Aims: To undertake a systematic review of the literature reporting the prevalence of thrombophilia in children with a first arterial ischaemic stroke (AIS).

Methods: Systematic review of case-control studies reporting data for prevalence of protein C, S, and antithrombin (AT) deficiencies, activated protein C resistance (APCr), total plasma homocysteine > 95th centile, the thrombophilic mutations factor V1691 GA, prothrombin 2010GA, and MTHFR C677T in children with first, radiologically confirmed, AIS.

Results: Of 1437 potentially relevant citations, 18 met inclusion criteria. A total of 3235 patients and 9019 controls had been studied. Results of meta-analyses were expressed as pooled odds ratios (OR) relating the prevalence of the thrombophilic condition in children with AIS to that in controls. The pooled OR (and 95% CI) were: protein C deficiency, 6.49 (2.96 to 14.27); protein S deficiency, 1.14 (0.34 to 3.80); AT deficiency, 1.02 (0.28 to 3.67); APCr, 1.34 (0.16 to 11.52); FV1691 GA, 1.22 (0.80 to 1.87); PT2010GA, 1.10 (0.51 to 2.34); MTHFR C677T, 1.70 (1.23 to 2.34); and total plasma homocysteine > 95th centile, 1.36 (0.53 to 3.51). There was no statistical heterogeneity within these data.

Conclusions: All factors examined were more common in children with first AIS than in controls, and significantly so for protein C deficiency and the MTHFR C677T mutation. The implications of thrombophilia for prognosis and recurrence need to be established before clinical recommendations can be made regarding investigation and treatment of children with AIS.

**Abbreviations:** AIS, arterial ischaemic stroke; APCr, activated protein C resistance; AT, antithrombin; FVL, factor V Leiden
a fixed effects meta-analysis model using the Cochrane Group RevMan program. The fixed effect model was used as little heterogeneity was expected in the results. The $\chi^2$ test with k–1 degrees of freedom was applied to identify heterogeneity. Where meta-analysis was not possible with RevMan (that is, where a zero value was recorded in the AIS groups), the data were reanalysed using the statistical package, Intercooled Stata 7.0.

RESULTS
Of the 214 papers identified, 211 full text articles were obtained and reviewed, including 17 foreign language papers (see ADC website, fig B).

Qualitative assessment of studies
Authors of 46 papers were contacted for further information. Authors of 16 papers provided all the information requested and authors of six of the papers provided some information. Several authors were contacted to distinguish adult and child data, and to confirm which tests were performed, and control selection methodology. All the laboratory assays were technically valid. To exclude acquired protein deficiencies due to consumption, measurement of protein C, S, and AT has to be carried out beyond the acute period. Most studies did this, but the time interval was not clear in some. Some studies specified homozygosity or heterozygosity for the thrombophilic mutations, but the numbers of each were too small to enable separate analysis. In the case of the MTHFR C677T mutation, the majority were homozygous or not specified.

All but one study was performed in a tertiary centre. The three main groups of patients were from Turkey, Germany, and London. Overall, eight studies listed exclusion criteria. The most common factor leading to exclusion from this review was lack of matched controls. Some studies (particularly those reporting on homocysteine levels) used published reference values. Most were excluded from the meta-analysis as these controls were not formally matched for age and were often derived from a different time and population. The only studies included applied the same exclusion criteria for the controls as the study group. Some authors described controls briefly, but said little about matching or included controls only for the children undergoing genetic analysis. Five papers described the matching of the study groups with controls of the same ethnic group (Caucasian and Indian). Sträter et al described the children in their study group as white and as having been matched with children from the same geographic area. Prengler et al described the ethnic mix of their group but were unable to match with controls. The other papers made reference to nationality or geography but not to the ethnicity of the patients or controls. There was a variety of information given regarding family history, other aetiology of AIS, and combination of thrombophilia factors, but none of this data was able to be explored in the quantitative analysis due to lack of detail.

Quantitative analysis
Eighteen studies were included. These included data from 3235 patients and 9019 controls. The pooled OR and 95% CI are summarised in table 1 (see ADC website). In all the conditions, there were positive odds ratios, consistent with an increased frequency of the thrombophilic factors examined in children with first AIS. However, with the exception of protein C deficiency (see fig A) and the MTHFR C677T mutation, the confidence intervals crossed 1, reflecting the small sample size for most of the conditions examined. Thus, analysis of the pooled data established an increased prevalence of protein C deficiency and the MTHFR C677T mutation in children with first AIS, but there were insufficient data to conclusively establish increased prevalence of the other factors examined.

Qualitative assessment of data
There was no significant heterogeneity in any of the meta-analyses (see final column in table 1, ADC website).

DISCUSSION
This systematic review of the literature has found that all the thrombophilic factors examined are more common in children with first AIS than in healthy children. This conclusion is most robust for patients with protein C deficiency and the MTHFR C677T mutation. Although all other thrombophilic factors appeared to be more common in

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**Figure 1** Forest plot showing the meta-analysis for studies comparing prevalence of protein C in children with first AIS to controls. The log OR is depicted on the horizontal axis; a positive OR indicates that protein C deficiency was more common in the patients and a negative OR indicates that it was more common in controls. Each horizontal line represents an individual study (listed on the left). The size of each filled box is proportional to the weight given to the individual study and the limits of the horizontal line represent the 95% CIs. The open diamond indicates the results of the meta-analysis, with the widest point indicating the pooled odds ratio and the horizontal limits indicating the 95% confidence intervals.
the AIS patients, insufficient patients were included for these findings to be conclusive. The increased frequency of these thrombophilic factors does not, however, establish that there is a direct causative relation between them and first AIS in childhood. As there is increasing evidence that both childhood AIS and thrombosis are multi-factorial disorders, it is likely that AIS is the result of the interaction between thrombophilia and other genetic and environmental risk factors for both thrombosis and AIS. However, the presence of thrombophilia could influence the severity of the ischaemic lesion, for example, by leading to more extensive thrombosis in the acute phase, or may increase the incidence of recurrent AIS.

The reliability of systematic reviews is dependent on inclusion of high quality, methodologically similar studies. Although a priori inclusion and exclusion criteria for this study were employed either in the acute stage or in the longer term. However, at present there is no evidence to suggest that specific management strategies should be employed either in the acute stage or in the longer term.

**REFERENCES**


ARCHIVIST

PEG 3350 for constipation

There have been no large randomised controlled trials of treatments for childhood constipation. Lactulose may cause bloating and abdominal pain because of its fermentation by colonic bacteria and it has been suggested that low-dose polyethylene glycols (PEG) could be a less troublesome alternative. Systemic absorption of PEG is said to here have been no large randomised controlled trials of treatments for childhood constipation. Lactulose may cause bloating and abdominal pain because of its fermentation by colonic bacteria and it has been suggested that low-dose polyethylene glycols (PEG) could be a less troublesome alternative. Systemic absorption of PEG is said to have been used in infants and children with constipation. PEG 3350 for constipation

They randomly assigned 100 patients aged 6 months to 15 years to PEG 3350 or lactulose (under 6 years, one sachet (2.95 g PEG 3350 or 6 g lactulose) per day; over 6 years two sachets per day; dose adjusted according to response) for 8 weeks. The children had constipation defined as at least two of four symptoms or findings: less than three bowel movements per week, encopresis (more than once a week), large amounts of stool every 7–30 days, or palpable faecal abdominal or rectal mass. Enemas were given to clear the rectum before starting the trial medication.

Ninety-one children completed the study. After 8 weeks of treatment success (at least three bowel movements per week and no more than one episode of encopresis every 2 weeks) was achieved in 26/46 in the PEG group and 13/45 in the lactulose group. The mean increase in frequency of bowel movement and decrease in frequency of encopresis were similar in the two groups. Patients taking lactulose were significantly more likely to complain of abdominal pain or of pain or straining at defeaction, and patients taking PEG 3350 were significantly more likely to complain of the taste. The authors of this paper consider that PEG 3350 should be the first choice treatment for childhood constipation.
**Figure A: Search Strategies**

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</tr>
<tr>
<td>2</td>
<td>explode CHILD/ all subheadings</td>
</tr>
<tr>
<td>3</td>
<td>explode COAGULATION/ all subheadings OR COAG* OR PROCOAG* OR THROM*</td>
</tr>
<tr>
<td>4</td>
<td>FACTOR V LEIDEN OR PROTEIN C OR PROTEIN S OR ANTITHROMBIN OR PLASMINOGEN OR 1691GA OR G1691A OR PROTHROMBIN OR 20210GA OR G20210A OR LIPOPROTEIN* OR HOMOCYSTEIN* OR MTHFR OR C677T</td>
</tr>
<tr>
<td>5</td>
<td>1 and 2 and 3 and 4</td>
</tr>
<tr>
<td>6</td>
<td>Article/ or Case control study/ or Controlled study/ or Major clinical study/ or Priority journal/ or “case control”. mp.</td>
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<td>7</td>
<td>5 and 6</td>
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</tbody>
</table>
Figure B: Stages of the systematic review

Potentially relevant citations (n = 1437)

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Studies retrieved for detailed evaluation (n = 214)

→

Studies excluded after evaluation of full text (n= 154)

(Unable to distinguish adult, perinatal or child data = 54, sickle cell disease or moyamoya as predominant condition = 23, single case reviews = 10, review articles = 20, other thrombotic event = 50)

→

Additional exclusions after more information from authors (n= 39)

(No controls or unmatched controls = 14, unable to distinguish adult, perinatal or child data = 13, data repeated in other publications = 4, all thromboses included = 3, insufficient methodological detail = 3, no children investigated for thrombophilia = 2)

→

Studies included in the systematic review (n = 18)

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Studies included in the meta-analysis (n = 18)
Table 1: Results of meta-analyses

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. studies</th>
<th>No. included in meta-analysis</th>
<th>No. AIS patients with factor of AIS patients tested</th>
<th>No. controls with factor of controls tested</th>
<th>Pooled odds ratio</th>
<th>95% confidence intervals</th>
<th>p value for $\chi^2$ test for heterogeneity</th>
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<tbody>
<tr>
<td>Protein C deficiency</td>
<td>11</td>
<td>11</td>
<td>39/470</td>
<td>11/1081</td>
<td>6.49</td>
<td>2.96,14.27</td>
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<tr>
<td>Protein S deficiency</td>
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<td>9</td>
<td>13/428</td>
<td>0/944</td>
<td>1.14</td>
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<td>9</td>
<td>71/629</td>
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<td>1.22</td>
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<td>AT deficiency</td>
<td>8</td>
<td>8</td>
<td>1/435</td>
<td>0/952</td>
<td>1.02</td>
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<td>APCr ratio</td>
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<td>3/63</td>
<td>2/65</td>
<td>1.34</td>
<td>0.16,11.52</td>
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<td>7</td>
<td>35/550</td>
<td>15/1902</td>
<td>1.10</td>
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<td>***MTHFR C677T</td>
<td>7</td>
<td>7</td>
<td>107/589</td>
<td>127/1678</td>
<td>1.70</td>
<td>1.23,2.34</td>
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<td>Total plasma homocysteine &gt;95th centile</td>
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<td>2</td>
<td>8/71</td>
<td>11/393</td>
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<td>0.53,3.51</td>
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</tbody>
</table>

* Where zero is presumed as the result for controls as no result was available in the publication or from attempted contact with authors
** Combines published and unpublished data
*** Pooled heterozygous and homozygous data

NB. Results from publications 9 and 10 were combined following correspondence with the authors as they contained patients in common