

Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

Addiction

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Cardiovascular disease

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Cardiovascular disease

High-dose NSAIDs may double risk of MI and heart failure

High doses of commonly used non-steroidal anti-inflammatory drugs (NSAIDs) could significantly increase the risk of major vascular and coronary events, a study in the *Lancet* has found.

This meta-analysis covered 280 trials of NSAIDs versus placebo, involving 124,513 patients, and 474 trials of one NSAID versus another, involving 229,296 patients. Daily treatment with cyclo-oxygenase 2 (COX 2) inhibitors, such as celecoxib and etoricoxib, or high-dose daily regimens of ibuprofen (2,400 mg), diclofenac (150 mg), and naproxen (1,000 mg) were analysed for cardiovascular and gastrointestinal side effects.

The primary vascular outcome was major vascular events (non-fatal MI, non-fatal stroke, or vascular death). Subsidiary vascular outcomes included major coronary events (non-fatal MI or coronary death); stroke; and hospitalisation for heart failure. The primary gastrointestinal outcome was upper gastrointestinal complications

(perforation, obstruction, or bleed).

Major vascular events were increased by about a third by a coxib, rate ratio (RR) 1.37 and diclofenac RR 1.41, see table 1 below. This was mainly driven by an increase in major coronary events: coxibs RR 1.76; diclofenac RR 1.70.

Ibuprofen also significantly increased major coronary events RR 2.22. However, neither ibuprofen nor naproxen significantly increased major vascular events.

Vascular death was increased significantly by coxibs RR 1.58 and diclofenac RR 1.65, non-significantly by ibuprofen, but not by naproxen.

Risk of hospital admission for heart failure was doubled by all NSAIDs, see table 1, below.

The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk.

All NSAID regimens increased upper gastrointestinal complications.

The authors conclude that the vascular risks of high-dose diclofenac,

and possibly ibuprofen, are comparable with those of coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs.

They calculate that of 1,000 patients allocated to a coxib or diclofenac for a year, there will be three more major vascular events, one of which will be fatal (baseline event rate 8/1,000/year).

This is a large analysis of trials across the globe and should further inform us to consider carefully the risk/benefit ratio of these drugs particularly for long-term use.

DR PETER SAVILL

● **Coxib and traditional NSAID Trialists' Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013, doi:10.1016/S0140-6736(13)60900-9** »

Table 1

Increased risks with high doses of NSAIDs

Major vascular events	Rate ratio	95% CI	P
Coxib	1.37	1.14-1.66	0.0009
Diclofenac	1.41	1.12-1.78	0.0036
Major coronary events	Rate ratio	95% CI	P
Coxibs	1.76	1.31-2.37	0.0001
Diclofenac	1.70	1.19-2.41	0.0032
Ibuprofen	2.22	1.10-4.48	0.0253
Vascular death	Rate ratio	99% CI	P
Coxibs	1.58	1.00-2.49	0.0103
Diclofenac	1.65	0.95-2.85	0.0187
Hospitalisation for heart failure	Rate ratio	95% CI	P
Coxibs	2.28	1.62-3.20	<0.0001
Diclofenac	1.85	1.17-2.94	0.0088
Ibuprofen	2.49	1.19-5.20	0.0155
Naproxen	1.87	1.10-3.16	0.0197

Mental health

Collaborative care is effective for depression

Collaborative care improves depression outcomes in both the short and medium term, a UK primary care study has found.

Fifty one practices were randomised to either collaborative care or usual care. Potential participants were identified by screening GP records for recent depression Read codes. They were enrolled if they met the ICD-10 criteria for depression when interviewed by a research worker.

In total, 276 patients were recruited from the collaborative care practices and 305 from the usual care practices. Overall 86% of participants had moderate or severe depression.

The intervention was delivered by care managers in liaison with GPs under the supervision of mental health specialists.

Care managers were either graduate psychologists or primary care mental health professionals who had been trained to deliver the collaborative care protocol.¹ They provided 6-12 patient contacts over a period of 14 weeks.

Collaborative care consisted of:

- Education about depression
- Medication management (monitoring of side effects, adherence and depression symptoms with appropriate treatment adjustments)
- Behavioural activation therapy (a form of CBT which focuses on reducing avoidance and increasing activity)
- Relapse prevention (teaching patients to recognise symptoms of depression relapse)

Compared with those receiving usual care, patients in the collaborative care group had lower mean adjusted

depression scores at both 4 and 12 months follow-up (1.33 PHQ-9 points lower (95% CI:0.35-2.31) at 4 months and 1.36 points lower (95% CI:0.07-2.64) at 12 months).

The effect size (0.26) was small and less than expected. The number needed to treat for one additional patient to meet the criteria for recovery at 12 months was 6.5.

Collaborative care is known to produce a small but significant improvement in depression outcomes (mean effect size 0.25 at 6 months)² but most of the studies have been carried out in the United States. This study demonstrates that similar results can be achieved in the setting of UK primary care.

Collaborative care is complex and expensive and the authors acknowledge the need to carry out a cost effectiveness analysis. Currently NICE only recommends collaborative care for patients with moderate to severe depression and a chronic physical health problem with associated functional impairment, whose symptoms have not responded to initial interventions.³

Case management (active follow-up, monitoring of adherence and depression symptoms with feedback of information to the GP) is a simpler and cheaper alternative which can be carried out by healthcare assistants. A German study achieved an identical effect size (0.26) with telephone case management provided over a period of 12 months.⁴

The NICE Quality Standard on depression recommends regular reassessment of patients treated with antidepressants at 2-4 week intervals, identification of non-responders with treatment adjustment, and maintenance treatment for at least 6 months after remission.⁵ In my opinion, this cannot be achieved without some form of enhanced care. However, the case for complex collaborative care rather than simple case management remains to be proven.

DR PHILLIP BLAND

● Richards DA, Hill JJ, Gask L et al. Clinical effectiveness of collaborative care for depression in UK primary care (CADET): cluster randomised controlled trial. *BMJ* 2013;347:f4913

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- 1 Richards DA, Hughes-Morley A, Hayes RA et al. Collaborative Depression Trial (CADET): multi-centre randomised controlled trial of collaborative care for depression - study protocol. *BMC Health Serv Res* 2009;9:188
- 2 Gilbody S, Bower P, Fletcher J et al. Collaborative care

for depression: a cumulative meta-analysis and review of longer term outcomes. *Arch Intern Med* 2006;166: 2314-21

3 National Institute for Health and Clinical Excellence. CG91. Depression in adults with a chronic physical health problem: treatment and management. NICE. London, 2009

4 Gensichen J, von Korff M, Peitz M et al. Case management for depression by health care assistants in small primary care practices. *Ann Intern Med* 2009;151:369-78

5 National Institute for Health and Clinical Excellence. Quality Standard on depression in adults. NICE. London, 2011

Diabetes

Can eating fruit prevent type 2 diabetes?

A large study in the *BMJ* suggests that eating whole fruit may reduce the risk of diabetes, and that some specific fruits may be more protective than others, but that increased intake of fruit juices may raise the risk of developing the disease.

This paper was based on data from three prospective cohort studies of American healthcare professionals. These studies followed the health outcomes of the study groups over many years, gathering detailed data about health and lifestyles. The Nurses' Health Study (1984-2008) covering 66,105 women, the Nurses' Health Study II (1991-2009), 85,104 women, and the Health Professionals Follow Up study (1986-2008), 36,173 men, together provided 3,464,641 person-years of follow-up.

The study population was predominantly of European ancestry, and participants were free of major chronic diseases at enrolment. Detailed questionnaires were completed every two years. These reported on all aspects of lifestyle. Diet assessment included reported consumption of fruit and fruit juices overall, but also specific questions on grapes or raisins, peaches, plums or apricots; prunes; bananas; cantaloupe melons; apples or pears; oranges; grapefruit;

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strawberries; and blueberries.

The fruit juices were also specifically listed as apple, orange, grapefruit or other juices. Questionnaires were validated against diet records where possible, but the authors acknowledge that recall may be a source of error. The study subjects were scored on their adherence to healthy lifestyles and given a healthy eating index score.

The incidence of self-reported diabetes was the study's outcome measure. Self-reported diabetes was validated by a supplementary questionnaire and checked against physician records where possible; 97% of the checked diagnoses were confirmed as accurate. The diagnostic thresholds for diabetes were lowered in June 1998 and the studies took account of this. Overall 12,198 subjects developed type 2 diabetes.

The researchers analysed the data to allow for personal, lifestyle and dietary risk factors for diabetes. After this adjustment the data showed a hazard ratio (HR) of 0.98 (95% CI:0.96-0.99) for those subjects who ate three servings a week of whole fruit. This equates to a small reduction of 2% in the risk of diabetes.

However, the same analysis of three servings a week of specific fruits showed a risk reduction of:

- 26% for blueberries HR 0.74, (95% CI:0.66-0.83)
- 12% for grapes and raisins HR 0.88, (95% CI:0.83-0.93)
- 7% for apples and pears HR 0.93, (95% CI:0.90-0.96)

The different results do not relate to the glycaemic index/glycaemic load of the individual fruits. Taking three servings of fruit juice a day increased the chance of developing diabetes by 8%, HR 1.08, (95% CI: 1.05-1.11).

The authors acknowledged the limitations of measurement from self-reporting, the estimate of physical activity and the problems of grouping some fruits together. However, the findings were consistent across each of the cohorts studied.

The authors suggest that the juicing process may remove some beneficial fruit compounds, and also the fibrous material that slows sugar absorption. The sudden rises in sugar may be responsible for triggering changes that lead to type 2 diabetes.

Individual fruits are thought to have properties that might explain the relative protection. The protective effects of blueberries, apples, pears and grapes may be related to their anthocyanin and polyphenol content.

These chemicals have been shown experimentally to enhance glucose uptake.

At present the advice in the UK is to have five portions of fruit or vegetables every day. There seems to be evidence from this paper that this good advice may be further refined to suggest including fresh apples, pears, grapes, and especially blueberries when possible for protection against developing type 2 diabetes.

However, patients might be advised to avoid regular intake of fruit juices as part of their 'five a day' as this may increase their risk.

DR MATTHEW LOCKYER

● Muraki I, Imamura F, Manson JE et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *BMJ* 2013; 347:f5001

Cardiovascular disease

Adequate sleep may help lower CVD risk

Sleeping for seven or more hours a night may reduce the risk of morbidity and mortality from cardiovascular disease (CVD), a Dutch study has found. Getting sufficient sleep and adherence to four traditional healthy lifestyle factors were all associated with a fall in risk. When sufficient sleep was added to these factors, the risk of CVD was further reduced.

The Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) looked at how adequate sleep might enhance the cardiovascular benefits of more traditional healthy behaviours.

This prospective study analysed data from 8,128 men and 9,759 women aged 20-65 years, living in the Netherlands, who replied to a lifestyle questionnaire in 1994 to 1997. All the

participants in the study were free of CVD at baseline. The authors defined four traditional healthy lifestyle habits, as follows:

- At least 3.5 hours/week cycling or doing other sports at a moderate to vigorous intensity
- Modified Mediterranean diet score ≥ 5
- Moderate drinking (≥ 1 drink of alcohol a month)
- Not smoking

To this list they added another, non-traditional, healthy behaviour: sleeping seven hours or more a night.

Cardiovascular morbidity and mortality were ascertained through national registers. Hazard ratios (HR) were adjusted for age, sex, and educational level. At baseline 6% adhered to one or fewer of the five healthy behaviours and 12% to all five. The follow-up period was 10-14 years.

There were 607 composite CVD events: 129 fatal CVD events, 367 non-fatal myocardial infarctions, and 111 non-fatal strokes.

Those participants who had four traditional healthy lifestyle factors had a 57% lower risk of composite CVD, HR 0.43 (95% CI:0.31-0.59) and a 67% lower risk of fatal CVD, HR 0.33 (95% CI:0.16-0.68) compared with those with none or one healthy lifestyle factor.

Sufficient sleep in addition to the four traditional lifestyle factors resulted in a 65% lower risk of composite CVD, HR 0.35 (95% CI:0.23-0.52), and an 83% lower risk of fatal CVD, HR 0.17 (95% CI:0.07-0.43).

Each healthy behaviour alone reduced the risk of CVD: ranging from a 12% lower risk with a healthy diet to a 43% lower risk for not smoking. The risk of fatal CVD ranged from 26% lower for being physically active to 43% lower for not smoking. Having sufficient sleep reduced the risk of CVD by 22% (HR 0.78) and fatal CVD by 43% (HR 0.57) compared with having insufficient sleep.

The authors postulate that insufficient sleep has an adverse impact on blood pressure and body mass index which could explain the findings. This data provides a strong argument for a new health message to give to our patients: try to go to bed a little earlier!

DR PETER SAVILL

● Hoevenaar-Blom MP, Spijkerman AMW, Kromhout D et al. Sufficient sleep duration contributes to lower cardiovascular disease risk in addition to four traditional lifestyle factors: The MORGEN study. *Eur J Prev Cardiol* 2013; DOI:10.1177/204748731

Sexual health

Do rapid HIV tests improve frequency of testing?

Rapid HIV tests did not result in a sustained increase in testing, although the rate of initial HIV testing increased by a third in a study of men who have sex with men (MSM).

This non-blinded randomised control study was based in the

Melbourne Sexual Health Centre. The men were aged >18, reported having sex with a man within the previous year, had had a negative HIV test within the previous two years, and were attending for clinical care.

A total of 400 MSM were randomised in a ratio of 1:1 to either on-going access at the health centre to rapid finger-prick point of care tests (intervention group) or conventional serological HIV testing (controls). The intervention group received their results in 20 minutes whereas those in the conventional testing arm received theirs in a week. Recruitment took place between September 2010 and March 2011.

All men were offered screening for other STIs. They were sent text messages at months 3, 9 and 15 recommending regular HIV testing and offering either an HIV test or a rapid HIV test according to their allocation. They were also emailed at 6, 12 and 18 months with a link to an online questionnaire.

Primary outcome was the incidence of HIV testing over the 18 months of follow-up – this included tests at the study clinic or elsewhere. As no other

rapid tests for HIV were approved in Australia at that time, tests at other sites would have been on serological samples. Men who stated that they had had HIV testing in other clinics had this verified by researchers.

Secondary outcome was incidence of testing for STIs such as chlamydia, gonorrhoea and syphilis to determine if rapid HIV testing would result in a decrease in testing for other STIs.

Among 200 men assigned to rapid testing, five were diagnosed with HIV (two at baseline), six were lost to follow-up and 189 completed 18 months' follow-up (94.5%). In the control group there were five HIV diagnoses of which three were at baseline, and 181 completed follow-up (90.5%).

The incidence of HIV testing in the rapid and conventional HIV testing arms over the 18 months of follow-up was 1.63 and 1.42 tests a year respectively; this represents a rate ratio (RR) of 1.15 (95% CI:0.96-1.38, P = 0.12). If only the first HIV test after enrolment were included, the rate was 1.32 in the rapid arm and 1.01 in the conventional arm; RR 1.32 (95% CI:1.05-1.65, P = 0.02). When the first HIV test after enrolment

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Apart from an initial increase in the frequency of HIV testing by a third in the rapid test arm compared with the conventional test arm, the study has not demonstrated a sustained increase in testing frequency over the follow-up period of 18 months.

Any novel approach needs to consider testing beyond conventional settings such as GUM clinics in order to improve coverage and access for

high-risk groups; such an approach will need to mobilise general practice, secondary care, internet and home testing. With any strategy, this needs to be linked to effective post-test counselling and referral for confirmatory HIV testing and treatment.

● Read TRH, Hocking JS, Bradshaw CS et al. Provision of rapid HIV tests within a health service and frequency of HIV testing among men who have sex with men: randomised controlled trial. *BMJ* 2013;467:f5086

If you would like to comment on any of the clinical reviews write to:
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