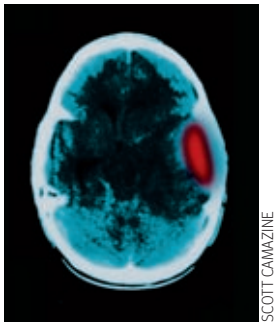
Prognostic modelling in traumatic brain injury

Can reliably estimate the probability of outcomes for groups but not for individuals



SCOTT CAMAZINE

RESEARCH, p 425

David Menon professor of anaesthesia, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ
dkm13@wbic.cam.ac.uk
David Harrison senior statistician, Intensive Care National Audit and Research Centre, London WC1H 9HR

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Hippocrates is said to have remarked in 400 BC that "No head injury is too severe to despair of, nor too trivial to ignore." While this prognostic scheme achieves absolute accuracy, its precision leaves something to be desired. More recently, many groups have attempted to produce more detailed risk adjustment models for predicting outcome in traumatic brain injury. In 2006, a systematic review concluded that most predictive models were inadequately validated, poorly presented, and based on studies from single centres with small samples that excluded patients from low income countries (where traumatic brain injury is most common).[1] In the accompanying paper, the Medical Research Council CRASH Trial Collaborators provide a series of prognostic models that attempt to remedy these shortcomings.[2]

Their models were developed on clinical data from the 10 008 patients recruited to a trial of corticosteroids in traumatic brain injury.[3 4] Separate variants of the models allow the option of including imaging data from computed tomography, and of selecting data on predicting outcomes for high income and low to middle income countries. The models have been made publicly available on a web based calculator, which allows entry of clinical and imaging data to produce an estimated risk of death or disability.

The CRASH models perform well within the population used for their development. They show high discrimination of the overall probability of a poor outcome (C statistic >0.8) and good calibration (measured by the degree of concordance between a range of predicted and observed probabilities of poor outcome). However, the generalisability of any model depends on validating its accuracy in a separate test population. The authors have conducted such an external validation in the IMPACT database,[5] which includes 8509 patients with moderate and severe traumatic brain injury in randomised controlled trials and observational studies conducted between 1984 and 1997. While the models continued to show reasonable discrimination in this exercise (C statistic 0.77), calibration was less well preserved for some of the models. Despite this, the CRASH models are an improvement on earlier attempts at predicting outcome in traumatic brain injury, and the authors suggest that the models may help in clinical trial design, comparative audit, and clinical decision making.

Use of the CRASH models is likely to improve the design of trials, given the poor record of neuroprotective trials in traumatic brain injury.[6] Many patients included in such trials have expected outcomes that are so irreversibly favourable or unfavourable that no intervention could realistically be expected to have an effect. Better stratification of patients at entry could greatly improve the balance between the treatment arms, particularly in small trials, and adjustment for baseline risk in trial analyses can improve precision and statistical power. An additional advantage of robust outcome prediction in this context would be the use of a technique called sliding dichotomy to assess the benefit of interventions.[7] Unlike conventional dichotomisation of outcomes, which compares the overall number of favourable outcomes between treatment and control arms, this approach compares predicted and observed outcomes on a case by case basis in two arms of a trial to detect significant treatment effects. Such an approach increases the efficiency of a trial and may greatly reduce the required sample size.[8]

These arguments also apply to comparative clinical audit, but with some caveats. Important limitations arise from the CRASH models being based on data from a randomised clinical trial (albeit a pragmatic trial). Well known limitations of randomised controlled trials include the effect of using inclusion criteria, the logistics of recruiting participants with sufficiently severe disease, and the possibility that patient outcomes tend to be better in randomised controlled trials, even in control groups.[9] Consequently, the outcome standards provided by such prognostic models should be validated in a "real world" setting and compared against existing schemes before they are used for comparative benchmarking.[10] Risk adjustment models may retain discrimination when transferred between clinical contexts, but their calibration—the degree of concordance between predicted and observed probabilities of poor outcome—often deteriorates (as was the case in the CRASH models). It is best to develop such models in the same context in which they will be used for clinical audit. Despite these reservations, in the context of trial design and clinical audit, the outcome predictions provided by prognostic schemes are applied to groups rather than individuals, and hence are relatively safe.

Far greater caution is needed if such a model is to be used for making decisions about treatment in individual patients. Estimates of outcome probability from the 10 000 patients in the CRASH trial are based on collective clinical experience beyond that achievable by any individual clinician, and these estimates may help educate clinicians and support clinical decision making. They cannot be used in isolation, however. Models can estimate the probability of a given outcome for a group of clinically similar patients with a high degree of

accuracy, but they cannot reliably predict outcome for individuals.[11] At least in the context of deciding whether or not to treat individual patients, it is important to continue to acknowledge, as did physicist Niels Bohr, that "prediction is very difficult, especially about the future."

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Preventing back pain

Advice to stay active may not be appropriate for people in manual jobs

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Niels Wedderkopp associate professor, Back Research Centre, Back Centre Funen, Funen Hospital, 5750 Ringe, Denmark
nwedderkopp@health.sdu.dk
Charlotte Leboeuf-Yde professor, Institute of Sport Science and Clinical Biomechanics, Faculty of Health, University of Southern Denmark, 5230 Odense M, Denmark

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Every month, back pain affects 18-45% of the adult Western population,[1] and the costs to society are between €200 (£150; $290) and €400 per capita per year.[2] People who do heavy physical work are particularly susceptible because back problems are likely to be exacerbated when the back is used in its full range of movements.

In the accompanying paper, Martimo and colleagues report a systematic review of the prevention of back pain in people whose jobs involve heavy lifting.[3] None of the randomised controlled trials or cohort studies included in the review found a positive effect of advice or training in working techniques—with or without lifting equipment—for preventing back pain or consequent disability.

Although the results are disappointing, they are not surprising, because few pathological and anatomical labels (such as a tumour, fracture, inflammatory disease, or acute disc protrusion) can be used to explain the aetiology of back pain.[4] After removing the relatively few cases with obvious pathology, most patients are labelled as having non-specific back pain,[4] and it is not easy to treat a condition without a clear understanding of its cause. This lack of diagnostic refinement may explain why most randomised controlled clinical trials of the treatment or prevention of back pain show relatively inconclusive results.[5]

The review by Martimo and colleagues confirms how little we know about how to prevent and treat back pain. This may be because back pain is a symptom and not a disease. Or perhaps the disorder cannot be reversed once it becomes established, so that no treatment could be effective.

Low back pain has been shown to start at puberty.[6 7] In adults it is likely to recur or to become persistent,[8-10] so perhaps we should aim to prevent the problem from occurring in the first place. Studies of prevention should therefore take place before puberty, but such studies are very rare.

So what further research needs to be done? Funding for studies on the causes of disease is harder to obtain than for studies that look at treatment. But we must identify the causes of low back pain before we study how we can prevent it. We would go so far as to suggest that randomised clinical trials of non-specific low back pain should be suspended as they include so many different types of back pain that the results are difficult to interpret.

What then can we do for our patients while we wait for further studies to be performed? The commonly given advice to patients to stay at work and be as physically active as possible may not be appropriate for people whose work involves heavy lifting and who have a history of recurrent back pain and several periods of sick leave. Continuing heavy manual work in their job and increasing leisure time physical activity may not be a good idea as no clearly effective treatment is available.[5] A change of job and (prudently) staying active in daily life may be the best way for these patients to regain command of their back and their occupation.

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Familial risks of oral clefts

Risk of recurrence is higher with cleft palate only

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Melissa Lees consultant in clinical genetics, North East Thames Regional Genetics Service and North Thames Cleft Service, Great Ormond Street NHS Trust, London WC1N 1EH
melissa.lees@gosh.nhs.uk

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Oral clefts, including cleft lip with or without cleft palate and cleft palate only, have a high rate of familial recurrence compared with many birth defects.[1] The cleft can occur in association with other congenital abnormalities, sometimes as part of an underlying recognisable syndrome, or more often as an isolated defect. Inheritance is complex and related to environmental and genetic factors.[2] Although a genetic component exists, the precise genetic basis is unclear.

The risks of having a child with an oral cleft that are used when counselling families at increased risk are based on empirical figures derived from studies that have several limitations, such as inclusion of syndromic cases, the grouping of all oral clefts together, incomplete ascertainment, and a lack of longitudinal data.

In their accompanying paper, Sivertson and colleagues report a longitudinal population based study of the risk of non-syndromic oral clefts in Norwegian families.[3] They analyse the type and the severity of the cleft in the index case. Norway has an excellent model for generating useful epidemiological data for oral clefting because of the high case ascertainment within a defined population and accurate documentation of clinical cases.

The study finds that the relative risk of cleft recurrence in first degree relatives is 32 (95% confidence interval 24.6 to 40.3) for any cleft lip and 56 (37.2 to 84.8) for cleft palate alone. This suggests that genetics contributes more to cleft palate alone than to cleft lip. The risk of clefts in children of affected mothers was similar to the risk of clefts in children of affected fathers, and the parent-offspring risk was similar to the sibling-sibling risk. The severity of the cleft in the presenting patient and the patient's sex did not affect the risk of having a cleft. There was also a threefold greater risk of cleft lip after a case of cleft palate alone, and vice versa (crossover risk).

The finding of a higher risk if the first degree relative has cleft palate alone compared with cleft lip differs from the risk figures commonly used in the United Kingdom,[4] where relatives of a person with non-syndromic cleft lip are thought to have had a higher familial risk than relatives of someone with non-syndromic cleft palate only. Previous studies have often excluded data on cleft palate alone, as this defect may be missed at birth, which makes accurate analysis difficult.[5]

Siverston and colleagues' data may alter the empirical risks given by geneticists and genetic counsellors to first degree relatives of people with cleft palate alone. A tabulated form giving the results as a percentage risk would be useful for clinicians involved in the care of patients with oral clefts. Parents can relate more to a percentage risk of a cleft in a further pregnancy, rather than being told that the risk is 56 times higher than in the general population. While these figures may apply to northern European populations, the heritability of oral clefts may vary in different ethnic groups. Other counselling questions could also be answered by the dataset, such as how does the risk vary for second and third degree relatives? And what is the risk for half siblings?

Recent evidence suggests that folic acid supplements may reduce cases of cleft lip with or without cleft palate by about a third, but not cases of cleft palate alone.[6] This is consistent with the greater familial risk reported for cleft palate alone, as genetic factors may be less susceptible to such environmental influences.

Cleft lip with or without cleft palate and cleft palate alone are thought to be genetically distinct. The specificity of the cleft type in Sivertson and colleagues study reinforces this notion, with a low crossover risk of three between cleft lip and cleft palate alone in families. This crossover risk may partly be accounted for by the contribution of dominantly acting genes, including MSX1 and IRF6, which may play a part in all forms of oral cleft.[7 8]

The reported absence of an effect of cleft severity on the risk of familial recurrence has implications for genetic counselling. Parents whose child has a mild form of cleft, such as a unilateral cleft lip, have the same risk of subsequently having a child with a severe cleft as those whose child has a severe cleft. In addition, a severe cleft in one child does not increase the risk of having another severely affected child.

The study raises questions about our understanding of the mechanisms of clefting. A multifactorial threshold model for oral clefts would predict that the greatest familial risks would be for relatives of the most severely affected cases in the least frequently affected sex (a bilateral cleft lip and palate in a female), but this was not shown. Differences between single gene disorders and complex inheritance are becoming less well defined, and the genetics of clefting is not easily explained by a single genetic model.

The genetic basis of non-syndromic clefting is complex and not well understood. Gene-gene and gene-environment interactions probably play important roles. Well designed epidemiological studies will help molecular research to tease out the contributing factors of this common birth defect and may lead to the identification of preventative factors in the future.

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The involvement of private companies in NHS general practice

May improve access but weakens the foundation of primary care in the NHS

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Chris Salisbury professor of primary health care, Academic Unit of Primary Health Care, University of Bristol, Bristol BS8 2AA
c.salisbury@bristol.ac.uk

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The involvement of private companies in the National Health Service always generates controversy. Some people believe that only commercial interests can bring innovation and efficiency to modernise the NHS. Others assume that the profit motive is incompatible with the pursuit of excellence in health care.

This debate has been reignited by the announcement that United Health Europe, a subsidiary of a large American health company, has won a contract to run three NHS general practices in London. This is the latest in a series of similar acquisitions by commercial companies throughout England. The government is also investing £250m (€335m; $487m) in establishing at least 150 new health centres, many of which will probably be run by private companies.[1]

These developments are meant to increase access to primary health care in areas where existing contractual arrangements have not provided adequate services.[2] The establishment of new health centres is linked to the aim of developing large polyclinics that offer extended services and wide opening hours.[3] However, these changes are also part of the broad policy direction to encourage a market within the NHS, with greater managerial control and competition between different types of provider, including private companies.[2]

Those in favour of private sector involvement argue that it brings entrepreneurial energy and ideas, backed by good management, which encourage innovation and challenge entrenched ways of working. The profit motive should ensure greater efficiency and a focus on the wishes of consumers. Opponents highlight the negative experiences of other countries, including higher overall health service costs, manipulation of the market, and "cream skimming" to select low cost patients. Rather than spreading innovation, new approaches to the delivery of care are copyrighted, branded, and marketed, with little regard for evidence or partnership. Perhaps most importantly, private provision can create conflicts for doctors between what is best for patients and best for profits, and this can undermine trust between patients and doctors.

What are the implications for patients of privately run general practices? They may be able to obtain care that is more easily accessible, of more consistent quality, and more "consumer friendly" than is sometimes the case within the NHS. The investment in new health centres will make a wider range of services available outside hospitals in smart new facilities, although these benefits would be evident whether they were run by commercial or non-profit organisations.

But this increased accessibility is likely to be at the cost of reduced personal care. Commercial companies seem to have won some contracts partly on the basis of price.[4 5] Because the greatest proportion of expenditure in general practice is on doctors' pay, their involvement in consultations will probably be reduced by triaging requests for appointments and using nurses and healthcare assistants to provide most care.[6] In addition, lower paid salaried doctors working in shifts, who are not subject to national agreements about pensions or employment rights, will probably be employed. Such posts will be more attractive to doctors who want short term sessional work with no commitment to the area or the practice. Some patients, especially young, healthy, and infrequent users of the service, value convenience and accessibility over a relationship with a particular doctor, which is generally more important to elderly patients and those with long term conditions.[7] Critics will point out that it is precisely this first group of patients that private providers will want to attract.[6]

For doctors, the potential effect on professional autonomy is perhaps the most profound. General practice in the United Kingdom has a strong professional identity and primary health care is well established. This forms the foundation for the equity, efficiency, and effectiveness of the NHS. The registered patient list system promotes a sense of responsibility for individual patients and local communities. Although variations in quality and problems with accessibility do occur in some areas, most practices are well organised and highly valued by their patients. Unlike in most other countries, the status and salaries of primary care doctors and specialists in the UK are comparable. Consequently, general practice attracts many of the best doctors, who are often motivated by getting to know their patients and being able to influence how care is provided rather than working in a large impersonal organisation. If privately run practices reduce costs by employing doctors as shift workers without recognising what motivates them, then general practice will again become the refuge for those who have "fallen off the ladder" towards a specialist medical career.[8] The consequences for patients and for overall healthcare costs, as well as for doctors, will be poor.

Where will these changes ultimately lead? Privately run practices could act as catalysts for change, permanently at the margins of mainstream general practice. But it is more likely that private companies view their first health centres as "loss leaders." General practice may follow the pattern established

in the UK by pharmacists, opticians, accountants, and other professions, with independent practices being gradually taken over by corporations until the market is dominated by large commercial chains. These developments have potential benefits of increasing the pace of innovation but also serious risks of damaging doctor-patient relationships, increasing inequities in provision, and weakening the professional autonomy of general practitioners. The current direction of change is being driven at great speed with minimal consultation and often in the face of strong local opposition. It is time for a serious public debate about the type of general practice that people want and need.

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Treatment delays in ST elevation myocardial infarction

Can be reduced by prehospital diagnosis and direct transfer to high volume catheterisation laboratories

Christian Juhl Terkelsen senior registrar
Christian_Juhl_Terkelsen@hotmail.com
Jens Flensted Lassen consultant cardiologist, Department of Cardiology B, Aarhus University Hospital, DK-8200 Aarhus N, Denmark

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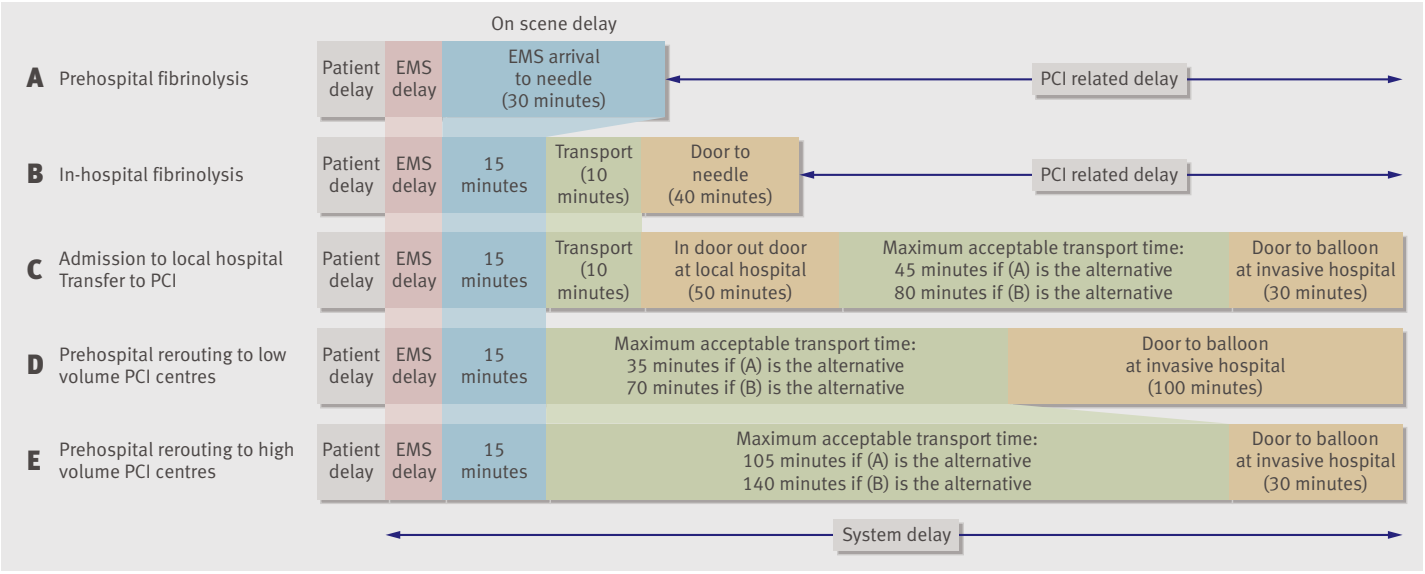
Quickly re-establishing coronary blood flow is vital in patients with ST elevation myocardial infarction. Two recently published systematic reviews summarise the evidence on this form of treatment.[1 2] The first review concluded that primary percutaneous coronary intervention (PCI) is the best reperfusion strategy if performed quickly, and it identified "door to balloon time" (the time from arrival at hospital to balloon inflation) as a key predictor of outcome in people given this treatment.[1] The second review stated that "inevitable transport delays commonly limit the benefit of PCI."[2] The reviews reflect an ongoing controversy in cardiology—when is PCI the best reperfusion strategy, and when should fibrinolysis be considered as an alternative?

What is an acceptable time window in which to deliver PCI? The review by Boden and colleagues and current guidelines recommend using fibrinolysis if the extra time needed to perform percutaneous coronary intervention (the PCI related delay) is more than 60 minutes, or if the time from the onset of symptoms to presentation is less than three hours.[2-4] However, one of the recent systematic reviews found no clear definition of an acceptable PCI related delay.[1] The idea of a 60 minute maximal PCI related delay was derived from an earlier meta-analysis by the same author that included 23 randomised trials comparing fibrinolysis with PCI.[5] For each trial, the benefit to mortality achieved when performing PCI instead of administering fibrinolysis was plotted against the PCI related delay seen at trial level. The 60 minute standard was derived from this regression analysis and introduced into subsequent guidelines.[3 4]

Unfortunately, the values used in this analysis to denote delay were underestimates. Also, in one trial, instead of separating data from patients who were transferred to an interventional hospital versus those directly admitted to an interventional hospital, a single value of 55 minutes was used for the PCI related delay. When the regression analysis is recalculated using the originally tabulated data the acceptable PCI related delay is 119 minutes, and if the data on transferred versus non-transferred patients are split the acceptable PCI related delay becomes 171 minutes. The idea of a 60 minute maximal PCI related delay has also been questioned in another meta-analysis.[6] It found a benefit of PCI over on-site fibrinolysis even when PCI was performed after 80-120 minutes.[6] Assuming that a PCI related delay of 120 minutes is acceptable, the maximal transport times to intervention centres may vary from 35 to 140 minutes depending on optional reperfusion strategies and the in-hospital delays in the particular region (figure).

Is door to balloon time an accurate predictor of outcomes, as a recent systematic review suggests?[1] It is logical that reducing any of the components of treatment delay (patient delay, emergency medical system delay, delay at local hospital, transfer delay, door to balloon delay at the invasive hospital) will reduce mortality. If patients are admitted to a local hospital and then transferred to another hospital for invasive treatment, door to balloon time comprises only a small component of the total system delay (figure). Accordingly, system delay (time from patient alerting the health system to balloon inflation) would seem a better indicator of outcome than door to balloon time. Out of hospital strategies such as prehospital diagnosis combined with bypassing



Typical delays according to reperfusion strategy. Maximum acceptable transport time was calculated for various PCI strategies on the basis of an acceptable PCI related delay of 120 minutes. EMS=emergency medical system; PCI=primary percutaneous coronary intervention

local hospitals and re-routing patients directly to catheterisation laboratories would eliminate many components of system delay (figure).[7]

What strategies could increase the number of patients with ST elevation myocardial infarction who are eligible for PCI? Low volume intervention centres were set up in local areas on the basis of the assumption that they would provide easier access to a catheterisation laboratory. However, these centres cannot quickly activate catheterisation laboratories on a 24 hour basis. This may explain why the door to balloon time is consistently around 100 minutes in the United States, where two thirds of centres perform fewer than 40 percutaneous coronary interventions each year.[8] On average, patients wait 10 minutes for an electrocardiogram; 60 minutes in the emergency room, coronary care unit, or intensive care unit; and 30 minutes in the catheterisation laboratory (figure).[8]

Setting up large volume centres in more remote locations might be the best option because treatment at such centres is associated with better outcomes, and door to balloon times of 30 minutes can be achieved. If door to balloon times were shorter, catchment areas could be bigger because longer transport times would be acceptable (figure). Prehospital diagnosis and rerouting directly to the catheterisation laboratory would be essential to achieve the optimum door to balloon time at high volume centres. This would bypass the local hospital, as well as the emergency room, coronary care unit, or intensive care unit at the interventional hospital (figure).[7 9]

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