethiazole ■ efficacy ■ neuroprotection

Clomethiazole (Zendra; Astra AB) is neuroprotective in models of focal ischemia in the rat1–3 and marmoset,4 as well as in global cerebral ischemia in the gerbil.5 Clomethiazole has sedative properties. However, intravenous administration of the drug to gerbils for 24 hours at plasma concentrations of 10 μmol/L produced almost total neuroprotection with little sedative effect.6 Clomethiazole has previously been reported to enhance GABAδ receptor activity.7–9 Activation of the GABAδ receptor-ion channel complex may produce membrane hyperpolarization. Counteraction of the depolarization induced by ATP depletion and glutamate release could thus be a critical property associated with the neuroprotective action.

A dose-escalation study was performed to evaluate the safety of intravenous clomethiazole when given to patients with acute ischemic stroke.10 An acceptable overall safety of clomethiazole was observed with a dose relationship for sedation. A dose of 75 mg/kg clomethiazole given as an intravenous infusion over 24 hours was found to be well tolerated with acceptable sedation. It produced a mean plasma concentration of about 13 μmol/L at the end of the infusion, which compares favorably with concentrations that are neuroprotective in animals. This dose was therefore considered suitable for further use in clinical efficacy trials on acute stroke patients.

In this study we evaluated whether intravenously administered clomethiazole in a dose of 75 mg/kg would improve functional and neurological outcome in patients with a clinical diagnosis of an acute hemispheric ischemic stroke. Functional outcome on the Barthel Index at 3 months was selected as the primary outcome measure.

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The principle investigators of the CLASS Study Group are listed in the Appendix.

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Subjects and Methods

Trial Organization
The Clomethiazole Acute Stroke Study (CLASS) involved 85 clinical centers, a central coordinating site in Sweden, 8 national coordinating sites, a steering committee, a data monitoring committee, and a review consultant (see the Appendix). There were 15 clinical centers in Canada, 15 in France, 6 in Hungary, 8 in the Netherlands, 4 in Norway, 18 in Spain, 12 in Sweden, and 7 in the United Kingdom. Each country had a local coordinating investigator. The investigator of each clinical center was responsible for the management of the study, usually with the assistance of a clinical coordinator/study nurse. The study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the local ethics committees. All patients or their representatives gave informed consent. Source verification of study data, including patient recruitment and evaluation, informed consent, time from onset of symptoms to start of treatment, administration of the study treatment, outcome assessments, and adverse events were performed for all patients by trial monitors from each national coordinating site. A complete check was made on a random sample (20%) of the patients at each center.

The independent data monitoring committee (IDMC) comprised 2 neurologists and a statistician. The members were recruited external to the sponsor and were not involved in any other study activities. Performance of interim analyses of safety data was planned on 3 occasions: after 200, 450, and 900 patients. Evaluation of efficacy data was planned after 450 and 900 patients, and group sequential boundaries were used. Only the IDMC had access to unblinded data during the course of the study.

All interim analyses were carried out according to plan, and the recommendation of the data monitoring committee on all occasions was that the study should continue.

The review consultant provided advice on the validity of an enrollment if it was in doubt. All validations were made with the treatment allocation blinded.

Patient Selection
Patients were considered for the trial if they had a clinical diagnosis of acute hemispheric (cortical or subcortical) cerebral infarction with onset of symptoms ≤12 hours before the start of the treatment. A CT scan was not required before inclusion, but if one had been performed the results had to be compatible with diagnosis of a cerebral infarction. Patients who were eligible according to the inclusion and exclusion criteria (Table 1) were included in the trial and randomized to receive active treatment or placebo. Randomization was stratified by center and 2 strata defined on time since the onset of symptoms (≤6 hours, 6 to 12 hours).

Treatment
Patients included received either clomethiazole (a total dose of 75 mg/kg) or placebo as an intravenous infusion over a 24-hour period. Treatment was carried out in a double-blind manner, with clomethiazole or placebo contained in identical bottles. All follow-up assessments of neurological and functional outcome were carried out by an investigator who was not present during the infusion or the period immediately after this, when the patient might be recovering from any sedative effect of the drug.

A 15-minute loading dose of the study treatment (8% of the total dose) was given under the direct supervision of the physician in charge, and sedation was carefully monitored with use of an assessment scale (see below). The flow was then reduced to the maintenance rate. However, if the patient became drowsy (a score of 3; see below) during the loading-dose phase, the flow rate was reduced immediately to the maintenance rate.

The patient’s level of sedation was carefully and regularly monitored during the maintenance phase. The maintenance infusion continued until the total infusion time (loading plus maintenance) was 24 hours. If the patient became markedly sedated (score of ≥4), the infusion was interrupted and then resumed again at half the previous rate. This stop/reduction procedure was repeated if required. If the patient was still profoundly sedated within 2 hours after the infusion was stopped, the study drug was not restarted.

Experimental and empirical treatments for acute stroke were not permitted during the most critical acute period, defined as the first 7 days. Insufficient data were available on the efficacy and safety of thrombolytic agents, aspirin, and anticoagulants in acute stroke at the time of the study, and these treatments were consequently not permitted until after day 7, with the exception of prophylactic treatment with low-dose subcutaneous heparin in patients at risk of deep-vein thrombosis. The patients were otherwise treated according to the routine therapeutic protocol of each participating center.

Assessments
Demographic details, medical and cerebrovascular history, general characteristics of the present stroke, a physical examination, and a full 58-point Scandinavian Stroke Scale (SSS-58) score11 were recorded at admission. In addition, the stroke was classified into various syndromes on the basis of clinical symptoms, according to the scheme of Bamford et al.12 Patients were classified under the total anterior circulation syndrome (TACS) heading if they had higher cerebral dysfunction (eg, cortical symptoms such as aphasia or neglect) plus motor and/or sensory weakness and homonymous visual field deficit. A partial anterior circulation syndrome (PACS) was defined by any 2 of the 3 TACS symptoms. Patients were classified as having a lacunar syndrome (LACS) if they had none of

TABLE 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1. Either sex, aged 40–90 y</td>
<td>1. Severe concurrent illness, left expectancy of &lt;6 months</td>
</tr>
<tr>
<td>2. Clinical diagnosis of acute stroke consistent with acute hemispheric cerebral infarction including hemiparesis and/or hemiplegia involving the arm, leg, or both</td>
<td>2. Hemorrhage on CT scan (when done before randomization) or evidence of disease other than ischemic stroke as cause of stroke symptoms</td>
</tr>
<tr>
<td>3. Start of treatment with 12 hours of symptom onset</td>
<td>3. Severe respiratory insufficiency, eg, asthma, bronchitis, emphysema</td>
</tr>
<tr>
<td>4. SSS-48 of =40 with a sum of scores on arm, hand, and leg motor items of ≥14</td>
<td>4. Known severe hepatic or renal disorder</td>
</tr>
<tr>
<td>5. Fully conscious before treatment</td>
<td>5. Diastolic blood pressure &lt;50 or &gt;130 mm Hg</td>
</tr>
<tr>
<td>6. Symptoms present for ≥1 h</td>
<td>6. Neurological sequelae from previous illness</td>
</tr>
<tr>
<td>7. Functionally independent before the stroke (Barthel Index score of 100)</td>
<td>7. History of serious allergic or toxic drug reactions</td>
</tr>
<tr>
<td>8. Informed consent provided</td>
<td>8. Suspected or known alcohol or drug dependence, alcohol intake during the past 24 hours</td>
</tr>
<tr>
<td>9. Breast feeding/pregnancy/females of childbearing potential</td>
<td>9. Treatment since admission to hospital with experimental or empirical treatments for acute stroke, eg, nimodipine, isradipine, flunarizine, antiplatelet agents, anticoagulants, thrombolytic agents, treatments for cerebral edema due to stroke</td>
</tr>
<tr>
<td>10. Treatment since admission to hospital with experimental or empirical treatments for acute stroke, eg, nimodipine, isradipine, flunarizine, antiplatelet agents, anticoagulants, thrombolytic agents, treatments for cerebral edema due to stroke</td>
<td>11. Sedatives ≥1 dose/d during the past week, neuroleptics in sedative doses or hypnotics during the past 8 h</td>
</tr>
<tr>
<td>12. Cimetidine intake during the past week</td>
<td>12. Previous inclusion in this trial</td>
</tr>
<tr>
<td>13. Previous inclusion in this trial</td>
<td>13. Previous inclusion in this trial</td>
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</table>
the above symptoms but had either pure motor stroke, pure senso-
rimotor stroke, or ataxic hemiparesis. Posterior circulation syn-
dromes (POCSs) were excluded by the trial protocol. A CT scan was
conducted on all patients before the onset of symptoms (0 to 6 hours, 6 to 12 hours) was performed.

The level of sedation was recorded with a 6-grade rating scale as follows: 1, fully awake; 2, drowsy but answers when spoken to; 3, answers slowly even when spoken to; 4, reacts when spoken to but does not answer; 5, reacts only to painful stimuli; and 6, does not react to painful stimuli. All patients, including those with unrelated events, were followed up for a maximum of 90 days. At the first follow-up, at day 7, a general physical examination was carried out, and any adverse events that had not resolved at the 24-hour evaluation were followed up. Functional outcome on the Barthel Index was assessed at 7, 30, 60, and 90 days.

Before the start of the study, all centers received training in the use of the neurological and functional rating scales, usually with the help of a videotape. The principal investigator at each center ensured that appropriate training was given to the medical, nursing, and other staff involved.

### Sample Size and Statistical Analysis

By assuming that the difference in the percentage of patients reaching relative functional independence on the Barthel Index between the treatment groups was 9% and allowing for a maximum variance of a proportion, it was estimated that a difference between the 2 treatment groups could be detected with 90% power and 675 evaluable patients per treatment group at completion of the study. This was based on group-sequential 2-sided tests with 2 planned interim analyses and 1 final analysis and an overall nominal significance level of 5%. 14

All statistical comparisons were carried out as 2-sided tests, and statistical significance was declared at the final analysis at $ P \leq 0.043$. Statistical significance of interactions was tested at the 0.100 level. All confidence intervals were 2-sided, with a 95% confidence level.

Descriptive statistics were used to estimate demographic parameters for all patients randomized to the 2 treatment groups. ANOVA models and $ \chi^2 $/Fisher’s exact test, as appropriate, were used for the single purpose to highlight large baseline imbalances occurring by chance between treatment groups.

The main analysis of efficacy data was performed on all patients who were started on treatment and for whom at least 1 efficacy assessment (including death) was available. Principal focus was on the last rating scores, ie, the scores at day 90 or, in the case of dropouts, the last available score carried forward to day 90. Deaths were scored as zeroes in the main analysis of Barthel Index and the SSS but were also treated as a separate category in supplementary analyses.

The primary outcome measure, namely, the proportion of patients reaching relative functional independence ($ \geq 60 $ points on the Barthel Index) at 90 days, was assessed for differences between treatment groups using the $ \chi^2 $ test. An analysis stratified for center and the randomization stratum based on the time to start of medication from the onset of symptoms (0 to 6 hours, 6 to 12 hours) was performed by the use of the Cochran-Mantel-Haenszel $ \chi^2 $ statistic. A categorization of the Barthel Index scores into 3 categories (0 to 55, 60 to 90, and 95 to 100) was also considered in the analysis. This choice for additional cut-off values between categories was made on the basis of a recently published study 15 in which 95 was used as threshold value.

For the SSS, the total score for the long-term scale (SSS-48) as well as the sum of the arm, hand, and leg motor power scores (SSS-MP) was subjected to statistical analysis. Differences between the treatment groups for the absolute change from baseline was assessed with the Cochran-Mantel-Haenszel test, stratified for center and time stratum.

Mortality was appropriately summarized as death rates and compared between groups. Survival distributions were estimated with use of the Kaplan-Meier method and assessed for differences between treatment groups with the log-rank test. Surviving patients with a follow-up period of >100 days were censored on day 100.

### Table 2. Demographic and Medical History by Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clomethiazole (n=680)</th>
<th>Placebo (n=680)</th>
<th>Total (n=1360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, ±SD, y</td>
<td>71.7±1.0</td>
<td>71.2±1.1</td>
<td>71.4±1.1</td>
</tr>
<tr>
<td>Both strata combined</td>
<td>71.5±1.0</td>
<td>71.5±1.2</td>
<td>71.5±1.1</td>
</tr>
<tr>
<td>Time stratum 0–6 h</td>
<td>71.9±1.0</td>
<td>70.9±1.1</td>
<td>71.4±1.0</td>
</tr>
<tr>
<td>Mean weight, ±SD, kg</td>
<td>72.2±1.4</td>
<td>72.5±1.4</td>
<td>72.4±1.4</td>
</tr>
<tr>
<td>Mean height, ±SD, cm</td>
<td>167.1±9.2</td>
<td>167.3±8.9</td>
<td>167.2±9.1</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>364 (54)</td>
<td>381 (56)</td>
<td>745 (55)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>147 (22)</td>
<td>152 (22)</td>
<td>299 (22)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>107 (16)</td>
<td>102 (15)</td>
<td>209 (15)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>324 (48)</td>
<td>315 (46)</td>
<td>639 (47)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>127 (19)</td>
<td>111 (16)</td>
<td>238 (18)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>105 (15)</td>
<td>92 (14)</td>
<td>197 (14)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>124 (18)</td>
<td>113 (17)</td>
<td>237 (17)</td>
</tr>
<tr>
<td>Cardiac failure, n (%)</td>
<td>80 (12)</td>
<td>73 (11)</td>
<td>153 (11)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>78 (11)</td>
<td>89 (13)</td>
<td>167 (12)</td>
</tr>
<tr>
<td>Previous transient ischemic attack, n (%)</td>
<td>105 (15)</td>
<td>95 (14)</td>
<td>200 (15)</td>
</tr>
</tbody>
</table>
Incidences of adverse events were compared between groups with use of the $\chi^2$/Fisher’s exact test, as appropriate. Logistic regression modeling techniques were used to assess the influence of covariates on outcome as well as to evaluate possible treatment group by covariate interactions. The primary outcome measure was used as dependent variable in this analysis, but the categorization of Barthel scores into 3 categories was also evaluated, under the assumption of proportional odds. The interaction terms were tested 1 at a time in a model that included terms (main effects) for all covariates considered in the analysis. In the event of several significant interaction terms, each was fitted after the other to check whether any of the interactions were redundant. The baseline covariates specified in the protocol were time since onset, SSS score, age, gender, and cardioembolic versus noncardioembolic disease.

### Results

**Recruitment and Baseline Characteristics**

At completion of the study, 1360 patients were randomized; 4 patients did not receive treatment (1 randomized to clomethiazole, 3 to placebo). Four clomethiazole patients and 8 placebo patients did not complete the 90-day study period for reasons other than death. The safety analysis was carried out on the 1356 treated patients. No efficacy data were available for 3 (1 clomethiazole, 2 placebo). The remaining 1353 patients were included in the main efficacy analysis: 678 received clomethiazole, and 675 received placebo. A general feature of the demographic and baseline characteristics is that they were well balanced between the treatment groups (Tables 2 and 3). The most common stroke syndrome, according to Bamford et al., was a TACS, which occurred in approximately 40% of the patients. After the CT scan results were known, acute cerebral infarction was diagnosed in 93% of the patients. Centers were encouraged to enroll patients within the first time stratum (ie, 0 to 6 hours), and approximately 50% of the patients were randomized to this stratum. Their stroke symptoms were more severe on average compared with those of patients randomized after 6 hours (Table 3), but there were only minor differences in mean age (Table 2).

### Dose Administration

The mean dose administered was 66.4 mg/kg for the clomethiazole group, which is 88% of the target dose. The equivalent figure for the placebo group calculated from the volume administered was 71.4 mg/kg. The lower dose in the clomethiazole group resulted from the higher incidence of dose...
reductions or withdrawals because of sedation, which was in accordance with the study protocol.

Main Efficacy Analysis

Functional Outcome

At last rating, a total of 380 clomethiazole-treated patients (56.1%) reached relative functional independence compared with 370 patients in the placebo group (54.8%) (Figure 1). The difference of 1.2 percentage units was not statistically significant (OR = 1.05; 95% CI, 0.85 to 1.30; P = 0.649). The median Barthel Index scores at each assessment time are shown in Table 4. There was no significant difference between the treatment groups at any time point.

Outcome on the SSS

Outcome was similar in each treatment group for the analysis of the SSS-48 (P = 0.556) and the SSS-MP (P = 0.960) at last rating (Table 4).

Mortality

The incidence and distribution of deaths over time was very similar for each treatment group. The overall mortality was 19.5% (132/678) in the clomethiazole group and 19.7% (133/675) in the placebo group (OR = 0.99; 95% CI, 0.75 to 1.29; P = 0.913). The Kaplan-Meier estimates of the survival distributions are depicted in Figure 2 (P = 0.951 by log-rank test).

Influence from Covariates and Subgroups Analyses

Age and SSS score were found to be the protocol-specified baseline covariates that had overall prognostic importance for the recovery of patients, independent of treatment. Both covariates were highly significant (P < 0.001). Corrections for the small imbalances between clomethiazole and placebo with regard to age and SSS score (Tables 2 and 3) increased the OR to 1.14 (95% CI, 0.88 to 1.47; P = 0.321) in the analysis of the primary outcome measure.

After adjusting for age and severity, no effect of time since onset was apparent, either on the overall recovery or on the difference between treatment groups.

The investigation of a possible heterogeneity of differences between treatment groups pointed to an interaction between treatment group and baseline SSS-58 score (P = 0.030, categorized variable), so that in more severe patients a greater percentage reached relative functional independence compared with placebo-treated patients.

This result triggered an extended covariate analysis in which general characteristics of the present stroke and the

**Figure 1.** Distribution of categorized Barthel Index scores for clomethiazole (CMZ) and placebo (pbo) groups for all patients as well as for the 2 strata according to length of time from onset of symptoms.
syndrome classification into TACS, PACS, and LACS (according to Bamford et al) were added to the set of covariates. Besides age and SSS score, the Bamford classification and presence of aphasia were found to have overall prognostic importance, independent of treatment. Moreover, a differential effect of treatment with clomethiazole was suggested for patients classified as TACS versus the others (non-TACS), as reflected by the interaction test ($P=0.038$).

For patients with TACS, 40.8% of clomethiazole patients (117/287) reached relative functional independence compared with 29.8% (77/258) in the placebo group, a difference of 10.9 percentage units (OR = 1.62; 95% CI, 1.13 to 2.31; nominal $P=0.008$). The corresponding numbers for non-TACS patients were 67.3% (263/391) in the clomethiazole group and 70.3% (293/417) in the placebo group, with a difference between groups of 3.0 percentage units (OR = 0.87; 95% CI, 0.65 to 1.17; nominal $P=0.358$).

In TACS patients the absolute median change from baseline to last rating for the SSS-48 score was 7 for the clomethiazole group and 5 for the placebo group (nominal $P=0.094$). Mortality was 28.0% in the clomethiazole group and 32.2% in the placebo group (nominal $P=0.361$).

### Adverse Events

Table 5 shows adverse events occurring at an incidence of $\geq 5\%$ in either treatment group. Somnolence, which includes the term sedation, was the most common adverse event in the clomethiazole group. It was also the most common adverse event leading to treatment withdrawal, accounting for the withdrawal of 90 of 106 clomethiazole-treated patients (15.6%) because of adverse events compared with 21 of 29 placebo patients (4.2%). Vomiting was more frequent in the placebo group. Adverse events with an incidence of $<5\%$ and $P<0.05$ for the difference were hiccups, injection site reaction, thrombophlebitis, conjunctivitis, and abnormal lacrimation. All occurred at a higher incidence rate in the clomethia-

### Discussion

CLASS was designed to select a group of patients that offered a good possibility of demonstrating a treatment effect of a neuroprotective agent. The demographic and baseline characteristics of the patient group selected were balanced well between the treatment groups owing to the randomized trial design and the relatively large number of patients included. The small differences in age and severity between the treatment groups still influenced the odds ratio for a treatment
effect because of the large impact these covariates have on the overall recovery of patients.

The patient group selected was similar to that included in the ECASS t-PA trial in terms of demographic characteristics and severity of stroke, although ECASS had a 6-hour time window. The CLASS patient group also appears similar to the group included in the NINDS t-PA trial, which had a 3-hour window. However, the incidence of a medical history—particularly diabetes and hypertension—was lower in CLASS.

Clomethiazole was generally well tolerated and appeared to be a safe drug to use in the population studied. Although there was a higher incidence of treatment withdrawals due to sedation on clomethiazole, this was to some extent protocol driven. Treatment could not be restarted in patients who were markedly sedated 2 hours after a treatment interruption. Other adverse events were of low incidence. No statistically significant difference was found between the treatment groups on primary and secondary efficacy endpoints in the main efficacy analysis. Treatment had to be initiated within 12 hours of onset of symptoms, a time compatible with the current practice of stroke care. It is unlikely that a direct extrapolation of the time window in animal models can be made to stroke in humans. Imaging studies in stroke patients instead indicate a prolonged period in which penumbral tissue may be salvaged, indeed for up to 48 hours. To allow for the effect of time since onset of the symptoms to be specifically studied, the trial was designed to recruit a sufficient number of patients into the early and late strata. No effect of time since onset was seen, however, once we adjusted for the effect of severity and other covariates.

In contrast, subgroup analyses showed that outcome appeared to be better for clomethiazole compared with placebo in 2 largely overlapping groups of patients, those with a severe neurological deficit at baseline according to the SSS and those classified at baseline as having a total anterior circulation syndrome (TACS). These patients are who have been shown by others to have a large volume of infarction. Caution is required in the interpretation of subgroup analyses because the risk of a treatment difference arising by chance is increased. However, these analyses have generated the hypothesis that clomethiazole is effective in patients with clinical symptoms of a “large” stroke, possibly because such patients have a larger penumbral area as a target for therapy.

Appendix

CLASS Study Organization

Steering Committee
Tim Ashwood, Nils Gunnar Wahlgren (CLASS Coordinating Investigator).

Review Consultant
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Independent Data Monitoring Committee
Gudrun Boyesen, Hvidovre Hospital, Copenhagen, Denmark; Michael Harrison (Chairman), University College Medical School, London, UK; Stuart Pocock, London School of Hygiene and Tropical Medicine, London, UK.

Principle Investigators of the CLASS Study Group
(Numbers randomized per country are in parentheses; each national coordinator is indicated by an asterisk.)

Canada (177), Calgary: Foothills Hospital, Buchan A. Edmonston, Ronald Alexandra Hospital, Tai C. Halifax: Victoria General Hospital, Phillips S. Levis: Hotel Dieu of Levis, Patry G. Montreal: Montreal Neurological Hospital, Aube M; Hotel-dieu de Montreal, Marchand L; Jewish General Hospital, Mohr G; Hospital Maisonneuve-Rosemont, Teitelbaum J. Ottawa: Ottawa General Hospital, Hakim AM. Quebec: Hotel-dieu de Quebec, Patry G; Hospital de l’Enfant Jesus, Simard D. Regina: Plains Health Centre, Veloso F. Saint John: Saint John Regional Hospital, Bailey P. Saskatoon: Royal University Hospital, *Shaub A; Royal University Hospital, Voll C. Sherbrooke: Hotel-dieu de Sherbrooke, Lamontagne A. Vernon: Vernon Jubilee Hospital, Cutten T.


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References
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