Letters

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Analgesic effects of sweet solutions and pacifiers in term neonates

Suckling at the breast is better than sweet solutions and pacifiers

EDITOR—A breastfeeding mother spontaneously comforts her distressed infant by putting him or her to the breast. It is a pity that Carbajal et al, when assessing the analgesic effects of orally administered glucose and sucrose in healthy term neonates, did not include a comparison group of infants given breast milk, which is rich in lactose and naturally sweet.[1] It would also have been appropriate to compare the analgesic effect of using a pacifier with that of suckling at the breast before and immediately after the painful procedure.

Pacifiers and sugar solutions given unnecessarily to healthy neonates are not proved to be "simple and safe interventions," as Carbajal et al state. Exclusive breast feeding (for about the first six months) is the World Health Organization's recommendation.[2] Two of the evidence based "ten steps to successful breastfeeding," developed by the WHO/Unicef Baby Friendly Hospital Initiative, are step 6 ("Give newborn infants no food or drink other than breast milk, unless medically indicated") and step 9 ("Give no artificial teats or pacifiers, also called dummies or soothers, to breastfeeding infants").[3]

Anything that may interfere with the establishment of lactation or undermine the mother's confidence in breast feeding is to be avoided. I hope that this flawed piece of research will not result in either pacifiers or sugar solutions being "widely used for minor procedures in neonates."[1]

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Use of pacifier may modify responses measured on rating scale

EDITOR—Carbajal et al conclude that the analgesic effects of both pacifiers and sweet solutions are clinically apparent and that pacifiers are more effective than sweet solutions alone.[1] As a measure of pain they used a rating scale, douleur aiguë du nouveau-né (DAN), which has been described previously.[2]

This scale uses facial expression, limb movements, and vocal expression to give a score between 0 and 10. Low scores mean no or little pain, and higher scores mean that the infant experiences more pain. It is apparent that the results in the two groups treated with pacifier alone and with pacifier combined with sweet solution differ from the results in the other groups in two ways: the groups whose treatment included a pacifier have a lower mean score and show a less varied response to the stimulus of venepuncture.

I would suggest that the less varied response to the stimulus is due to the pacifier itself. The ability to express a range of facial expressions will be modified by sucking on a pacifier in a way that reduces the possible responses on the rating scale. It would be interesting to see ratings of infants who do not have venepuncture and their ratings on the rating scale with and without pacifier.

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Surely evidence is not needed to justify cuddling babies in pain

EDITOR—The results of Carbajal et al's trial were not surprising.[1] The study concluded that non-nutritive sucking on a pacifier (dummy) was more successful in producing analgesia in neonates during venepuncture than the use of glucose or sucrose solutions.

In the accompanying editorial Choonara states that "parents know that a crying baby needs comforting and will hold their infant close. Breastfeeding mothers will give their infants the opportunity to breast feed, even if they are not hungry."[2] Choonara tells us how the study confirms that these actions of mothers are appropriate, but I question whether we need a scientific study to support deeply engrained human responses that have been witnessed to work throughout the ages.

The paper's authors comment that the mechanism by which pacifiers induce analgesia is unknown. I would offer instinct and conditioning as two possible mechanisms. Most parents know to hold their distressed offspring, but it is equally true that children naturally seek proximity to their attachment figures when in pain or distress. The pacifier mimics the breast, and psychobiological processes associated with the mother-child relationship and reduction in distress are perhaps triggered in the infant; the relation between reduction in distress and reduction in perception of pain is well recognised.

A growing body of evidence suggests that disruption of the natural, instinctive "knowledge" and interaction between mother and child can have detrimental effects on emotional development; the effect of postnatal depression is an example.[3] We can all recognise a basic need for safety and security, and it seems unsurprising that children need the same to develop emotionally.

Choonara believes that the use of interventions including cuddling for pain control needs to be evidence based. Why? As he acknowledges, parents will not change their behaviour in the face of research findings. They would be right not to: they know that cuddling works. Science does not offer us absolute truths; instead it offers us answers with a given degree of certainty. This certainty will never be large enough to justify attempted suppression of the natural, magical responses evoked in a mother by her distressed baby.

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Measures of pain must be validated in young children

EDITOR—Using a behavioural pain score (facial expression, movement, and vocal expression), Carbajal et al concluded that oral sugar solutions and non-nutritive sucking were analgesic in neonates.[1] Their study shows not analgesia but a reduced behavioural response to pain in neonates.

There are two main problems: firstly, what is meant by the term analgesia, and, secondly, how can you check the validity of a pain scoring system? Analgesia is defined as the absence of pain on noxious stimulation, and pain is defined as always a subjective experience.[2] Subjective self report measures of pain that are used in adults are impossible to use in children before they can talk. Therefore proxy responses such as behaviour (loudness and duration of cry, facial expression, body posture, mobility, alert-

ness), physiology (heart rate, blood pressure, respiratory rate, palmar sweating, oxygenation, intracranial pressure), and endocrine responses (concentrations of cortisol, catecholamine, glucose) are used. The difficulty is that these are all non-specific markers and are influenced by factors such as fear, anxiety, and medical problems.

The sole use of behaviour as a measure of pain can be misleading.[3] "Sweet flavoured pacifiers can calm a crying baby but should never be regarded as providing major analgesia."[3] Likewise measurement of the endocrine response alone is inadequate.[4] An example is that dummies (pacifiers) reduce the behavioural response to pain (sleep, alertness, crying) but do not reduce the endocrine response (cortisol concentration).[5] Colloquially, we do not use the term analgesia to describe techniques such as distraction or rubbing of a sore leg, which influence only one dimension of pain.

The second problem is that scoring systems can be tested for internal validity such as consistency between different observers and showing that there is an increased response to what is perceived as increasingly painful circumstances. Rarely, pain scores are validated against other pain scoring systems, but we have no gold standard for comparison.

This is more than semantics. We need to validate our clinical scoring systems against all dimensions of pain, including behaviour, physiology, endocrine response, development, culture, and environment. Until we have better measures of pain in children before they have can talk we should be wary of concluding more than the evidence shows. If all that sugar and sucking does is reduce the external expression of pain then we are treating ourselves, the carers, rather than the children.

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Trial of drug treatment to alleviate pain in neonatal intubation is needed

EDITOR—Carbajal et al address the issue of neonatal pain relief,[1] and in the accompanying editorial by Choonara health professionals are encouraged to study the painfulness of clinical procedures and use measures to prevent pain.[2]

Neonatologists agree on the importance of pain relief for newborn babies undergoing invasive procedures, such as placement of a chest drain. Analgesia decreases the incidence of accidental extubation and provides pain relief for ventilated newborn babies.[3] Yet for the most painful procedure—intubation—neonatologists in the United Kingdom have been cautious. American and Australian neonatal intensivists have been using intravenous drugs for some time when patients need intubation.

Evidence suggests that intubation done when the neonate is awake is associated with higher spikes in intracranial pressure than that done when general anaesthesia is given.[4] Even awake neonates who have been paralysed have shown significant increases in mean arterial blood pressure and intracranial pressure, indicating the effect of pain.

Adequate anaesthesia prevents swings in blood pressure and thus potentially the development of intracranial haemorrhage. Although one study showed that there was no hypertensive response in neonates who were intubated while awake, changes in intracranial pressure were not measured.[5]

So that we know whether or not to follow the practice used abroad, a trial of drug treatment to prevent pain in neonatal intubation is necessary.

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Authors' reply

EDITOR—Currently, most minor procedures in neonates are performed with little or no analgesia. We found that pacifiers can effectively relieve pain and that the analgesic effect is synergetic with sucrose. To our knowledge, this latter effect, which has practical implications, had not been reported before our study. Recently, Blass and Watt reported the same effect.[1]

Campbell wonders why we did not include breast milk or suckling at the breast before and immediately after painful procedures. Our study included six groups, and it would have been difficult to add more—firstly, because of the masking constraints imposed by a randomised double blind study, and, secondly, because we aimed to compare the analgesic effects of non-nutritive sucking with those of sugary solutions. A single study cannot answer several questions at once.

Analgesia induced by milk has been shown in newborn infants.[2] This effect was not related to lactose and was modest compared with that of sugar. We do not agree with Campbell when she states that pacifiers and sugar solutions given for analgesic purposes are given unnecessarily. We adhere to the "ten steps to successful breastfeeding" and consider that, with regard to step 6, relief of neonatal pain with pacifiers and sugar solutions is medically indicated. We do not think that occasional use of pacifiers or small volumes of sterile glucose or sucrose solutions for a painful procedure should be regarded as equivalent to frequent or routine use.

Blomstrand suggests that the less varied response to venepuncture in infants treated with a pacifier may be due to these infants' inability to express a range of facial expressions during the treatment. This hypothesis can be rejected for at least two reasons. Firstly, when one evaluates facial expressions on the rating scale that we used the modification of only one of eye squeeze, brow bulge, or nasolabial furrow is enough to determine the intensity of this item. Eye squeeze and brow bulge are not incompatible with sucking. Secondly, infants who suck a pacifier make several pauses between sucking bursts, which gives them the opportunity to express grimacing.

Morris asks if evidence is needed to justify cuddling a baby in pain. Obviously not. However, studies that determine the efficacy of behavioural interventions in preventing pain in neonates are welcome for, as Choonara states,[3] they can encourage health professionals to modify their behaviour. Morris's hypothesis offering instinct and conditioning to explain the mechanism by which pacifiers induce analgesia is interesting. Blass and Watt have suggested that antinociception and pain blockades induced by orogustatory and orotactile mechanisms are likely to be occurring at the level of the dorsal horn of the spinal cord.[1]

Rogers's concern about the difference between analgesia and reduced behavioural response to pain is theoretically valid. As he states, pain has been defined as a subjective experience. This definition has led to many advances, but it challenges our understanding of pain because it does not apply to living organisms that are incapable of self report. This includes neonates and older infants and many adult patients.[4]

The biological and behavioural reactions to pain are evident in term and preterm neonates. The fact that neonates' expression of unpleasantness does not fit within the strict definition of pain contributes to the failure to recognise and aggressively treat pain in children.[4] Increasing evidence supports the specificity of facial expressions as a manifestation of pain in neonates. As we stated in our paper, we assumed that the more pronounced the facial expressions, limb movements, and vocal expressions the greater the pain in the neonates.

Rashid makes an important point. Endotracheal intubation is a powerful noxious stimulus with potential adverse effects. Although premedication is mandatory for endotracheal intubation in adults, most neonatal units do not sedate neonates before intubating them. Recently, Bhutada et al showed that the heart rate and blood pressure of neonates who are premedicated with thiopental before intubation remain

nearer to baseline values than do those of similar infants not given premedication.[5]

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Diagnose and be damned

Corroboration is important when children's illnesses are diagnosed

EDITOR—Marcovitch's arguments about treatment of the chronic fatigue syndrome (myalgic encephalomyelitis) in children are illogical.[1] He writes of the "hatchet job" performed by *Panorama* in the programme of 8 November and refers to the *Washington Post*'s policy that news requires corroboration.

One of the responses to his article, by Wessely [published here, p 1005], states, "contrary to the message of the programme, the management of chronic fatigue syndrome in children is not contentious."[2] In referring to a case reported by *Panorama* Marcovitch states that "parents' views and those of the local medical team were in conflict." Yet the programme made clear that the dispute was between the parents supported by their own medical advisers and the local medical team, so perhaps there is greater disagreement than has been asserted.

Marcovitch discussed at length Munchausen's syndrome by proxy; *Panorama* labelled one of the cases of myalgic encephalitis as being a case of this syndrome. No one likes receiving emotional, intemperate outbursts, even from people who think they have been wrongly accused. But what is sauce for the goose is surely sauce for the gander. Even doctors sometimes make mistakes, yet Marcovitch disregards the possibility that parents, knowing themselves innocent, may feel themselves to have been receiving exactly the same type of vituperative attack that he objects to when doctors are on the receiving end. Such allegations turn on fact rather than clinical opinion so should be subject to Marcovitch's own test of corroboration.

Innocent people are made angry by accusations that, if made without justification in any other context, could end in High Court actions for defamation. They often react vigorously to them, to give paramount importance to the interests of their children and to preserve the integrity of their families. Clinical opinion may be highly speculative in nature. Yet alone of professionals, some doctors seem to regard their opinions as paramount, even when they fly in the face of the facts. Lawyers may form professional opinions about cases but expect to see them challenged during legal proceedings. Journalists, as Marcovitch himself has suggested, should seek corroboration of their views.

Much heat could be taken out of the situation if some doctors approached the care of children with myalgic encephalomyelitis with greater humility and understanding. They should attempt to build the type of partnership with parents that is clearly best practice and in line with the intentions of legislation on child care.

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Doctors must remember their rights and obligations to infants and children

EDITOR—Marcovitch's article on doctors who have exposed cases of child abuse is unfair.[1] The NHS inquiry into some of the work carried out by the department headed by Professor Southall was set up to investigate concerns with research that we had raised through our member of parliament. To date no one has been able to refute our allegations or alleviate our concerns. All our evidence is written by the researchers themselves, and we have never accused any clinician of anything we could not substantiate.

The complaint about continuous negative pressure ventilation has never been a campaign directed at Southall or child protection issues. We have attacked a system that allows maverick clinicians to conduct research in an ungoverned manner and the culture of subterfuge that surrounds the gaining of consent and the patient information given. We have attacked the handling of complaints and the attitudes of the trusts, which close ranks.

Doctors should be accountable for their actions and should be able to justify their decisions to their patients. Patients are often forced to look to the media to expose their plight because of the lack of cooperation and misleading information from the trusts.

The *Guardian* was probably the only newspaper to write an article based on the BMA's and Southall's press release about a campaign to obstruct his child protection work[2]—the other newspapers realised its inaccuracies. The *Guardian* quickly made a public apology after publishing the article, and the BMA, which also published it,[2] is considering its position after we suggested that Southall's statement in the press release could be libellous.

If Southall had made it clear to Channel 4 that he could not discuss the use of continuous negative pressure ventilation before the broadcast, why did he then proceed to answer questions around the issue? He was not obliged to and could have refused. Indeed, his own hospital was not happy that he should be involved with any media that pre-empted the various inquiries about research in general and more specifically his own work.

Marcovitch ends by saying that it is time the profession hit back. Surely now is the time for the medical profession and the public to work together. Scandals have evolved because of self regulation and damage limitation. This outdated "them and us" attitude has no place in a modern system of public involvement and working in partnership. Openness, transparency, and accountability are the only way forward.

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2 BMA. Leading paediatrician hits back at orchestrated campaign to obstruct child protection work. (Press release 1999 Oct 11.) (www.bma.org.uk)

Inquiry should be held into doctors involved in child abuse investigations

EDITOR—Since the publication of Marcovitch's article on doctors who have exposed child abuse[1] and my initial electronic responses to it (published here, in the following cluster)[2] there have been several developments. Professor Southall and Dr Samuels (one of his colleagues) were suspended without prejudice during investigations into their child protection work.[3] The expert opinion given by Professor Sir Roy Meadow in a murder trial was criticised by colleagues,[4 5] and concerns are to be incorporated into an inquiry into Munchausen's syndrome by proxy by the Royal College of Paediatrics and Child Health (L Tyler, secretary of the college, personal communication). The BMA's press release[6] was withdrawn. With inquiries under way Marcovitch might have been wiser to wait rather than to offer hostages to fortune.

Marcovitch claims that doctors who work with cases of child abuse are being hounded. But most doctors work unobtrusively, and without generating complaints, to protect children from abuse within the framework laid down by parliament after the "Cleveland scandal," when child abuse was reported in Cleveland. He should ask why a very small proportion of doctors—paediatricians for the most part—have exposed themselves to sustained complaints. The answer is that they would not accept after the Cleveland scandal that child protection was a multiagency task and that doctors must not use untested diagnoses before they had been accepted by the profession.[7] The diagnosis that has led to so much reaction—Munchausen's syndrome by proxy—may at last be given proper scientific review.

When Marcovitch says: "Southall … has received threats of violence, and … his charity's equipment has been destroyed. There is, however, no evidence to link this darker side of campaigning to Morgan or the public faces of the movement…." I have to speculate that the second sentence was inserted on legal advice, because what follows ("Surely Channel 4 News, the *Sunday Times*, the *Independent*, and others have been barking up the wrong

tree. The real story is what drives Morgan and others like him, how the 'loose network' is funded, the backgrounds of its supporters, and whether its campaign has destroyed some children's protection") suggests that there is after all a sinister side.

Marcovitch's suggestion is a two edged sword; he and the colleagues he defends must submit to an investigation as well. I would welcome an inquiry by the health select committee into the part played by paediatricians and child and adolescent psychiatrists in child abuse investigations in the decade after the Cleveland scandal. The inquiry should also look at the quality of evidence given by medical experts behind the closed doors of family courts in secret proceedings under the Children Act 1989.

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Management of CFS in children is not contentious

Editor—I congratulate Marcovitch on his exposition of the methods used by some activists to hound those paediatricians who are prepared to consider that parents do not always act in the best interests of their children.[1] He draws attention to an edition of *Panorama* on the equally contentious subject of the chronic fatigue syndrome in children. This was a particularly biased and pernicious account of an area where balance and reason are needed, not polemic and distortion.

Contrary to the message of the programme, the management of the chronic fatigue syndrome in children is not contentious. Programmes of rehabilitation rather similar to those now shown to be effective in adults—including some form of support, encouragement, behavioural management, and activation—are now the mainstay of treatment in virtually all centres helping children with the syndrome and their families. Indeed, it is hard to find dissenting voices in the professional literature.

Such programmes, including the one run at King's College Hospital, necessarily involve collaboration, not confrontation, with both the child and the family. Colleagues and I will shortly be presenting an uncontrolled case series, adding to the literature showing both the effectiveness and the acceptability of such approaches. We have just started a randomised controlled trial as part of the normal process of showing efficacy in the most scientific fashion.

Any parent who watched the one sided *Panorama* programme might be forgiven for thinking that management of the chronic fatigue syndrome in children involves coercion and the courts and might be discouraged from seeking help. Of course cases of parents harming their children—even, occasionally, with good intentions—do exist. Some appear nowadays under the guise of the chronic fatigue syndrome or bizarre allergic disorders,[2] and when a doctor believes that this is happening he or she has statutory duties to fulfil. But such cases are fortunately extremely rare—we have not yet encountered such a problem at King's—and tell us little about the general management of the syndrome.

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"Correcting" bmj.com

What happened to the false allegation in *bmj.com*?

Editor—Several months ago I received an email from a reader puzzled by a reference that I had made in an earlier rapid response[1] to Marcovitch's article on doctors who have exposed child abuse[2] [a shortened version of that earlier response is published here as the third letter in the previous cluster, p 1004]. I had written that Marcovitch had made a false allegation of perjury, but the reader was puzzled because there was no such false allegation when he came to read the response.

Soon after I wrote my response a "rapid correction" was made and a retraction of the allegation posted. The reader was not to know this, for soon after that, and before he read the response, the allegation was deleted from the text in *bmj.com* and the correction was also deleted. The correction appeared in *bmj.com* on the same day that Marcovitch's article was published in the paper journal. Any readers who see only *bmj.com* would be puzzled because both Marcovitch's allegation and *bmj.com*'s correction have been deleted from *bmj.com*.

The allegation and the correction appear in the printed *BMJ*, which must be assumed to be the definitive text. The trend now is towards electronic versions of biomedical journals having different content from the printed ones, by design, and there being online journals with no printed version. Is there no one who shares my concern that internet publications should have the same permanent authenticity as printed ones?

If publishers may remove text, or even add text, what evidentiary value do such documents have as source materials?

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Editor's reply

Morgan raises an important question. It is clearly impossible to correct errors in the paper journal after publication by correcting every copy. It is, however, possible to correct *bmj.com* by deleting the error or correcting it. But should we do that?

We have decided not to in general. Instead, we will correct errors as we usually do by publishing a correction. That correction is then linked to the piece it is correcting, so that anybody reading it will be aware that there is a correction. The electronic medium does thus have an advantage over the paper medium.

We have adopted this policy to leave a trail of errors and corrections. They may well prove to be important at some future time. There is something unnerving—and totalitarian—about "rewriting" history.

An exception to our policy is when a lawyer tells us to remove something, which is what happened in the case that Morgan is writing about. Perhaps lawyers and the law will eventually take a different view.

Richard Smith *Editor, BMJ*

How much to do at the accident scene?

Paramedic agrees with most of comments about prehospital care

Editor—I agree with most of Cooke's comments about prehospital care by paramedics in the United Kingdom[1] but would like to raise a few points. As a paramedic in London, I realise that my remarks may not have national generalisability, but their essence should travel across regional boundaries.

Cooke is correct in his assertion that "Changes are needed if the paramedic is to be an independent practitioner." Paramedics are the product of doctors; we are what they made us. The idea of having extended role ambulance staff began during the 1970s and '80s. Unfortunately, the original aspirations of our worthy fathers were overtaken by political posturing.

The original concept was for a small cadre of highly trained paramedics who would be targeted at the small percentage of 999 calls where the patient would benefit from extended skills before reaching hospital. The emphasis was initially on calls for patients with cardiac problems; later this was extended to patients with trauma. When the ambulance dispute in 1989 was eventually concluded a promise was made that there would be a paramedic in each vehicle. This went against the original concept of sending a paramedic to every call made about a life threatening condition—which would have required accurate and effective assessment and deployment.[2]

Cooke is correct that paramedics need the underpinning knowledge to make appropriate decisions about patients' treatment. Degree programmes will help provide this knowledge, along with experiential learning. The proposed development of practitioners in emergency care will certainly address this issue.[3] Education alone, however, will not alter some of the problems currently encountered in the prehospital phase:

(1) Paramedics need to question what more can reasonably be done for their patient after securing the airway and checking breathing at the scene. Problems with circulation should be dealt with on the way to hospital.[4]

(2) The choice of hospital needs to be addressed. Preventable deaths may be avoided by transporting the patient to the most appropriate multidisciplinary hospital, not the nearest hospital.[5]

(3) The fact that little direct communication occurs between the receiving hospital and the ambulance crew needs to be considered.

Research into prehospital care is needed and should include input from paramedics; they could be part of the research team. The old maxims of "stay and play" and "load and go" could perhaps be replaced with "play while running" to the most appropriate hospital. That way we might be able to make a real, quantifiable difference.

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Anaesthetists are best people to provide prehospital airway management

Editor—Although I agree with Cooke's general conclusions that airway and breathing problems must be treated at the roadside and circulation ones in hospital, I disagree with his statement that the airway can be easily secured at the scene.[1]

Two studies examining prehospital deaths from trauma in the United Kingdom have shown significant morbidity and mortality from airway obstruction. Hussain and Redmond concluded that up to 85% of patients who die with survivable injuries before reaching hospital may do so because of airway obstruction.[2] In another study airway obstruction was thought to have contributed to death from major trauma in 28% of patients treated by ambulance crew.[3] These figures do not support the assumption that the airway can easily be secured at the scene.

The airway is often compromised because of limited skilled help; poor lighting; a difficult patient position; blood, vomit, and debris in the upper airway; and poor views at laryngoscopy due to stabilisation of the cervical spine; in addition, the patient must be managed in a moving ambulance. Prehospital airway management is therefore difficult, even for anaesthetists with extensive experience in airway management. Paramedics in the United Kingdom who start in this environment having performed just 20 intubations do not have sufficient training to manage many of the more difficult cases. Furthermore, because paramedics are not trained to use neuromuscular blocking drugs, the only patients with trauma who are sufficiently obtunded to tolerate endotracheal intubation by them have invariably got non-survivable injuries (G Davies, personal communication).

Having completed training in endotracheal intubation, an average paramedic will intubate only about eight patients a year, and not all ambulance services undertake formal refresher training in airway management. Difficult clinical scenarios and limited training may explain why only 63% of attempts at intubation by paramedics are successful.[3]

Paramedics do not have the necessary skills to deal with the airway in patients with major trauma. Prehospital airway management must be undertaken by those with much greater experience than 20 intubations. Graduate courses will not improve airway management; what is required is much more practical training in airway skills. Currently the only group able to provide advanced prehospital airway management are anaesthetists, who have practical experience and can use neuromuscular blocking drugs and induction agents. The United Kingdom is the only country in Europe that does not routinely employ this standard of prehospital care; until it changes its practice, inadequate airway management will continue to contribute to the unacceptable prehospital morbidity and mortality of patients with trauma.

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Prehospital interventions prolong prehospital time

Editor—The question of how much prehospital care to give to patients ("scoop and run" versus "stay and play")[1] is very relevant in Denmark, where the ministry of health is considering extending the ambulance technicians' curriculum. We have carried out a prospective study (unpublished) of the relation between prehospital interventions and time at the scene.

The study was of all 5571 patients with acute conditions transported to hospital by ambulances from two ambulance stations in the county of Roskilde in 1998. No selection of patients took place. The ambulances cover a mixed urban/rural area with roughly 150 000 inhabitants. Prehospital interventions took place for a wide variety of indications: 2479 of the patients received oxygen at the scene or in the ambulance, and ambulance technicians carried out electrocardiography on 1131 patients. The median time at the scene was 8.0 minutes, and the median transport time to hospital was 12.0 minutes.

Despite the variety of indications for prehospital interventions the technicians had relatively little experience. In 1998 each technician was present, on average, on 7.9 occasions when drugs were given for angina, on 4.0 occasions when drugs were given for asthma, at 3.4 cardiopulmonary resuscitations, and at 3.0 defibrillations.

For most prehospital interventions there is little evidence of a positive effect on outcome,[2] while shorter total prehospital time may be an important factor in survival for patients with trauma.[3] We found that use of each kind of prehospital intervention implied a prolonged time at the scene and that there was a direct correlation between the number of basic prehospital interventions used and the time at the scene.

When the scope of the ambulance technicians' curriculum is considered, several factors should be borne in mind: the limited experience of the technicians, the lack of evidence of a positive effect on outcome of most prehospital interventions, and the prolongation of the time at the scene. New interventions will usually be technically demanding, their use will rarely be indicated, and the skills requiring the most technical knowledge deteriorate the fastest.[4]

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Predicted impact of intravenous thrombolysis

Patients who died or recovered fully should have been included in analysis

Editor—Jørgensen et al report a simulation of the impact of intravenous thrombolysis on prognosis for a general population of stroke patients.[1] Although we do not argue with their conclusion that comparatively few patients with acute ischaemic stroke will benefit from thrombolytic treatment, we believe that their analysis of the data is flawed.

During their retrospective analysis Jørgensen et al identified patients who fulfilled the criteria for thrombolysis and then excluded patients who died or had a

full recovery. They subsequently excluded the same groups of patients from the ideal scenario in which all patients were admitted within the time window for thrombolysis. Had thrombolysis actually been given, the outcomes for these patients would have been unknown at the time of administration. These patients should therefore have been included in the analysis.

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1 Jørgensen HS, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. Predicted impact of intravenous thrombolysis on prognosis of general population of stroke patients: simulation model. *BMJ* 1999;319:288-9. (31 July.)

Another trial is needed

Editor—The paper by Jørgensen et al provides a small counterbalance to the enormous propaganda behind an expensive, minimally tested, and potentially harmful intervention.[1] The real ratio of benefit to risk of thrombolytics for stroke may even be far worse than Jørgensen et al calculate, for the following reasons.

Firstly, even fewer stroke patients in community practice would qualify for treatment with alteplase if a strict three hour cut-off point for completion of all diagnostic activities and initiation of the drug were used.

Secondly, inclusion of even a few of those patients with seizure, tumour, infection, etc, whose condition mimics stroke and who constitute perhaps 15-25% of patients diagnosed as having "stroke" in community practice but were rare in the expert based National Institute of Neurological Disorders and Stroke (NINDS) trial,[2] could easily overwhelm any benefits of alteplase, since such patients cannot possibly benefit from treatment but can certainly be harmed.

Thirdly, treatment of even a few patients with subtle haemorrhage, undetected because the computed tomography scan was not read by a neuroradiologist, would have the same effect—and there is good evidence that very few general radiologists, neurologists, or emergency physicians are able to identify most or all such haemorrhages.

Fourthly, treatment outside the specialised environments used in NINDS, and without the experts participating in such studies, could lead to far more harm when a drug that produces such a high rate of intracranial haemorrhage under ideal conditions is used.

Fifthly, of seven trials of lytics in stroke to date, only the fairly small NINDS trial has had positive results—the results of the six that have been either neutral or negative (including several with dramatically increased mortality in patients treated with thrombolytics) are typically ignored.

"Another trial is needed" is a generous summary of the available evidence. Given the extremely limited evidence of efficacy, the marginal nature of that efficacy (under the best of circumstances), and the strong likelihood that such efficacy will not translate into effectiveness in community practice—as well as the real potential for harm—approval of this drug in the United Kingdom, for the treatment of stroke should be withheld unless and until far more definitive evidence (for effectiveness as well as for efficacy) is forthcoming.

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Author's reply

Editor—Our simulation model of intravenous thrombolysis (using alteplase) in patients with acute stroke model had two purposes: firstly, to estimate the target population for intravenous thrombolysis in an unselected population of patients with acute stroke; and, secondly, to estimate the number of patients who would actually benefit from this treatment—provided that the results of the only trial with positive reults so far, the National Institute of Neurological Disorders and Stroke (NINDS) trial,[1] can be reproduced.

In the study we included the 1197 patients from the Copenhagen stroke study, a community based study in which all patients with acute stroke from a well defined catchment area of Copenhagen had all their acute treatment and rehabilitation in one large stroke unit regardless of their age, the severity of the stroke, and their comorbidity prior to stroke. In the first part of our analysis we estimated the target population for alteplase treatment using the inclusion criteria from the NINDS trial. We included patients who eventually died or who recovered fully. A disappointing rate of only 4% of the patients fulfilled the inclusion criteria.

To estimate the number of patients who would have benefited from intravenous thrombolysis we excluded the patients who either recovered fully and had no functional disability after completed rehabilitation or who died during hospital stay. Berwaerts et al argue that these patients should have been included as the outcomes for them would have been unknown at the time of drug administration. We believe, however, that it was justified to exclude them from the analysis of the number of patients who would actually benefit from alteplase treatment. None of these patients would have benefited from treatment because they either had a complete recovery without thrombolysis or they died. As the NINDS trial shows, alteplase treatment has no effect on overall mortality.

The results of our study in combination with the arguments offered by Hoffman should raise serious questions about the approval of intravenous thrombolysis in patients with acute stroke. The possible, but not proved, marginal benefit of intravenous thrombolysis in a very small number of patients (1 out of 160 patients in our simulation model) should be considered in contrast to the marked benefit of treatment and rehabilitation of unselected patients in specialised stroke units,[2–5] regardless of their age, sex, severity of stroke, and comorbidity. Economic resources are limited and should be used where they benefit most patients in the most effective way—in this case by providing early, intensive rehabilitation to all patients in dedicated stroke units.

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Intention to treat analysis is related to methodological quality

Editor—In their survey of all randomised controlled trials published in 1997 in four major medical journals, Hollis and Campbell found that only 48% of the reports explicitly mentioned intention to treat analysis.[1] In a considerable proportion it was insufficiently described and sometimes inadequately applied. Their results are confirmed by our assessment of all randomised controlled trials published between 1993 and 1995 in the same four journals.[2] In addition to our assessment of ethical issues, we calculated the proportion of randomised controlled trials reporting intention to treat analysis in accordance with different descriptive and methodological characteristics.

In our review of 608 randomised controlled trials, we found that 290 of the trials (47.7%) explicitly mentioned that they applied the principle of intention to treat analysis. The reporting of this issue increased slightly between 1993 and 1995 (although the increase was not significant). Trials with a greater number of participants and those funded by the pharmaceutical industry were more likely to report the application of the intention to treat principle (table). In the multivariable logistic regression analysis, when we controlled for the general characteristics previously described, we found that trials with survival of patients as the principal outcome were

Reporting of intention to treat analysis in published clinical trials (1993-5)

	Total No	No (%) reporting intention to treat	Crude odds ratio for not reporting the use of intention to treat (95% CI)	Logistic regression multivariable model adjusted odds ratio (95% CI)	Odds ratio (95% CI) adjusted for descriptive characteristics
All sample	608	290 (47.7)			
Descriptive characteristics of the trials					
Journal:					
N Engl J Med	219	122 (55.7)	1	1	
JAMA	81	37 (45.7)	1.50 (0.90 to 2.50)	1.64 (0.92 to 2.92)	
BMJ	105	44 (41.9)	1.74 (1.09 to 2.79)	1.80 (0.96 to 3.39)	
Lancet	203	87 (42.9)	1.68 (1.14 to 2.46)	1.54 (0.95 to 2.50)	
Year of publication:					
1995	211	108 (51.2)	1	1	
1994	195	92 (47.2)	1.17 (0.79 to 1.73)	1.20 (0.78 to 1.86)	
1993	202	90 (44.6)	1.30 (0.89 to 1.92)	1.14 (0.73 to 1.77)	
Country of authors:					
Europe (except United Kingdom)	164	86 (52.4)	1	1	
United Kingdom	127	61 (48.0)	1.19 (0.75 to 1.90)	0.90 (0.52 to 1.55)	
United States	240	120 (50.0)	1.10 (0.74 to 1.64)	1.24 (0.75 to 2.07)	
Other	77	23 (29.9)	2.59 (1.45 to 4.60)	2.59 (1.38 to 4.85)	
Main specialty of authors:					
Medical specialties	432	213 (49.3)	1	1	
Surgery or medical-surgical	106	45 (42.5)	1.32 (0.86 to 2.02)	1.23 (0.76 to 1.99)	
Intensive or emergency care	37	18 (48.6)	1.03 (0.52 to 2.01)	1.08 (0.51 to 2.29)	
Public health	16	7 (43.8)	1.25 (0.46 to 3.42)	1.60 (0.54 to 4.74)	
Other	17	7 (41.2)	1.39 (0.52 to 3.72)	1.29 (0.44 to 3.82)	
Number of participating subjects:					
>500	171	109 (63.7)	1	1	
51 to 500	322	167 (51.9)	1.63 (1.11 to 2.39)	1.68 (1.12 to 2.53)	
⩽50	115	14 (12.2)	12.66 (6.68 to 24.10)	12.43 (6.24 to 24.36)	
Source of funding:					
Pharmaceutical industry	206	129 (62.6)	1	1	
Public agency	165	73 (44.2)	2.11 (1.39 to 3.20)	2.11 (1.34 to 3.34)	
Other	126	52 (41.3)	2.38 (1.52 to 3.75)	2.01 (1.22 to 3.30)	
Not reported	111	36 (32.4)	3.49 (2.14 to 5.68)	2.35 (1.34 to 4.10)	
Methodological characteristics of the trials					
Outcome:					
Survival	142	104 (73.2)	1		1
Other	466	186 (39.9)	4.12 (2.72 to 6.24)		2.86 (1.77 to 4.60)
Sample size estimation:					
Shown	281	167 (59.4)	1		1
Not shown	327	123 (37.6)	2.43 (1.75 to 3.37)		2.28 (1.55 to 3.37)
Compliance with treatment:					
Stated	532	261 (49.1)	1		1
Not stated	76	29 (38.2)	1.56 (0.95 to 2.56)		1.71 (0.98 to 2.99)
Reporting follow up or withdrawals:					
Reporting the number of patients withdrawn or lost to follow up	194	100 (51.5)	1		1
Not giving information about number of patients lost to follow up	414	190 (45.9)	1.25 (0.89 to 1.76)		1.45 (0.98 to 2.14)

A higher odds ratio means a higher probability of not reporting the use of the intention to treat principle.

more frequently reported to follow the intention to treat principle. In addition, those randomised controlled trials that gave no information about sample size were less likely to report the use of this principle (table). Randomised controlled trials not reporting the number of withdrawals or losses to follow up and those not reporting information about compliance with treatment were also less likely to report the intention to treat principle, although these results were not significant.

Our data support the relation between a higher methodological quality of the trials and the reporting of the intention to treat analysis. Our results reinforce the conclusions of Hollis and Campbell that the application of this principle still needs to improve because it seems that there has been no improvement between 1993 and 1997.[1] A joint effort of editors and researchers is needed to meet the CONSORT guidelines[3] and the authors' recommendations favouring intention to treat analysis.[1] A better quality of reporting will help readers to assess the design, conduct, and analysis of randomised controlled trials more critically.

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Using anticoagulation or aspirin to prevent stroke

Research was methodologically flawed

Editor—The paper by Hellemons et al is not justified in concluding that aspirin is the prophylactic choice in primary care for atrial fibrillation, if there is no clear indication for full anticoagulation.[1]

The study is methodologically flawed. As clinicians, we ask ourselves: "Which patient in atrial fibrillation should be given anticoagulants?" This is a statistical question about the risks and benefits of aspirin or warfarin for that individual patient.

In the power calculation Hellemons et al asked whether low anticoagulation (international normalised ratio 1.1-1.6) or aspirin should be used—but this is the wrong question. The choice should have been between aspirin and standard anticoagulation (INR 2.5-3.5). The increased incidence of major intracranial bleeding in the aspirin group compared with the anticoagulated groups (0.75% per patient year *v* 0.35%) calls into question the sagacity of using one tailed statistical tests.

As the study was underpowered, the question of whether standard anticoagulation or aspirin was better in preventing major cerebral infarction cannot be answered. Although there is a trend towards full anticoagulation (hazard ratio 0.67), the 95% confidence intervals are so wide (0.11 to 4.1) that the result is meaningless.

The arbitrary exclusion from standard anticoagulation of all people who were 78 years or older also undermines the study, for although it may have reduced the complication rate from anticoagulation, it will have also reduced the potential benefit.

This paper highlights the problems in reporting "negative" or "no difference" studies. It has failed to show "no difference" between standard anticoagulation and aspirin prophylaxis in atrial fibrillation, as clinically important differences could well exist within the confidence limits. The study adds little to previous work that does demonstrate benefit from anticoagulation[2] and may be misinterpreted as an excuse for

a nihilistic approach to the prevention of embolic episodes in primary care.

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Study does not have the power to show that aspirin is as good as anticoagulation

EDITOR—We welcome the data provided by Hellemons et al on the relative merits of anticoagulation or aspirin for stroke prevention in atrial fibrillation in a primary care population.[1] However, we feel that their interpretation of the data is misleading, and that the study raises more questions than it answers.

The arm comparing standard anticoagulation with aspirin involved 272 patients followed up for an average of three years, during which time there were 22 primary outcome events. The hazard ratio was 0.78 (95% confidence interval: 0.34 to 1.8) in favour of anticoagulation. The wide confidence interval does not exclude a potentially important advantage of anticoagulation over aspirin. Taken with the existing evidence for the superiority of anticoagulation over aspirin, this inadequately powered study provides no evidence to support the authors' conclusion that aspirin should be preferred to standard anticoagulation in primary care.[2 3]

Patients aged 78 years or more were excluded from standard anticoagulation and were randomised to receive low intensity coumarin or aspirin. Because half of patients with atrial fibrillation are older than 75 years, a crucial question is how people over this age should be treated.[4] Hellemons et al have confirmed the finding of the Stroke Prevention in Atrial Fibrillation Investigators that low intensity anticoagulation is ineffective,[5] and their study had (just) sufficient power for testing this comparison. However, the study avoids the more important and unanswered question of whether standard anticoagulation should be used for patients in this age group, in whom the risk of stroke is higher, but possibly so is the risk of haemorrhage.

We will shortly begin recruiting to a general practice based trial, the Birmingham atrial fibrillation treatment assessment study, which will specifically address this issue, randomising patients aged 75 years or over to receive warfarin (target international normalised ratio 2.5) or aspirin (75 mg).

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Anticoagulation has a major role in primary prevention of stroke in general practice

EDITOR—The paper by Hellemons et al[1] emphasises the conclusions of the Stroke Prevention in Atrial Fibrillation Investigators,[2] that not all patients with non-rheumatic atrial fibrillation benefit from therapeutic anticoagulation with warfarin. Their study population included a high proportion of patients (40%) with lone atrial fibrillation, who would not be expected to benefit from anticoagulation. Excluding patients with chronic heart failure and not randomising patients who were more than 78 years old to the standard anticoagulation limb would further reduce the power of their study to detect a reduced number of events in patients given warfarin.

The decision to prescribe anticoagulants requires careful assessment of the patients' risk of stroke and bleeding (including compliance difficulties and risk of falling). We are reassured by the low rate of bleeding ($<1\%$) in the anticoagulation arm of the trial which used local anticoagulation services.

It is important not to draw the conclusion that aspirin is as effective as an adjusted dose of warfarin for primary prevention in all patients with atrial fibrillation. Anticoagulation has a major role in managing patients with atrial fibrillation who are at high risk of stroke, but it requires more than the blanket approach of "atrial fibrillation therefore warfarin"[3] There is good evidence that warfarin is underused in clinical practice, which may be because consensus is lacking on who benefits from treatment.[4] Guidelines exist for rational use of aspirin and anticoagulation in atrial fibrillation.[5] These should be applied when assessing patients for prophylactic antithrombotic treatment.

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Results of the study cannot be generalised to the general practice population

EDITOR—Hellemons et al studied antithrombotic treatment in patients with non-rheumatic atrial fibrillation in general practice.[1] By using a screening method (checking the pulse) they were able to find more patients with atrial fibrillation than are usually known to the general practitioner. In a previous article about this study, they mentioned a prevalence of atrial fibrillation of 5.1% in patients aged 60 years or over.[2] This is comparable to the prevalence of 4.7% found by Sudlow et al in a community study in people aged 65 years and older.[3] In studies in general practice prevalence is about 50% lower. In our study conducted in general practice in the Netherlands we found a prevalence of 2.4% in patients aged 55 years or more (unpublished data). A general practice study in the United Kingdom found the same prevalence in patients aged 50 years or over.[4]

Thus a considerable proportion (50%) of the population with atrial fibrillation in the study by Hellemons et al had not previously been diagnosed with atrial fibrillation, whereas the other 50% were known to have such a diagnosis. It seems plausible that the cardiovascular risk profile of the previously "unknown" patients with atrial fibrillation is more advantageous than that of those with "known" atrial fibrillation. The inclusion of many low risk patients with atrial fibrillation could be the cause of the low cardiovascular event rate in the present study and of the lack of difference in efficacy between aspirin and coumarin treatment. We are therefore hesitant to generalise the results of this study to the general practice population, in contrast to the authors. In addition we wonder whether the power of Hellemons et al's study allows for the conclusion that aspirin is equivalent to coumarin. The confidence limits are rather wide.

We are interested to know whether the authors analysed the "known" and "unknown" patients with atrial fibrillation separately, whether there was a difference in prognostic determinants between these two groups, and whether this influenced the treatment effect. A difference could explain the contrasting results with other randomised controlled trials conducted in referred patients.

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Patients should be assessed for risk factors before deciding on prophylaxis

EDITOR—Hellemons et al reported that standard adjusted dose oral anticoagulation was no more beneficial than aspirin in primary care for patients with non-rheumatic atrial fibrillation.[1] As 30% of patients in this study were excluded from the trial because they were already taking oral anticoagulants, and patients at high risk of stroke (those aged more than 78 years) and hypertensive patients were excluded from the randomisation to dose adjusted warfarin, the results apply to only about 20% of patients with atrial fibrillation seen in primary care.

With only a 1% annual rate of stroke recorded in the study for patients aged less than 78 years, it is not surprising that no difference was observed in the treatment arms. The results from this preselected group of patients should not be applied to most patients with atrial fibrillation in the community. In the low risk group 3% of patients randomised to receive aspirin had a stroke, whereas 10% of the higher risk group had strokes. This illustrates the need for improving prophylaxis for high risk patients—the very patients excluded from being treated with an adjusted dose of anticoagulant. Furthermore, the risk of serious haemorrhage in the group treated with aspirin needs to be emphasised. As 3% of these patients had a major haemorrhage or cerebral bleed, aspirin should not be assumed to be a safer option.

Large hospital based clinical trials comparing dose adjusted anticoagulation with low dose warfarin and aspirin treatment have shown a consistent reduction in the rate of stroke in favour of dose adjusted oral anticoagulation, with no increase in bleeding complications. The third trial on stroke prevention in atrial fibrillation looked at high risk patients for stroke,[2] and the Copenhagen atrial fibrillation, aspirin and anticoagulation 2 study[3] and recent Italian studies[4] did not exclude patients at high risk for adverse events (in contrast to Hellemons et al's study). The patients most at risk from stroke are those with a history of thromboembolic disease, diabetes, hypertension, and cardiac failure and those female patients more than 75 years old. Most of the patients in primary care with atrial fibrillation fall into this category, with the treatment of choice being adjusted dose warfarin to achieve an international normalised ratio of 2-3. Hellemons has shown that some patients with non-rheumatic atrial fibrillation are at low risk of stroke. The conclusion that this may be the first choice for patients with atrial fibrillation in general practice is misleading. A proper clinical risk assessment for stroke and haemorrhage is required for all patients with atrial fibrillation before the best approach to prophylaxis is decided on. The report should not be used in primary care to justify the routine use of aspirin in preference to standard anticoagulation, however onerous monitoring warfarin treatment might seem.

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Aspirin is the logical choice for non-rheumatic atrial fibrillation

EDITOR—Hellemons et al's randomised controlled trial is one of only a handful of "head to head" comparisons of anticoagulation with aspirin.[1] The trial shows that aspirin is at least as good as anticoagulation in patients with non-rheumatic atrial fibrillation. However, anticoagulation is widely recommended as the best treatment for patients with non-rheumatic atrial fibrillation, on the grounds that the risk of stroke is reduced by 62% in comparison with placebo.[2] Aspirin is viewed as a suitable alternative only if anticoagulation is contraindicated, because aspirin is less effective in reducing the risk of stroke—22% in comparisons with placebo.[2] However, risk reductions are less impressive if all vascular deaths are considered.

Referral rates to anticoagulation clinics have increased dramatically over the past decade.[3] Hellemons et al's evaluation of standard anticoagulation versus aspirin shows no significant difference in the primary outcome. As shown in table 2, the hazard ratio comparing standard anticoagulation with aspirin for the primary outcome is 0.78 (95% confidence interval 0.34 to 1.80), which is equivalent to standard anticoagulation being 66% worse than aspirin and as much as 80% better than aspirin. But how much better would anticoagulation have to be to make it the treatment of choice? A look at cost effectiveness may help in making a decision. As a policy of widespread anticoagulation costs 15 times the use of aspirin alone,[4] anticoagulation would have to be 15 times as effective as aspirin and cause no adverse effects to achieve equal cost effectiveness. At the baseline rate of vascular events on aspirin of those eligible for standard anticoagulation in Hellemons et al's trial (2% a year), this translates to an event rate on anticoagulation of 0.13% a year. Hellemons et al's trial was more than adequately powered to detect such a difference and, taken with previous studies, indicates that a 15-fold advantage of anticoagulation over aspirin is extremely unlikely.

A preliminary systematic review of all trials comparing antiplatelet drugs with anticoagulants, including Hellemons et al's findings, gives a pooled relative risk of vascular deaths on anticoagulation of 0.97 (95% confidence interval: 0.73 to 1.27), suggesting that there is little to choose between these two options in terms of efficacy. If cost and safety are considered, then it is clear that aspirin is the logical choice.[5]

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1 Hellemons BSP, Langenberg M, Lodder J, Vermeer F, Schouten HJA, Lemmens Th, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ* 1999;319:958-64. (9 October.)
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Authors' reply

EDITOR—Ellis and Hans conclude that in the primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation study only 20% of the targeted general practice patients with non-rheumatic atrial fibrillation were studied. We did not include the group of patients who had already had a stroke or who had rheumatic heart disease because these patients do not represent a problem of prevention to the general practitioner in the context of our study question. A few patients refused to participate because they did not want to take coumarin.

Our population had less comorbidity compared with other atrial fibrillation studies (lone atrial fibrillation percentage was high). Based on population studies we could not have predicted the low incidence we found in our younger patients nor such a high prevalence in our elderly patients. We asked general practitioners to screen their population using pulse counts, and these patients might not be found in other studies.[1]

Thrombosis services in the Netherlands have a lot of clinical experience and are reluctant to give coumarin regularly to patients aged over 80 years for indications such as non-rheumatic atrial fibrillation, so our trial limited this treatment to patients aged 80 years or less.[2] In our prevalence

study the enhanced comorbidity showed that the risk of interfering comedication was realistic, as confirmed by the relatively high incidence of bleeding in the aspirin arm in patients >80 years.[3] Ellis and Hans noticed the important problem of bleeding, particularly in elderly patients.

Our data show that in general practice, for patients with atrial fibrillation who have little comorbidity, the benefit of coumarin does not outweigh potential haemorrhagic risks and that aspirin may suffice. For outpatients aspirin is a better option in terms of logistics rather than safety, as our study showed. From our trial we cannot conclude that low intensity coumarin solves this problem. Ellis and Hans state that the conclusion from our study that aspirin suffices for primary care patients is false, because we did not investigate the high risk patients. At the same time they state that our patients were at the same risk as patients in AFASAK, stroke prevention in atrial fibrillation III[4] and the trial by Pengo et al.[5] The rate of events in our study differed, as did baseline measurements (more elderly patients, different comorbidity).

Which patient should be given preventive therapy with regular dose coumarin (international normalised ratio 2.5-3.5): a man of 61 years with lone atrial fibrillation? A woman aged 95 years? A woman aged 76 with rheumatic disease and nervousness, who occasionally falls and uses non-steroid anti-inflammatory drugs frequently? The proper clinical risk assessment for stroke and haemorrhage is needed here, as is more evidence that in certain patients a regular dose of coumarin is indicated.

We regret that our results could lead to a nihilistic approach for prevention in primary care, because primary prevention of stroke and thromboembolism is an important task for the general practitioner. Conclusions from investigations with referred patients are biased towards including patients with a higher degree of comorbidity than is expected in general practice. So these conclusions cannot always be applied to the general practice population, as may be concluded from our study.

We welcome the initiative of the Birmingham atrial fibrillation treatment assessment group to perform a study on a regular dose of coumarin in elderly outpatients, because there is not enough evidence to justify the use of this dose of coumarin in these patients. We hope that Mant and colleagues will succeed in recruiting enough patients in this age group.

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Evidence of a CJD epidemic may still be missed

EDITOR—The United Kingdom faces the possibility of an epidemic of new variant Creutzfeldt-Jakob disease as a result of bovine spongiform encephalopathy,[1] but the referral of brain tissue to neuropathologists to determine the cause of degenerative diseases of the brain has virtually stopped. Public concerns over the retention of tissues for investigation after postmortem examination make it is easy to see how this has happened.[2]

In the United Kingdom most postmortem examinations on adults are performed because they are directed by law. The main reason is to ascertain a natural medical cause of death for certification, thereby removing the need for an inquest. In the past, retaining the brain for examination was a routine part of the practice of pathologists, but it is now clear that many relatives of the deceased person may not have been aware of this. Because of concerns over the legitimacy of organ retention the true cause of a degenerative brain disease is now hardly ever being established after a postmortem examination, even though the brain has been examined by the inadequate method of slicing during the necropsy. Simply certifying that a person has died of a disease such as pneumonia, in the face of a decline as a result of a degenerative brain disease, is giving a mechanism of death rather than its true cause. This has implications for estimating misclassification rates in epidemiological studies.[3] I suspect that many families will be concerned that they were not given the opportunity to benefit from appropriate investigations. Guidelines from the Royal College of Pathologists (www.rcpath.org) will be released soon, but medical and public confidence has already been lost.

So far, the cases of new variant Creutzfeldt-Jakob disease have been in a distinct subset of the population.[1] We have no knowledge of the ways in which new variant Creutzfeldt-Jakob disease may become manifest, especially in elderly people. Unless a positive statement is made to reassure the public, medicolegal authorities, and pathologists, the situation of "not looking" will prevail and we run the risk of missing any emerging epidemic.

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Competing interests: Professor Lowe recieves funding from the UK Department of Health for surveillance of the incidence of Creutzfeldt-Jakob disease. He is a member of the council of the Royal College of Pathologists and has contributed to the formulation of its document *Guidelines for the Retention of Tissues at Post-mortem Examination.*

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Correction

Stages of change model for smoking prevention and cessation in schools

An editorial error occurred in this authors' reply by Paul Aveyard and others (5 February, p 447). "Smoking cessation" was omitted in the last sentence of the second paragraph, which should have read: "On this basis, it seems more likely that the smoking cessation expert system for adults, the only one that can be compared with the system for adults, should be more successful and require fewer sessions, yet we found no effect."