Letters to the Editor

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Contribution of *Stroke* to the Cochrane Stroke Group Trials Register

To the Editor:

The formulation of evidence-based stroke care practice guidelines is guided by the results of randomized trials. We sought to determine what proportion of all trial reports are published in *Stroke*, and what proportion might be missed by electronic search methods.

One of us (B.T.) performed a page-by-page search of every issue of *Stroke* (1970–2001), applying standard criteria to identify all reports of relevant randomized trials and controlled clinical trials appearing in articles, editorials, letters, conference abstracts, or any other text. Reports of trials of interventions for the treatment, rehabilitation, and secondary prevention of stroke are included in the Cochrane Stroke Group Trials Register. Reports of trials outside the scope of the Group are forwarded for inclusion in the Cochrane Central Register of Controlled Trials in the Cochrane Library. We developed a detailed search strategy for MEDLINE, which includes controlled vocabulary and free text terms, and extends to 56 lines of search statements. The strategy is published in the Stroke Group’s module in the Cochrane Library and is designed to be highly sensitive and optimally specific to detect reports of randomized trials and controlled clinical trials. We compared the lists of reports found by handsearching (the gold standard search) with the list identified by the MEDLINE search of *Stroke* for publication years 1970 to 2001.

*Stroke* is the most important single source of relevant trial reports in the Stroke Group Trials Register, accounting for 803/5771 (14%) of all trial reports in our Register to December 2001. The complete retrospective handsearch identified 803 relevant stroke trial reports including 365 original articles, 382 conference abstracts (and other abstracts), and mentions of trials in letters in 56. We identified a further 67 reports of trials in patients with nonstroke conditions. The Abstracts of Literature section of the journal (now discontinued) was a useful source of an additional 331 reports of stroke trials published in other journals.

The Figure shows the increasing numbers of the different categories of stroke trial reports published in the journal since 1970. Three major Stroke conferences published their proceedings in the journal in 2000, which accounts for the large number of abstracts found in that year. Since 1970, *Stroke* has included proceedings from 44 conferences.

The search of MEDLINE identified 1605 references published in *Stroke* from 1970 to 2001. A comparison with our gold standard handsearch showed that the MEDLINE search identified 353 of the 803 found by handsearching (sensitivity 44%). The remaining 1252 were not reports of relevant trials (precision 22%). Of the 450 trial reports in *Stroke* not identified by the MEDLINE search, 376 were abstracts, 42 were original articles, and 32 were letters.

*Stroke* is an increasingly rich source of reports of stroke trials, and the journal accounts for a significant proportion of all trial reports in our Register. The search also allowed us to assess the sensitivity of our electronic search strategy. Although a significant number of the reports of trials in *Stroke* were not identified by the MEDLINE search, 91% of the missed reports were either letters or abstracts from sections of the journal that are not indexed in MEDLINE. Our aim is to identify all reports of relevant trials from the planning stage to full publication and, whilst a search of MEDLINE will identify major trial results, such indirect reports may be the only clue to the existence of an unpublished or ongoing major trial. Many of these trials may, of course, be subsequently published in full elsewhere, and we are planning to investigate and characterize those trial reports, published as abstracts or letters, that never come to full publication. Equally, it is well known that many trials (especially "negative" ones) may never be published as full papers.

We have been able to demonstrate, using *Stroke* as an example, that handsearching important specialist journals is an essential component in our search for trials in systematic reviews, and limiting the search to MEDLINE may result in exclusion of potentially relevant trials. The Stroke Group Trials...
Register is now a comprehensive and up to date source of stroke trials. It contains over 6000 stroke trial reports and has supported the publication of 65 Cochrane reviews and 32 protocols for reviews in progress.

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1. The Cochrane Collaboration. Handsearch Training Resources. Available at: http://www.cochrane.us/hsmain.htm

Clinical Use of C-Reactive Protein for Prognostic Stratification in Ischemic Stroke: Has the Time Come for Including It in the Patient Risk Profile?

To the Editor:

Dr Winbeck et al demonstrated in a recent article in Stroke that increased levels of C-reactive protein (CRP) within 12 to 24 hours after stroke onset represent a strong predictor of future vascular events and a worse outcome, whereas increased concentration measured earlier at admission or after the 24 hours were not correlated with outcome. Their results extend our knowledge concerning the role of CRP in the prediction of prognosis after an ischemic stroke. Furthermore, the observations by Winbeck et al suggest some practical questions concerning the clinical use of CRP for prognostic stratification in ischemic stroke patients.

What is the value of CRP as a prognostic marker in ischemic stroke? Although no large study has prospectively assessed the value of CRP for prognostic short- and long-term stratification of patients with ischemic stroke, many data suggest that CRP might be of great value in this group of patients. The data are strong and consistent for the mild- to long-term prognosis, for which the relative risk (RR) observed in different studies is similar (RR = 2.5). However, the data are less consistent for the in-hospital prognostic stratification of these patients, although it is reasonable to presume that CRP levels may also constitute a good marker in this condition. When studying patients with an acute ischemic stroke, no value should be discharged as too high, because after stimulation, CRP levels can increase a thousand-fold, and there is evidence that in some patients constitutional hyperresponsiveness might lead to very high CRP levels even in the first hours after stroke. Of course, in the presence of overt inflammatory and infection disease, the data should be interpreted cautiously; a possibility CRP titration repeated at least 2 times after the underlying disease has resolved in a long-term stratification standpoint.

When to sample? The available data suggest the utility of a sample taken at admission, within 12 to 24 hours after stroke onset. However, when samples were also taken at discharge, CRP levels are better predictors of the mid- to long-term prognosis than those at admission. This is probably due to the fact that discharge levels more closely reflect the baseline inflammatory status of the patients and thus their intrinsic risk due to inflammatory activity. It is reasonable to assess the CRP levels at entry and when possible at discharge; 1 to 3 months later may be useful, because it is likely that the highest risk of future events is confined to patients with persistently elevated levels of CRP.

What to do when CRP levels are elevated? The lack of a specific therapy that has been proved to reduce levels of CRP and risk makes this question quite questionable. However, the demonstration that statins are effective in the presence of high CRP levels and that the efficacy of antplatelet therapy in secondary prevention appears to be directly related to the level of inflammatory markers is already a first response. High CRP levels, associated with a higher risk, suggest a more aggressive medical therapy. The use of biochemical markers as a guide to the therapy will no longer be a controversial issue in the future and there is no doubt that CRP has all characteristics to be one of the ideal markers. However, additional well-designed epidemiological studies are needed to validate these findings.

Has the time come for including CRP in the risk profile? Despite the increasing number of studies on CRP in ischemic stroke, the role of a marker of inflammation in the list of outcome predictors commonly used is still not clear. To be of clinical utility, CRP must be shown to add substantially to our ability to predict risk beyond that achievable by use of the traditional outcome predictors. CRP might be a good candidate because its levels are affected by little other than inflammation, its risk prediction is independent of other known cardiovascular risk factors, and highly sensitive reproducible assays are available. However, inflammation appears an important, common, but nonnecessary or a sufficient condition and hence the predictive accuracy of CRP measurement can only be limited, just like it is the case for isolated traditional prognostic factors. Moreover, it is likely that the prevalence of inflammatory component in acute ischemic stroke may vary according to age, sex, environmental condition, as well as in different ethnic group. Only multicenter, carefully controlled studies in ischemic stroke patients that include information on stroke severity and other important prognostic factors are needed to determine whether CRP evaluation has utility in secondary prevention of ischemic stroke before to recommend its use in common clinical practice.

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Response

We thank Drs Di Napoli and Papa for the interest in our report1 and the practical questions he asked concerning the prognostic impact of CRP measurements in acute ischemic stroke. We agree with them pointing out that CRP might be an ideal marker in the future to guide the therapy in stroke patients, that CRP might be useful for the short- and long-term stratification of these patients
regarding prognosis, and that we need a large an well-designed multicenter study in stroke patients to evaluate the prognostic impact of CRP measurement for secondary prevention of stroke. However, there are two points that we would like to comment in more detail.

First, Drs Di Napoli and Papa considered that although CRP might be a good parameter to determine the short- and long-term risk of stroke patients, the impact in the acute phase of brain infarction is less strong, as CRP levels can increase a thousandfold in this situation, especially in patients with constitutional hyperresponsiveness. Therefore, they argued that the discharge CRP levels might better reflect the prestroke and baseline CRP levels, and that the CRP levels at discharge and 1 to 3 month after stroke may be useful for the evaluation of long-term outcome. This might be true if we could completely exclude an in-hospital infection and secondary complications after ischemic stroke. In our study, we are interested to analyze whether an early serial CRP determination is useful for the long-term prognostic outcome of stroke patients. Interestingly, we found that the CRP increase within 24 hours after ischemic stroke was an independent prognostic factor in these patients and that later CRP levels were not independently associated with outcome. Additionally, another advantage of the serial CRP determination in acute ischemic stroke might be the early prognostic evaluation of the patient’s risk. Large multicenter studies in healthy adults already identified CRP as a strong independent risk factor for cardiovascular disease that adds to the predictive value of risk models based on usual factors alone.

Second, Drs Di Napoli and Papa recommended that before CRP evaluation could be added to the known prognostic factors after ischemic stroke, multicenter and carefully controlled prospective studies should be performed. In the light of evidence-based medicine, we encourage this standpoint. However, we suggest that at least in patients with an acute ischemic cerebral event and lack of traditional risk factors, the CRP value should be considered to evaluate the individual risk and potential therapy strategies, eg, statin administration.

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Postmortem MRI as a Useful Tool for Investigation of Cerebral Microbleeds

To the Editor:

We read with interest the article by Dichgans et al about cerebral microbleeds in CADASIL.1 The authors demonstrated a high frequency of focal areas of signal loss on gradient-echo MRI, suggesting past microbleeds, in CADASIL patients. They also performed postmortem examinations on the brains of 7 additional CADASIL subjects and found old microbleeds, defined as focal accumulations of hemosiderin-containing macrophages, in 6 of the 7 brains. In their article, the authors regret that none of these had previously been investigated by gradient-echo MRI, thus precluding a correlation study between neuroimaging and postmortem findings.

We felt obliged to suggest that the absence of previous in vivo MRI, however, does not absolutely preclude imaging-pathologic correlation. It has been demonstrated that MRI of excised and formalin-fixed brains, ie, postmortem MRI (pMRI), also called in vitro MRI, is a feasible and reliable method for delineating normal brain anatomy and detecting intracranial lesions.2–4 It can make correlative studies possible in those cases in which in vivo MRI is lacking, and it also has the advantage of imaging the brain just at the time of pathology, whereas correlation with previous in vivo MRI may be flawed because of changes that occurred between examination and the death of the patient. Changes caused by the fixation process must be considered before extrapolating brain pMRI findings to in vivo MRI, but they have been well described in previous studies.5–8 According to the literature and to our own experience with this technique, started as far as approximately 10 years ago,9,10 its value and usefulness vary according to lesion nature and location. In January 2000, we started a prospective MRI and pathological study of autopsy specimens to be examined for medico-legal purpose. Soon after removal, the brains were placed in buckets of formol saline and allowed to float in the fixative liquid for a minimum of 3 weeks, during which the formol was repeatedly changed. Between 6 and 12 h before the MRI examination, the brains were placed in tap water. MRI was performed, with the whole brain in a plastic box completely filled with water, by means of a superconducting 1.0-T system (Magnetom Expert Impact, Siemens) with head coil. Sagittal, axial, and coronal 5-mm spin-echo (600/23/TR/TE), turbo spin-echo (4800/96), turbo-fluid attenuated inversion recovery (7000/105) and gradient-echo (600/26) images were obtained. After MRI, the brains were again kept in formol saline until they were sliced into coronal sections 1 cm thick with the help of 2 brass right angles. When abnormal findings were present on MRI and/or macroscopic examination, the corresponding slice/s was/were subjected to MRI again. For this MRI examination, a surface coil was used; initially (case 1) the slices were put into a plastic box filled with water, but subsequently water was no longer used as a medium because of major disadvantages encountered, and the slices were examined in air. Two series of 5-mm coronal images were obtained for each 1-cm-thick slice. Then, sections 15 μm thick were cut from the macroscopically and/or MRI-evident abnormal regions and stained histologically, if necessary, specific stains being used. Stained histological sections, they are likely to be missed in autopsy studies. Owing to the high sensitivity of MRI in detecting even minimal lesions, pMRI can be a potent help to neuropathologists for addressing detailed and microscopic examination in the light of the signal abnormalities detected, making it possible to optimize the pathological study; examination with gradient-echo pulse sequence, which has been well demonstrated to increase the sensitivity of MRI for hemorrhages, is optimally suited to assess the presence and pattern of past microbleeds. We also found pMRI very sensitive for detection of recent infarcts (which were revealed by MRI as very high signal lesions and diagnosed by subsequent MRI-guided histology), whereas it was of little value with those lesions (well evident at macroscopic pathological examination, however) located superficially, such as cortical contusions and subarachnoid hemorrhages, owing to susceptibility artifacts. Therefore, pMRI appears to be especially
suited for detection of deeper lesions, eg, cortico-subcortical junction and white-matter abnormalities. We would like to emphasize several advantages of pMRI. Fixed brains can be imaged at various distances of time from death, and on standard MR imagers. MRI information from the whole-brain multiplanar study gives a preliminary overall view of the brain condition while it is still intact, can be obtained repeatedly, and makes it possible to optimize the cuts in a single case in order not to miss minimal and/or deep lesions as well as initial changes. MRI of single slices, focusing the attention of the neuropathologist to abnormal regions, will indicate the site of microscopic investigation, ensuring that the signal abnormality is contained in the tissue slice being examined for histologic studies. Predissection multiplanar images of the whole brain will be left as a document once the brain has been sectioned and specimens have been obtained for microscopic examination.

To conclude, we would suggest that pMRI might provide a means for overcoming the limitation of not having in vivo MRI obtained in correlative studies; microbleeds are lesions for which this technique appears to be well suited.

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Response
We thank Drs Messori and Salvolini for their interest in our study. The authors suggest postmortem MRI as a tool for studying cerebral microbleeds. We fully agree. In fact, we would like to draw their attention to 2 studies that were cited in our article.1,2 Fazekas et al performed postmortem MR imaging on the brains of 11 patients who had died of intracerebral hemorrhage.1 They found small areas of signal loss on gradient-echo T2*-weighted images in 7 brains. These changes correlated well with focal hemosiderin deposits on histological sections. Similar results were obtained in the study by Tanaka et al.2

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Improving the Assessment of Outcomes in Stroke: Use of a Structured Interview to Assign Grades on the Modified Rankin Scale
To the Editor:
We read with interest the article by Wilson et al,1 describing the use of a structured interview for the modified Rankin Scale (mRS). We attempted a similar exercise to validate the assessment of the mRS over the telephone by nonphysician interviewers using an analogously structured interview.

Thirty-four patients with a discharge diagnosis of stroke participated in the study 3 to 6 months from the day of admission. All patients were seen in person first, where they provided informed consent, by two trained personnel (one stroke neurologist or one of three stroke nurses). Each patient was interviewed consecutively by two interviewers in the Stroke Prevention Clinic or, for badly disabled patients, at a current place of residence (long-term care facility, nursing home, or rehabilitation facility) and the mRS assigned. Each face-to-face interview was followed by a telephone interview conducted by trained interviewers following a structured questionnaire within 5 days of the original interview. No proxy interviews were used. Each person rated the patient on the mRS, blind to the other raters’ score. Overall, three observers scored each patient’s outcome.

Two telephone interviewers were not medical professionals (RN or MD) but had 5 or more years of experience with telephone interviewing, had completed a course in telephone interviewing, and were considered experienced. Questions were scripted and deviations from the script were not permitted. The study was approved by the local Ethics Review Board.

Agreement, assessed using unweighted κ statistics with 95% confidence limits, was excellent between the two observers in the stroke clinic (κ=0.72 [0.55 to 0.89]), but less impressive between either clinical observer and the telephone interviewer (κ=0.38 [0.21 to 0.55] and κ=0.30 [0.13 to 0.47]). The telephone interviewer was most likely to agree with the in-clinic observer at the extremes of the scale (mRS=0 or mRS≥4). In the mid-range where the scale is commonly dichotomized (0 to 2 versus 3 to 5 and 0 to 1 versus 2 to 5), the telephone interviewer correctly rated the patient only 50% of the time.

Predictably, a structured interview for the mRS improves reliability between observers. However, our experience suggests that telephone assessment of the mRS may result in substantial variability in scoring. It remains important for physicians and/or trained nurses to score patients in person rather than relying on telephone interviewers.

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Response

Telephone interviews are a popular method of assessing outcome after stroke because of their low cost and simplicity. Studies have indicated that information concerning activities of daily living after stroke can be reliably obtained by telephone.\(^1\)\(^,\)\(^2\) In contrast, Hill and colleagues found low interobserver agreement for the modified Rankin Scale (mRS) when using a structured questionnaire.

The report sounds an appropriate cautionary note and serves as a reminder that it has not been fully established what contributes to the success or failure of telephone interviews. For example, it is not clear whether it is better to adhere to a script or allow rephrasing of questions when there appear to be communication problems. Telephone interviews tend to elicit shorter, less informative responses than face-to-face contact, and this may contribute to disagreement between interviewers. Use of skilled interviewers, as here, should help to minimize these problems. However, in addition to standardizing the questions, we specified the criteria that are used to interpret the responses.\(^3\) The midrange of the mRS is particularly problematic in this respect, because the categories are not well defined and therefore open to rater interpretation. Differences in interpretation are more likely when interviewers come from different professional backgrounds, and this may also contribute to the low agreement found by Hill et al. Previous work shows that differences in observers may be more important than differences in modality.\(^1\)

We have not yet specifically tested the modified Rankin Scale structured interview (mRS-SI) in a telephone interview, but we hope that the significantly improved interrater reliability of the mRS-SI would be reproduced in this setting. By specifying the definition of each level of the mRS, the mRS-SI removes a large part of the subjectivity that blights distinction between shades of disability. Further work has confirmed that the benefits of the mRS-SI are more striking when raters from varied backgrounds are involved.

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Contribution of Stroke to the Cochrane Stroke Group Trials Register
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