Systematic reviews of clinical trials have shown that patients who are managed in a stroke unit are more likely to survive, return home, and regain independence than those who do not receive stroke unit care.1,2 Stroke units have also been shown to be cost-effective in most high-income health-care systems and are the recommended model of care in most clinical practice guidelines.3–7

However, some trials of stroke unit care have mostly or exclusively recruited patients with ischemic stroke, and most descriptions by the trials of the effects of stroke unit care have not been stratified by the pathological type of stroke.1 Consequently, patients with intracerebral hemorrhage are assumed to benefit from stroke unit care, with some support from observational studies,4 but this view is not universally held. For example, the American Heart Association guidelines9 recommend management in an intensive care unit because an observational study found that this care setting benefitted patients with intracerebral hemorrhage.10

Therefore, we updated a systematic review of stroke unit care in order to describe the types of care provided to patients with intracerebral hemorrhage recruited into stroke unit trials and to determine whether stroke unit care benefits patients with intracerebral hemorrhage and ischemic stroke equally in controlled clinical trials.

Background and Purpose—Patients with any type of stroke managed in organized inpatient (stroke unit) care are more likely to survive, return home, and regain independence. However, it is uncertain whether these benefits apply equally to patients with intracerebral hemorrhage and ischemic stroke.

Methods—We conducted a secondary analysis of a systematic review of controlled clinical trials comparing stroke unit care with general ward care, including only trials published after 1990 that could separately report outcomes for patients with intracerebral hemorrhage and ischemic stroke. We performed random-effects meta-analyses and tested for subgroup interactions by stroke type.

Results—We identified 13 trials (3570 patients) of modern stroke unit care that recruited patients with intracerebral hemorrhage and ischemic stroke, of which 8 trials provided data on 2657 patients. Stroke unit care reduced death or dependency (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.471–0.92; \( P = 0.0009 \); \( I^2 = 60\% \)) with no difference in benefits for patients with intracerebral hemorrhage (RR, 0.79; 95% CI, 0.61–1.00) than patients with ischemic stroke (RR, 0.82; 95% CI, 0.70–0.97; \( P_{\text{interaction}} = 0.77 \)). Stroke unit care reduced death (RR, 0.79; 95% CI, 0.64–0.97; \( P = 0.02 \); \( I^2 = 49\% \)) to a greater extent for patients with intracerebral hemorrhage (RR, 0.73; 95% CI, 0.54–0.97) than patients with ischemic stroke (RR, 0.82; 95%, CI 0.61–1.09), but this difference was not statistically significant (\( P_{\text{interaction}} = 0.58 \)).

Conclusions—Patients with intracerebral hemorrhage seem to benefit at least as much as patients with ischemic stroke from organized inpatient (stroke unit) care. (Stroke. 2013;44:00-00.)

Key Words: hemorrhagic □ meta-analysis □ outcome □ stroke □ stroke units

Systematic reviews of clinical trials have shown that patients who are managed in a stroke unit are more likely to survive, return home, and regain independence than those who do not receive stroke unit care.1–2 Stroke units have also been shown to be cost-effective in most high-income health-care systems and are the recommended model of care in most clinical practice guidelines.1–7

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Therefore, we updated a systematic review of stroke unit care in order to describe the types of care provided to patients with intracerebral hemorrhage recruited into stroke unit trials and to determine whether stroke unit care benefits patients with intracerebral hemorrhage and ischemic stroke equally in controlled clinical trials.

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Methods

Protocol and Registration. This is an updated analysis of a systematic review of clinical trials of stroke unit care that was published by the Cochrane Library after registration of a protocol.1

Eligibility Criteria. For this analysis, we sought truly or quasirandomized controlled clinical trials, including patients with intracerebral hemorrhage and ischemic stroke, comparing organized inpatient (stroke unit) care with conventional care in an alternative setting and reporting death or dependency as an outcome. These trials had to have been published after 1990 in any language, had to have carried out brain imaging in ≥80% of patients (to minimize misclassification of stroke type), and had to be able to report outcomes for patients with intracerebral hemorrhage and ischemic stroke separately so that the benefits of stroke unit care could be assessed for these 2 types of stroke.

Information Sources. We updated a detailed literature search, which was described in detail in the previous review, and included a search of the Cochrane Stroke Group Trials Register1 to identify all relevant trials reported before January 2013.

Study Selection and Data Collection Process. Two authors (P.L. and P.F.) screened titles and abstracts of articles and read studies in full where necessary to determine their eligibility. We also extracted study characteristics from published reports using a standardized report form and contacted the investigator(s) of each trial for a description of:

1. The trial methods and conduct (the nature of the random treatment allocation process was the principal assessment of the risk of bias);
2. The type of stroke unit (acute, comprehensive, rehabilitation, mixed; for definitions, see the previous review1);
3. The departmental base in which the stroke unit was housed;
4. The staffing structure and type of professional specialties available;
5. The typical pathway of care, which included information about:
   • Methods of patient assessment and diagnosis,
   • Acute medical and surgical treatments available and given,
   • Policies for early mobilization and early rehabilitation,
   • Differences that existed between the management of patients with intracerebral hemorrhage and ischemic stroke; and
6. Patient outcomes at the end of scheduled follow-up:
   • Death (from all causes),
   • Dependency (a modified Rankin scale score of 3–5 or nearest equivalent),
   • Place of residence (home, hospital, institutional care), and
   • Length of hospital stay.

Statistical Methods

We analyzed dichotomous outcomes as the risk ratio with 95% confidence interval using the Mantel–Haenszel technique and a random-effects model. We included all patients recruited and analyzed the results for intracerebral hemorrhage and ischemic stroke as separate subgroups and calculated subgroup interactions using established methods.11 Death or dependence at the end of scheduled follow-up was the primary outcome. Secondary outcomes were death alone, death or requiring institutional care, and length of stay in a hospital or institution. We analyzed data on length of stay using the standardized mean difference with random effects. We quantified inconsistency between studies using the I² statistic.11 We performed a sensitivity analysis restricting to trials with truly randomized treatment allocation. All analyses were carried out using Revman 5.1.

Role of the Funding Source

The study sponsors had no role in study design; collection, analysis, and interpretation of data; writing of the report; nor in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study Selection. The search strategy served to update the previous review1 that had identified 31 controlled clinical trials of stroke unit care. In this cycle, we identified 5320 new titles, of which 59 were reviewed as abstracts and 8 described potentially eligible trials (Figure 1). Of the 39 trials identified, we found 26 studies to be ineligible, leaving 13 stroke unit trials eligible for inclusion (3570 participants), of which we did not have usable data for 5 (n=913 participants), finally leaving 8 trials (2657 participants; 74% of eligible) that could provide the relevant information (Figure 1). These trials were from Akershus (Norway),12 Athens (Greece),13 Goteborg (Sweden),14 Helsinki (Finland),15 Huaihua (China),16 Newcastle (United Kingdom),17 Orpington (United Kingdom),18 and Trondheim (Norway).19

Study Characteristics. Table 1 shows the features of the included clinical trials. Seven trials14,15,17–19 used truly randomized treatment allocation. Five trials14,15,17–19 were at low risk of bias with concealed treatment allocation and blinded follow-up of outcome. The trials were carried out in departments of neurology, internal medicine, and geriatric medicine, and included 5 comprehensive stroke units, 1 acute stroke unit, and 2 mixed units. All had multidisciplinary staffing with specialist stroke interests. Table 2 outlines the characteristics of care in the included stroke units. All units described carrying out a standard clinical history and examination with basic investigations incorporating blood tests, ECG, and CT brain scanning. Most units had a policy of active fluid management.
with intravenous saline; careful monitoring and treatment of pyrexia, hyperglycemia, and hypoxia; plus early treatment of suspected infections. Blood pressure reduction tended to be restricted to very high blood pressure levels. Intracerebral hemorrhage patients tended to be mobilized early, in some cases within the first 24 hours. In 1 unit, mobilization was delayed if there was intraventricular rupture of blood. The main differences reported between management in the stroke unit and that in conventional care were that the stroke unit usually had policies of earlier mobilization and avoidance of bedrest.

Across both stroke subtypes, stroke unit care was associated with a significant reduction in the odds of death or dependency (RR, 0.81; 95% CI, 0.71–0.92; I²=60%; overall effect, P=0.0009; Figure 2). The reduction in death or dependency was similar for intracerebral hemorrhage (RR, 0.79; 95% CI, 0.61–1.00) as for ischemic stroke (RR, 0.82; 95% CI, 0.70–0.97) with no significant subgroup interaction (I²=0.77). Repeating the analysis using only truly randomized trials produced similar results (RR, 0.79; 95% CI, 0.67–0.92; I²=65%; overall effect, P=0.002). A similar pattern was seen for the outcome of death at the end of scheduled follow-up (Figure 3), when stroke unit care reduced case fatality (RR, 0.79; 95% CI, 0.64–0.97; F=49%; overall effect, P=0.02), and this reduction was greater for intracerebral hemorrhage (RR, 0.73; 95% CI, 0.54–0.97) than for ischemic stroke (RR, 0.82; 95% CI, 0.61–1.09) but with a nonsignificant subgroup interaction (P=0.58). In both analyses, there was significant heterogeneity, which was only partly explained by the subgroup analysis. For the outcome of death or institutional care (7 trials involving 2260 participants), stroke unit care resulted in a significant reduction (RR, 0.84; 95% CI, 0.66–1.07) and ischemic stroke (RR, 0.80; 95% CI, 0.67–0.95; test for subgroup interaction, Pinteraction=0.71). The analysis of length of stay for all stroke patients showed a borderline significant reduction of 2.2 days associated with stroke unit care compared with conventional care (95% CI, 4.1–0.3; P=0.02). Patients with intracerebral hemorrhage showed a nonsignificant increase (mean difference, 2.1 days; 95% CI, −0.6 to 4.7; P=0.13).

Discussion

Patients with intracerebral hemorrhage seem to benefit at least as much as those with ischemic stroke from a standard package of stroke unit care for the prevention of death or dependency. This may be attributable, in part, to the greater average severity of intracerebral hemorrhage and the recognized association between stroke severity and patient response to stroke unit care, which is likely to be mediated through the prevention of complications. The strengths of this analysis are that we carried out a comprehensive search for relevant trials and obtained standardized unpublished data stratified by stroke type, incorporating both descriptions of stroke unit care and patient outcomes in 8 controlled clinical trials. The subgroup of stroke unit trials that were eligible for this analysis appeared to be representative of

Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Timing of Follow-up</th>
<th>Control Service</th>
<th>Stroke Unit</th>
<th>Specialist in Stroke</th>
<th>Multidisciplinary Team Meetings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akershus (Norway)</td>
<td>Controlled clinical trial</td>
<td>No</td>
<td>Hospital discharge</td>
<td>General medical wards</td>
<td>Neurology CSU</td>
<td>Medical, nursing, physio, OT, SALT</td>
<td>Yes</td>
</tr>
<tr>
<td>Athens (Greece)</td>
<td>RCT (sealed envelopes)</td>
<td>No</td>
<td>12 mo</td>
<td>General medical wards</td>
<td>Internal medicine AU</td>
<td>Medical, nursing, physio, OT, psychologists</td>
<td>Yes</td>
</tr>
<tr>
<td>Goteborg (Sweden)</td>
<td>RCT (opaque sealed envelopes)</td>
<td>Blinded Follow-up</td>
<td>12 mo</td>
<td>General wards</td>
<td>Neurology and internal medicine CSU</td>
<td>Medical, nursing, assistants, physio, OT, (SALT, neuropsychologist, SW)</td>
<td>Yes</td>
</tr>
<tr>
<td>Helsinki (Finland)</td>
<td>RCT (sealed envelopes)</td>
<td>Blinded Follow-up</td>
<td>12 mo</td>
<td>General wards</td>
<td>Neurology Mixed</td>
<td>Medical, nursing, physio, OT, SALT, other</td>
<td>Yes</td>
</tr>
<tr>
<td>Huaihua (China)</td>
<td>RCT (method uncertain)</td>
<td>Uncertain</td>
<td>12 mo</td>
<td>General wards</td>
<td>Neurology CSU</td>
<td>Published information only</td>
<td>Yes</td>
</tr>
<tr>
<td>Newcastle (United Kingdom)</td>
<td>RCT (blinded)</td>
<td>Blinded Follow-up</td>
<td>6 mo</td>
<td>General wards</td>
<td>Geriatric medicine Mixed</td>
<td>Medical, nursing, physio, OT, SALT, SW</td>
<td>Yes</td>
</tr>
<tr>
<td>Orpington (United Kingdom)</td>
<td>RCT (telephone randomization)</td>
<td>Blinded Follow-up</td>
<td>12 mo</td>
<td>Mobile team in general medical wards</td>
<td>Geriatric medicine CSU</td>
<td>Medical, nursing, physio, OT, SALT, other, SW</td>
<td>Yes</td>
</tr>
<tr>
<td>Trondheim (Norway)</td>
<td>RCT (numbered opaque sealed envelopes)</td>
<td>50% both blinded and open assessments at 52 wk</td>
<td>12 mo</td>
<td>General medical wards</td>
<td>Internal medicine CSU</td>
<td>Medical, nursing, physio, OT, SALT</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ASU indicates acute stroke unit; CSU, comprehensive stroke unit; mixed, not exclusively managing stroke patients; OT, occupational therapy; RCT, randomized controlled trial; SALT, speech and language therapy; and SW, social work.
Table 2. Aspects of Care in Included Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Assessment</th>
<th>Acute Medical Management</th>
<th>Mobilization/Rehabilitation</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akershus12 (Norway)</td>
<td>Clinical history and examination; bloods (biochem, hematology); ECG; CT; scan; intracranial pressure was not monitored</td>
<td>IV saline first 24 h; paracetamol for pyrexia; insulin for ↑ glucose; oxygen for hypoxia; selective BP reduction (if &gt;230/120 on 2 readings); early antibiotic for suspected infection</td>
<td>Patients without reduced consciousness or extensive intraventricular rupture of blood were mobilized out of bed within the first 24 h, and activation and rehabilitation was started as soon as possible</td>
<td>Criteria for referral to surgery; cerebellar hemorrhage &gt;3 cm and signs of deterioration, or supratentorial hemorrhage between 3 and 6 cm and signs of deterioration</td>
</tr>
<tr>
<td>Athens13 (Greece)</td>
<td>Clinical history and examination; bloods (biochem, hematology); ECG; CXR; CT scan</td>
<td>Monitoring of temperature, O2 saturation, heart rate, blood glucose during first 48–72 h; use of automated monitoring</td>
<td>Mobilize on day 1–2</td>
<td>No systematic difference from management ischemic stroke except for avoiding anticoagulant and antiplatelet therapies</td>
</tr>
<tr>
<td>Goteborg14 (Sweden)</td>
<td>As per Athens13</td>
<td>Conventional stroke unit care</td>
<td>There was a tradition of more careful mobilization in hemorrhagic strokes among the general ward–cared patients</td>
<td>No systematic difference from management ischemic stroke except for avoiding anticoagulant and antiplatelet therapies</td>
</tr>
<tr>
<td>Helsinki15 (Finland)</td>
<td>As per Athens13</td>
<td>Conventional stroke unit care; antibiotic for infection</td>
<td>Early mobilization</td>
<td>No systematic difference from management ischemic stroke except for avoiding anticoagulant and antiplatelet therapies</td>
</tr>
<tr>
<td>Hualiu16 (China)</td>
<td>Uncertain</td>
<td>“Received medical, … treatment according to their conditions”</td>
<td>“Received … rehabilitative and language training and psychological treatment according to their conditions”</td>
<td>Information only available from the published paper</td>
</tr>
<tr>
<td>Newcastle17 (United Kingdom)</td>
<td>As per Athens13</td>
<td>Selected used of IV fluids; paracetamol, insulin, oxygen</td>
<td>…</td>
<td>No systematic difference from management ischemic stroke except for avoiding anticoagulant and antiplatelet therapies</td>
</tr>
<tr>
<td>Orpington18 (United Kingdom)</td>
<td>As per Athens13</td>
<td>IV saline first 24 h; paracetamol for pyrexia; insulin for ↑ glucose; oxygen for hypoxia; selective BP reduction (if &gt;230/120 on 2 readings); early antibiotic for suspected infection</td>
<td>Mobilize on day 0–1</td>
<td>No systematic difference from management ischemic stroke except for avoiding anticoagulant and antiplatelet therapies</td>
</tr>
<tr>
<td>Trondheim19 (Norway)</td>
<td>As per Akershus12</td>
<td>IV saline first 24 h; paracetamol for pyrexia; insulin for ↑ glucose; oxygen for hypoxia; selective BP reduction (if &gt;200 systolic on 2 readings); early antibiotic for suspected infection; automated monitoring for severely impaired patients</td>
<td>Early mobilization &lt;24 h if possible</td>
<td>Control of physiological homeostasis; acute BP lowering in ischemic stroke if systolic BP &gt;250 mm Hg; acute BP lowering in hemorrhages if systolic BP &gt;200 mm Hg; antithrombotic therapy only in ischemic strokes</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CT, computerized tomography; CXR, chest x-ray; and IV, intravenous.

all stroke unit trials identified in view of the similarity of our results to the overall reduction in death or dependency noted in the Cochrane Database systematic review.2

The main weaknesses were that we were unable to obtain the relevant information from 5 eligible trials, which involved 26% of all potentially eligible participants. The main reason for this was that the relevant data were no longer available, although the trials spanned a similar period (1995–2004) to the included ones (1991–2004). The descriptive data about the components of stroke unit care were reported by investigators and were provided some time after the trials had completed. We have not been able to provide extensive details of specific management strategies; however, most trialists reported little systematic difference in the routine care of intracerebral hemorrhage and ischemic stroke patients. The included trials tended to exclude very severely impaired patients (in a coma), so we cannot comment on the management of this specific patient group. It is possible that some patients with intracerebral hemorrhage had hemorrhagic transformation of an ischemic stroke because these can be difficult to distinguish. Any misclassification of stroke subtypes would tend to dilute apparent differences in patient outcome.

The main implication for clinical practice is that patients with stroke, whether or not attributable to intracerebral hemorrhage, should be managed on a stroke unit.1,2 Indeed, patients with intracerebral hemorrhage—who may currently be managed on general medical wards, neurosurgical wards, and stroke units—seem to benefit at least as much as their counterparts with ischemic stroke from care on a stroke unit. We could find no reason to alter the basic components of stroke unit care to provide a radically different form of management for patients with intracerebral hemorrhage. Stroke units entail a complex package of care, incorporating a range of interventions, including (1) active management (such as that of physiological variables relating to fluid balance, pyrexia, oxygenation, and glycaemia); (2) early mobilization out of bed; (3) skilled nursing; and (4) multidisciplinary rehabilitation.23 However, some believe that patients with intracerebral...
hemorrhage require a different pathway of care, for example, nursing the patient with a 30-degree head-up tilt, despite the lack of inclusion of such patients in the small observational studies that have been performed, or the avoidance of early mobilization, despite the lack of evidence that this is harmful.

The first implication for future research is that further randomized controlled trials are required to test the key components of stroke unit care to see whether the constituent interventions, such as blood pressure reduction (http://www.interact2.org), early mobilization (http://www.florey.edu.au/research/stroke/a-very-early-rehabilitation-trial-avert-phase-iii), oxygenation (www.so2s.co.uk), fluid balance, and neurophysiological monitoring, influence outcome. Second, randomized controlled trials are needed to compare stroke unit care with alternative settings (such as high-dependency or neurological intensive care units) to see if the devastating outcome after intracerebral hemorrhage, which has changed little over several decades, can be further improved, as one

Figure 2. Stroke unit vs conventional care: death or dependency at the end of scheduled follow-up. The figure shows the risk ratio (95% confidence interval) for the combined outcome of death or dependency in activities of daily living at the end of scheduled follow-up together with the number of patients who had outcome events of the total number randomized to stroke unit or conventional services. Results are presented for subgroups of patients categorized according to whether their imaging indicated hemorrhagic or nonhemorrhagic (ischemic) stroke. The diamond indicates the estimated risk ratio (95% confidence interval) for each subgroup of patients (Subtotal) and for all patients together (Total).

Figure 3. Stroke unit vs conventional care: death at the end of scheduled follow-up. The figure shows the risk ratio (95% confidence interval) for the outcome of death at the end of scheduled follow-up. Results are presented as Figure 2.
observational study suggests. That research should define the important components for improving outcome. Finally, we still need trials of important specific strategies for intracerebral hemorrhage patients, such as blood pressure reduction, neurosurgical interventions, and hemostatic drugs.

In summary, our meta-analysis of randomized controlled trials confirms the benefits of stroke unit care for patients with intracerebral hemorrhage, which have been noted in observational studies, and the scale of benefit is at least as much as for patients with ischemic stroke. Further work is needed to determine which components of stroke unit care have the greatest influence on outcome and which benefit patients with intracerebral hemorrhage in particular.

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References
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