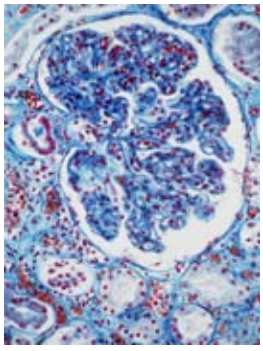
Glomerular filtration rate and the risk of stroke

Measuring kidney function may improve stratification of cardiovascular risk and targeting of preventive treatments



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Stroke is a common cause of death and disability that affects not only the patient but his or her family and the broader community. Prevention of stroke, through the identification and management of risk factors, is thus a public health priority.

Chronic kidney disease is common, particularly in people at high risk of cardiovascular disease.[1] Chronic kidney disease is a strong risk factor for cardiovascular events,[2] even after adjusting for other known risk factors. Much less is known about the relation between chronic kidney disease and specific types of cardiovascular events, such as stroke. This is important because stroke has several subtypes that may have different associations with individual risk factors and therefore treatments. For example, lipid lowering treatments[3] and antiplatelet treatment[4] protect against cardiovascular events overall but may increase the risk of haemorrhagic stroke.[5]

In the linked systematic review[6] Lee and colleagues assess the association between kidney function, defined by estimated glomerular filtration rate (eGFR), and the subsequent risk of stroke. The overall risk of stroke was 40% higher in people with an eGFR below 60 ml/min/1.73 m^2 (relative risk 1.43, 95% confidence interval 1.31 to 1.57). This increased risk was graded, with a 28% higher risk for people with an eGFR of 40-60 ml/min/1.73 m^2 but 77% higher for those with an eGFR below 40 ml/min/1.73 m^2. Causality cannot be proved, however, because the studies analysed were observational, although the persistence of the association after adjustment for known cardiovascular risk factors increases the likelihood that it is real.

The association between chronic kidney disease and stroke was present across most subgroups and was similar for ischaemic and haemorrhagic stroke. The association was stronger in Asian people, in whom stroke is more common and the association between blood pressure and stroke steeper than in white people.[7] Given the vast population of Asia and the rapidly increasing burden of cardiovascular disease, stroke, and chronic kidney disease in the region, understanding this association and identifying preventive strategies is a public health priority.

Lee and colleagues could not identify any modification of the association by albuminuria, the other key manifestation of chronic kidney disease. This may be the result of poor statistical power because few studies provided the relevant data. A previous systematic review identified a similar relation between albuminuria or proteinuria and stroke,[8] and a more recent meta-analysis clearly showed that albuminuria and eGFR values are independent risk markers for cardiovascular events,[2] suggesting that both parameters should be assessed to obtain the best information.

What are the implications for clinical practice? At the very least, evidence suggests that the presence of chronic kidney disease (either reduced eGFR or albuminuria, but especially both) should act as a "red flag" that triggers cardiovascular risk assessment and implementation of appropriate preventive strategies. Current cardiovascular risk calculators that are widely used do not systematically incorporate kidney function variables in their algorithms, except in the context of diabetes with nephropathy, because it is not yet clear whether the inclusion of such data will improve the discriminative ability of these tools. This is an important and required next step, particularly as some reports suggest that chronic kidney disease is as important a risk predictor as established risk factors, such as blood pressure and lipids.[9]

A second linked study by Di Angelantonio and colleagues is useful in this regard.[10] In a large cohort, the authors confirmed that baseline kidney function predicted cardiovascular outcomes (mainly myocardial infarction). More importantly, they assessed the effect of adding measures of chronic kidney disease to the classification of risk category. Overall, adding kidney function improved risk prediction, but the improvement was small and kidney function is clearly a less important risk factor than diabetes or smoking status. The measurement of proteinuria was imprecise in this study, however, because it relied on dipstick testing, and the creatinine measurements were not calibrated. Consequently, the value of kidney function in improving risk prediction may have been underestimated, and similar analyses of other datasets are needed.

Once chronic kidney disease is identified in a patient at high risk of cardiovascular disease, what interventions are needed? Blood pressure lowering seems to achieve similar relative risk reductions in cardiovascular disease in people with chronic kidney disease as in the general population, leading to larger absolute effects as a result of the higher baseline risk in this group.[11] Post hoc analyses suggest that antiplatelet treatment is likely to be at least as effective in people with chronic kidney disease as in the general population.[12] The effects of lipid lowering remain uncertain, and the results of the Study of Heart And Renal Protection (SHARP) are eagerly awaited.[13] In the absence of clear evidence that a different approach is appropriate, it therefore seems sensible to implement those strategies already shown to be effective in the general population.

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Prevention of migraine

Combining behavioural management and preventive drugs optimises outcome

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Drugs for the prevention of migraine have been shown to reduce its frequency, improve migraine specific quality of life,[1] and reduce the overall costs of migraine related care.[2 3] Unfortunately, however, they are underused. In a recent population based study, fewer than 20% of people deemed eligible for preventive treatment had received a preventive drug.[4]

In clinical practice, the approach to patients who need preventive drugs goes beyond simply writing a prescription. Patients should also be given advice on identifying and managing triggers, making lifestyle modifications, and using biobehavioural techniques (such as relaxation and cognitive behavioural therapy) when appropriate and on optimising the acute treatment of attacks.[5] However, the comparative efficacy of these strategies has not been systematically evaluated.

In the linked randomised placebo controlled trial Holroyd and colleagues randomised 232 people who remained disabled, despite an optimised 30 day run-in of acute treatment, to the addition of one of four preventive treatments.[6] These treatments were a β blocker (propranolol up to 240 mg or nadalol up to 120 mg), placebo, behavioural migraine management (BMM) plus placebo, or BMM plus β blocker. BMM included education, trigger management, relaxation, pain management, and optional biofeedback or stress management. Treatment was blinded only for the preventive drug and not for the BMM component. Electronic headache diary recordings were taken over 16 months.

All four groups showed significant improvements for the outcome measures of a change in migraine attacks per 30 days (primary outcome), number of days with migraine per 30 days (secondary outcome), responder rate per 30 days (proportion of participants with >50% reduction in migraine attacks), and migraine specific quality of life at month 10 compared with baseline. However, only the combination of β blocker and BMM improved outcomes over optimised acute treatment alone at both 10 and 16 months. Neither β blocker alone nor BMM alone was superior to optimised treatment alone. In fact, the responder rate for the optimised acute treatment plus placebo group (40%) was greater than that for the optimised acute treatment plus β blocker (34%) and optimised acute treatment plus BMM (36%) groups.

The lack of a significant difference between the optimised acute treatment and β blocker groups is surprising. The relatively high placebo response rate and low response rate to β blockers may account for this finding. The placebo responder rate (40%) is high for a study of long term migraine prevention, especially as the participants were relatively resistant to treatment—only those who remained disabled after acute treatment was optimised during the run-in-baseline phase were randomised. The placebo response rate in a meta-analysis of migraine prevention studies was 21%.[7] One explanation for this discrepancy may be that participants had a 50% chance of receiving the active drug. In addition, the 34% response rate with propranolol is significantly lower than the 55% response rate reported in a meta-analysis of all placebo controlled studies of propranolol for migraine prevention.[8]

Other factors make the results of this trial difficult to interpret. Several of the outcomes were not clarified. It is not clear how the authors defined "optimised" in the optimised acute treatment arm. Only those subjects who remained "disabled" (not defined) and whose attacks remained "uncontrolled" (no definition) were randomised. The number of patients who remained disabled despite aggressive measures to optimise treatment suggests that the authors used a high threshold to measure response. If 77 participants were excluded after the optimising acute treatment run-in period, but only 33 were excluded because they did not meet the migraine severity criteria (no definition), this suggests that the 232 participants who were finally randomised with uncontrollable attacks had especially severe and treatment resistant migraine. This makes the placebo response rate of 40% in the optimising

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acute treatment plus placebo group all the more difficult to reconcile.

Despite these observations there are several important and novel findings from this trial. Firstly, it is important to optimise the acute treatment of attacks and this approach should be considered even in patients who are treated with preventive drugs. However, in patients with frequent and disabling attacks, it is not sufficient or advisable to optimise acute treatment alone, particularly with recent evidence of the potential for triptan induced latent neuronal sensitisation,[9] and the well established risk of headache resulting from overuse of acute drugs (such as triptan).[10]

Secondly, patient outcomes will not improve merely by writing a prescription for a preventive drug. Migraine is a complex disorder that requires a comprehensive disease management model of care that incorporates the influence of lifestyle and environmental factors, and, as shown by this trial, behavioural migraine management.[11] Finally, because of the long duration of the trial and low rate of attrition, the authors could show that the significant improvement with optimised acute treatment plus β blocker and BMM was sustained over 16 months.

It would be useful to know whether preventive treatment plus optimised acute management is superior to optimised acute management alone in patients with relatively frequent attacks (for example, ≥4 per month) who respond to optimal acute management. Moreover, in a 16 month trial such as this one, it may be possible with a large enough sample size to determine whether the addition of a preventive drug to optimised acute management reduces the incidence of conversion to chronic headache (>15 days per month), as it is still unclear whether preventive drugs prevent the conversion from episodic to chronic migraine in people with frequent attacks. Finally, future studies could determine which preventive treatment improves the response to acute drugs, even in the absence of a reduction in the frequency of attacks, because this is a commonly reported clinical observation.

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Bacteria in the respiratory tract and wheeze in children

Colonisation is more common in symptomatic children, but causation is not established

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In the linked cohort study Bisgaard and colleagues assess the association between wheezy symptoms in young children and the presence of bacteria in the airway.[1] Lower respiratory tract illnesses presenting with cough, shortness of breath, or wheeze are common in preschool years.[2] It has been proposed that, for the management of preschool wheeze, a distinction is made between episodic and multiple trigger wheeze.[3] Episodic wheeze is defined as wheeze in discrete episodes of up to two to four weeks' duration, usually triggered by a viral infection, and with the child being well in between. In multi-trigger wheeze, the child has distinct episodes of wheeze but also has intermittent symptoms, such as cough and wheeze at night or in response to exercise, crying, laughter, mist, and cold air, between these episodes. Viral infections are again the most common triggers, but multi-trigger wheeze is often associated with allergic features, and many children with preschool multi-trigger wheeze progress to chronic asthma. Current guidelines recommend the use of bronchodilators for wheezing episodes.[3] Children with multi-trigger wheeze may also benefit from inhaled corticosteroids and leukotriene receptor agonists. Antibiotics have not been recommended for the treatment of preschool episodic wheeze or multi-trigger wheeze.

This approach is contested by Bisgaard and colleagues' study.[1] The authors included 361 infants born to asthmatic mothers who were followed until the age of 3 years. They confirmed a positive association between viruses and preschool wheeze (odds ratio 2.8, 95% confidence interval 1.7 to 4.4) and also found a significant association between bacteria and preschool wheeze (2.9, 1.9 to 4.3), which was independent of viral detection. For all episodes of lower respiratory tract illness the children were seen in the study centre and the condition was classified as wheeze or "clinical pneumonia," which was defined as tachypnoea, fever, and crepitations over the lungs without wheeze. In addition, children were scheduled to be seen once a year. At each visit hypopharyngeal aspirates were taken for bacterial culture and rhinopharyngeal aspirates were taken for polymerase chain reaction analysis of viruses and atypical bacteria.

Viruses were detected in 40% of asymptomatic children,

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in 65% of wheezy episodes, and in 70% of episodes with clinical pneumonia. Bacteria were detected in 62% of asymptomatic children, 86% of wheezy children, and 93% of children with clinical pneumonia. Most commonly *Streptococcus pneumoniae* was identified, followed by *Haemophilus influenzae* and *Moraxella catarrhalis*. Atypical bacteria were detected in fewer than 2% of the children. Thus in both conditions—wheezing and non-wheezing lower respiratory tract illnesses—viruses and bacteria were detected significantly more in affected children than in asymptomatic children. The positive association with the detection of bacteria remained significant after adjusting for the detection of viruses. The authors suggest that this might have important effects on the treatment of preschool wheeze if the role of bacteria can be confirmed.

The high bacterial detection rate reported in asymptomatic children in this study casts some doubt over a causative role for bacteria. The findings confirm a previous study investigating bacterial colonisation of newborns by conventional culture methods.[4] All nose and throat smears from 3 day old babies produced positive cultures. Another study using culture independent molecular methods for the detection of bacteria has shown that the lower respiratory tract—which was thought to be sterile—is highly colonised by bacteria. Bronchoscopy was performed on 24 adults and 20 children and found that every cm^2 contained a mean of 2000 bacterial genomes, including *H influenzae* and *S pneumoniae*.[5] Thus, positive bacterial cultures may merely reflect colonisation of the upper and lower respiratory tract rather than indicating that bacteria are the cause of the infection. Viral infections may indirectly facilitate bacterial growth, thereby increasing detection rates in acute episodes.

Ultimately, only controlled clinical trials with antibiotic treatment can resolve this debate, as the authors rightly acknowledge. Besides the studies discussed by Bisgaard and colleagues,[6 7] the findings of two other randomised controlled trials might be more informative. These trials investigated the effect of adding an aminopenicillin to standard care of acute exacerbations of asthma in children[8] and adults,[9] and they found that antibiotics had no benefit. These findings are particularly interesting because aminopenicillins are generally effective against *H influenzae* and *S pneumoniae*—the most commonly detected bacteria in this study. However, these trials are limited by the small number of people included (44 and 71). Unless well designed and high powered clinical trials unambiguously show a benefit of antibiotic treatment there is no need to revise the management guidelines for preschool wheeze.

The findings are nonetheless interesting because they emphasise the need for a better understanding of the role of bacteria in the development of asthma and acute exacerbations of the disease. The advent of culture independent molecular methods that can detect much higher numbers of known and unknown bacteria will allow a better understanding of the role of bacteria in the colonisation of mucosal surfaces in the airways, their interaction with local host immune responses, and eventually their contribution to disease onset and progression.

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A new professional code in sports medicine

Provides ethical and legal guidance for sports and exercise medicine practitioners

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In July 2010 the Faculty of Sports and Exercise Medicine (FSEM) published a professional code.[1] The code supplements the General Medical Council's *Good Medical Practice* guidance with additional guidance specifically for sports and exercise medicine practitioners.

The publication of the code could not be more timely, as it follows yet another scandal involving elite athletes: the so-called Bloodgate affair in rugby union, where a player was persuaded to fake a blood injury, and aided by the coach, a physiotherapist, and doctor to this purpose.[2] This is not an isolated incident. In the Summer Paralympics in Sydney in 2000, for example, 10 of the 12 athletes of the gold medal-winning Spanish basketball team faked disability.[3]

Although doctors are not the only corruptible professionals, a doctor implicated in this way not only contributes to the erosion of credibility of sports, but can also expose sportsmen and women to avoidable health risks, thus contravening one of the primary imperatives of medicine: first do no harm.

The code contains a number of important ethicolegal clarifications relating to the role, rights, and responsibilities of sports physicians (those most relevant to sports and exercise medicine are highlighted in the box).

One key message is that sports physicians have a primary duty to protect the health and safety of the patient. "The health and the welfare of a patient must prevail over the


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interests of any competition, economic or political considerations."[1]

Although this stricture seems prima facie laudable, it raises an important ethical question: how can sports physicians be primarily concerned with the health and welfare of the patient when many elite sports are inherently dangerous (boxing, for example), or become dangerous when practised at competitive levels?

By the very nature of their profession, sports physicians must act in accordance with goals that go beyond those of standard medicine. They help athletes to achieve their targets often to the detriment of their health and safety. Doctors may allow athletes to compete in spite of severe injuries: Valentino Rossi returned to racing one month after suffering severe fractures, while still on crutches, with his doctors' permission.[4] The FSEM professional code also allows the use of anaesthetic injections or similar analgesic methods, enabling sportsmen and women to work out or compete through pain.[1] Not to mention the long term musculoskeletal injuries that may result from competitive training and the extreme risks involved in some sports.[5]

Sports and exercise medicine challenges us to reconsider the balance between welfare and harm. An athlete may be forced to withstand physical distress, and even face extreme risks, in order to achieve their competitive goals. Sports physicians have the delicate and complex role of facilitating these pursuits while minimising harm and maintaining standards of fairness.

Only by acknowledging this dilemma will the profession be assisted in framing clearer boundaries of ethical legitimacy.

The code raises several other controversial points, one of which is drug testing. The code allows the use of non-steroidal anti-inflammatory drugs and analgesics during training or before competition. This raises the question as to why some performance-enhancing drugs are allowed while others are banned, when the effects may be similar (an athlete is able to do something they would not otherwise be able to), and the athlete gives valid consent to the administration of those drugs.

Another controversial area is that of fitness testing, which involves a series of measurements of a person's health and fitness level in order to evaluate their physical capability to safely engage in the sport or physical activity they wish, and the design of tailored and appropriate training programmes. The code argues that "in normal circumstances" fitness tests should not be performed, and that medical certificates may be required only for competitive sports.[1] This guidance contradicts a well-established principle in sports and exercise medicine, that every individual who wishes to undertake supervised sports or physical activities should be carefully screened. The American College of Sports Medicine, among others, provides clear and detailed guidelines as to how to screen and, eventually, test exercisers.[6]

Finally the code mentions sex testing.[1] More ethical questions arise: are sex tests ethical or reliable? What is their purpose? Can they effectively prevent unfair advantage? And what is "unfair advantage"?

Finally, the code is not limited to, but is focused especially on, elite and competitive sports. However, sports and exercise medicine could benefit a much larger community than elite athletes: for example, disabled people, pregnant women and new mothers, older people, obese children, and exercisers with eating disorders.[7] Ethical practice requires that all these types of exercisers or potential exercisers are given the support needed to practice safe and effective physical activity, and specialised medical assistance may be needed in many of these cases. Moreover, sedentary life is responsible for serious health risks, and the benefits of physical activity against premature morbidity and mortality are well established.[8] The FSEM and similar organisations should remind sports and exercise medicine practitioners that there is a wider circle of challenges, outside elite sports, which they may be called on to tackle.

Key points of the FSEM code

Governing principles
- Maintaining trust
- Respect for patient dignity
- Maintaining professional competency
- Patient involvement in decision making

Information and consent
- Informed consent
- Incapacitated patient
- Refusal of care/advice
- Consent by third party
- Consent and collection of biological material (eg, for drug testing)

Confidentiality/privacy
- Disclosure
- Conflict of interests
- Disclosing medical information to employing agencies/sporting clubs
- Non-health related intervention and privacy

Care and treatment
- Care while outside the UK
- Cultural and religious tolerance

Rights and duties of healthcare providers

Protection and promotion of the sportsperson's health
- Discouraging activity on health grounds
- Fitness to participate
- Adequate medical provisions at sporting venues
- Local anaesthetic injections

Ensuring medical support for sporting bodies

Probity
- Research
- Financial and commercial dealings

Dealing with children

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Read Domhnall MacAuley's blog on sports doctors at www.bmj.com/blogs

News: Doctor accused of covering up faked rugby injury is suspended by GMC (*BMJ* 2009;339:b3873)

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Prohibition of cannabis

Is not achieving its aims in the US, and may even worsen outcomes

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A new report, *Tools for Debate: US Federal Government Data on Cannabis Prohibition*, focuses on the effects of the enforcement of drug prohibition in recent decades in the United States.[1] It shows that efforts to suppress the selling and use of cannabis increased substantially. Adjusting for inflation, the US federal antidrug budget increased from about $1.5bn (£0.95bn; €1.1bn) in 1981 to more than $18bn in 2002. Between 1990 and 2006, annual cannabis related arrests increased from fewer than 350 000 to more than 800 000 and annual seizures of cannabis from less than 500 000 lb (226 798 kg) to more than 2 500 000 lb. In the same period the availability of illicit cannabis and the number of users rose: the retail price of cannabis decreased by more than half, the potency increased, and the proportion of users who were young adults went up from about 25% to more than 30%. Intensified enforcement of cannabis prohibition thus did not have the intended effects.

The report then turns to "unintended consequences" of prohibition, arguing that both in the US and in countries supplying the markets of affluent countries, drug prohibition contributed to increased rates of violence because enforcement made the illicit market a richer prize for criminal groups to fight over. The report concludes with a brief discussion of the alternatives to prohibition—decriminalisation and legalisation—arguing that experience with regulation of alcohol and tobacco offers many lessons on how a regulated market in cannabis might best be organised.

The report's conclusions on the ineffectiveness in the US of "supply control" (the conventional term for enforcement of drug prohibition) are in line with reviews of the evidence from a global perspective.[2 3]

Tools for Debate joins a bookshelf of reports from the past half century describing perverse effects of drug prohibition and charting ways out of the maze. So far, no government has dared to follow the thread all the way. Now, with the proposition of setting up a legal regulatory system on the California ballot in November,[4] the international drug prohibition system may find itself facing a non-violent popular revolution. Half a century after the present international system was consolidated by the 1961 Single Convention on Narcotic Drugs, the drug prohibition wave may finally be ebbing.

There is a precedent. A wave of alcohol prohibition swept over the international scene a century ago, with 11 countries adopting prohibition between 1914 and 1920.[5] Eventually the wave receded, with US repeal in 1933 marking the end of alcohol prohibition at the national level. Prohibition was replaced by restrictive regulatory regimes,[6] which restrained alcohol consumption and problems related to alcohol until these constraints were eroded by the neoliberal free market ideologies of recent decades.[7]

Because the international drug prohibition movement was originally an offshoot of the movement to prohibit alcohol,[8] a detailed examination of the experience with alcohol is particularly relevant. The RAND modelling of the effects of legalising marijuana in California projects an increase in consumption, probably a substantial one,[9] but experience with the repeal of alcohol prohibition shows that with substantial state regulation, consumption can be constrained. However, the alcohol control regimes of that time were far more restrictive than they are now in the United Kingdom and in many English speaking jurisdictions.

Analysis shows that these strong alcohol regulatory systems limited the harms from drinking in the period before about 1960, but the lessons have not been applied to regulating cannabis or other drugs. In some places, state control instruments—such as licensing regimes, inspectors, and sales outlets run by the government—are still in place for alcohol and these could be extended to cover cannabis. For instance, state retail monopolies for off sale of alcohol in Canada (except Alberta), the Nordic countries (except Denmark), and several US states would provide workable and well controlled retail outlets for cannabis, as has been proposed in Oregon.

The US has a particular hurdle with respect to regulating cannabis: US court decisions on "commercial free speech" question restrictions on advertising and promotion of a legal product.[10] Barriers also exist at an international level. Psychoactive substances such as cannabis (and alcohol and tobacco) should be exempted from World Trade Organization free trade provisions.[11] The requirements in the drug control treaties for criminalisation of non-medical production and use need to be neutralised, at least with respect to domestic markets. For countries following this thread, adopting a new framework convention on cannabis control could allow a regulated legal domestic market,[3] while keeping in place international market controls as a matter of comity (whereby jurisdictions recognise and support each other's internal laws).

The evidence from *Tools for Debate* is not only that the prohibition system is not achieving its aims, but that more efforts in the same direction only worsen the results. The challenge for researchers and policy analysts now is to flesh out the details of effective regulatory regimes, as was done at the brink of repeal of US alcohol prohibition.[12]

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