On lightening up

There is little that is more irritating than being told to lighten up when putting together an issue of Bandolier. For some issues it may, just, be possible. For others, it is a little more difficult.

This issue has been harder than most, because in one fell swoop we have tried to answer three difficult questions, and get Bandolier’s head around some really complicated stuff. In not one of these cases is there a simple answer, even a simple wrong one. And yet each is important.

The first question examines increasing information from the literature concerning the involvement of acid suppression in increased risk of osteoporotic fracture. The evidence looks good, with biological plausibility, large effects, increasing with dose and duration. Just the sort of stuff that begs the question of causation. And yet there is increasing evidence that other commonly used drugs are associated with increased fracture risk: is it all a big dose of confounding in iller, older, people?

The second looks at eGFR, something that many of Bandolier’s readers are struggling with. The bottom line is that very low eGFR is a bad thing (and may increase risks of fracture and cardiovascular events), though that is no surprise. The problem is the grey area between very low and normal, and how fussed we need to get. The third is whether back surgery works, with a (failed) randomised trial and a cohort study to look at.

Cholesterol fairy

So to keep Bandolier sane, the cholesterol fairy popped in with a tale of how doing what we are doing about statins and risks looks as if it works as well in clinical practice as clinical trial theory. At least that lightens the atmosphere, and allows us to say that the boys and girls done good.

PPIs and fractures

Proton pump inhibitors are among the safest drugs we know, and have been used increasingly in older people for conditions like reflux oesophagitis, especially since omeprazole came off patent and prices fell. In recent years the advent of very large databases has increased our ability to examine for rare adverse events, and such an eventuality now impacts on acid suppression, and particularly on proton pump inhibitors (PPIs). Several pieces of information now implicate long term use of PPIs, especially at high dose, on increased risk of osteoporotic fractures, especially hip fracture.

PI and hip fracture [1]

The link between PPI use and increased risk of hip fracture comes from a large case-control study using the UK General Practice Database (UKGPRD). The study cohort was 1.8 million people registered for a year or more in the years 1988-2003, 50 years or older, and without hip fracture before the study started. There were 192,000 users of PPI and 188,000 users of histamine antagonists (H2A) receiving at least one prescription, with 1.4 million non-users of acid suppression medicines.

Cases were people with a first occurrence of hip fracture at least one year after the start of follow up. Up to 10 controls were matched for each case, based on age, sex, and some other relevant factors. Considerably information was collected on cases and controls about demographics, medication use, and health conditions. The primary exposure of interest was PPI therapy of more than one year before the date of fracture.

Results

There were 13,500 hip fractures and 135,000 controls. The average age at enrolment was 77 years, and 80% were women. The crude incidence rate of hip fracture was 4.0 per 1000 person years in those with more than one year of PPI therapy, and 1.8 per 1000 person years in controls. Those with a hip fracture were more likely to have received medicines of have health conditions associated either with osteoporosis of risk of falling, and these criteria were used to adjust the comparisons to remove the effects of these known confounders.

Overall, patients taking PPI or H2A for one year or longer had an increased risk of hip fracture (Table 1). The effect was significantly larger for those taking PPI alone than users of H2A alone. The effect was significantly larger in men than women.

In this issue

- PPIs and fractures ................................................... p. 1
- Estimated glomerular filtration rate (eGFR) ...... p. 4
- Statins in clinical practice ................................. p. 7
- Back surgery poser .............................................. p. 8
For PPIs especially the effect on hip fracture was related to dose (Figure 1). The average dose was 1.75 doses per day. Those with higher doses (≥1.75 a day) were mostly taking medicines twice a day, whilst 90% of those at lower dose were taking it once a day. For PPIs the effect on hip fracture was related to duration of PPI use (Figure 2).

**PPI and fracture risk [2]**

A large Danish study [2] was one report of several relating drug therapy of various types to fracture risk. It used as cases all those people in Denmark (population 5.3 million) who sustained any fracture during the year 2000, with three controls matched by age and sex chosen randomly. Denmark has an almost unique ability to link various databases together, so information could be obtained from hospital discharge registers and medication use.

**Results**

There were 125,000 people with fractures and 374,000 controls. The average age was 43 years, about equally split between women and men. There were many differences between people sustaining a fracture and those who did not, in demographics, use of medical services, and drug therapies.

Recent use of PPI (within one year) was associated with increased risk of hip or spine, and any fracture. No increased risk was seen with H2A, with some suggestion of a reduced risk. For PPIs, use within the last year the odds ratios were 1.2 (1.1 to 1.4) for overall fracture risk, 1.5 (1.3 to 1.7) for hip fracture, and 1.6 (1.3 to 2.0) for spine fractures. There was little in the way of dose response, though the effects were not apparent for PPI use more than one year previously.

**Reflux oesophagitis and vertebral fractures [3]**

A paper from Japan reported a small survey of 75 postmenopausal Japanese women aged 52-97 years of whom 18 had refractory reflux oesophagitis with use of PPI for at least six months for symptom relief. The use of PPI in other women was not reported, but the implication was that PPI was not used because they did not have reflux oesophagitis.

Women with reflux had significantly higher rates of multiple vertebral fractures and hiatus hernia than those without.

**Comment**

This is all a bit new, and frankly unexpected. As best Bandolier can find, there is no other evidence from clinical studies, though there is a limited experimental literature. We have two large and well-done observational studies providing much the same answer. Moreover, there is evidence that there is a dose response and a duration response for PPIs.

Nor is the effect trivial. Hip fracture is an important cause of death and morbidity in the over 65s, especially in women. In the mid-1990s in the UK 57,000 people had hip fracture every year, accounting for 20% of all orthopaedic beds, with an average cost of stay of £5,000 and a total cost to the NHS of hospital care alone of about £280 million [4]. We know that mortality immediately after fracture is about 20%. An East Anglian audit [5] found that:

- Fewer than a quarter of patients both survived and returned to their pre-fracture level of function by 90 days.
- Of survivors, less than one-third returned to their pre-fracture level of function.
- Of survivors, 42% were receiving extra help with at least half of their daily living activities.
Of survivors, 21% required an increased level of residential or hospital care. Of patients who returned home 35% required additional community health and social service visits.

The rate of hip fracture in over 65s is higher in women than men, but overall runs at about 1,100 per million. That means that the annual risk of hip fracture in over 65s runs at roughly 1 in 900 (higher in women and at higher age, of course). The risk of dying is about 1 in 4,500. So anything that doubles the risk produces an additional risk of 1 in 900 of a hip fracture and 1 in 4,500 of dying as a result of a hip fracture. This additional risk can be portrayed on a Paling Perspective Scale (Figure 3) for long-term use of a PPI.

These are not trivial risks, and are of the same sort of order as others we worry about (and some we don’t, because we do not have a particularly coherent view of risk as yet).

This is a time for thought. We have no clear idea about any mechanism, but it is likely to be a combination of reduced calcium absorption and inhibition of ion transport in osteoclasts. Perhaps the main message is that high dose PPIs are not a good idea over the long term, and that we should be more careful about their use, especially in people with risk factors for osteoporosis. With a rapidly growing population of what might be called the older old, this is a topic that needs careful watching.

And finally

Just to make sure that we all realise just how complicated this business of drug therapy and fracture risk is going to be, the Danish group have published two other analyses from their large database [6,7].

On balance, it looks as if certain NSAIDs may be associated with increased risk, and current use of ibuprofen, diclofenac and naproxen (where there were large numbers of users) are implicated as having increased risk (Table 2 shows risk of any fracture). Neither rofecoxib nor celecoxib was associated with any different risk from nonuse, but the bad news was that other commonly used analgesics like paracetamol, tramadol, and morphine agonists were also associated with higher fracture risk. Paracetamol, diclofenac and ibuprofen were consistently associated with increased risk of hip fracture.

There is a really important reminder here. If you don’t look, you won’t find. For rare but serious adverse events, ignorance is bliss. The reality is that almost all drugs and interventions will have some rare but serious adverse event, but because they are rare we might never make the connection. Over the next decade or so the power of large databases will grow, making it possible to investigate this area more thoroughly than ever before.

Be prepared for lots of bad news like this. It makes our inability to explain and use risk information much more of a handicap than we would have thought a few short years ago.

References:

Table 2: Association between analgesic drug use and fracture at any site

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of users (approximate)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>91,000</td>
<td>1.76 (1.82 to 1.81)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>74,000</td>
<td>1.39 (1.35 to 1.44)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>23,000</td>
<td>1.37 (1.29 to 1.46)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>7,000</td>
<td>1.02 (0.96 to 1.07)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>2,000</td>
<td>0.94 (0.84 to 1.04)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>n/a</td>
<td>1.45 (1.41 to 1.49)</td>
</tr>
<tr>
<td>Morphine and morphine agonists</td>
<td>n/a</td>
<td>2.20 (2.08 to 2.32)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>n/a</td>
<td>3.08 (2.99 to 3.17)</td>
</tr>
</tbody>
</table>
ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)

For Bandolier eGFR is another case of angels fearing to tread. The estimation of GFR from serum creatinine and demographic characteristics (age, sex, ethnicity) is usually done using equations derived from blood samples taken during a baseline period of the Modification of Diet in Renal Disease study [1]. The methodology used was excellent, with 1,600 patients split between derivation and validation cohorts and using an independent measure of GFR. Most samples were taken in the morning following a period of fasting, and so provide a somewhat idealised population.

Since about 2002, following general consensus that measuring eGFR was a good thing, many laboratories have been providing an eGFR result routinely when biochemistry has been ordered on a blood sample. The problem many doctors have is how to use this information, and whom to treat, especially when eGFR is linked to the staging classification of chronic kidney disease (Table 1). For classes 2 and 3 the advice is about observation, with control of blood pressure and risk factors. Despite caveats in guidance this has the potential to cause confusion.

The problems

The kidney has much redundancy. The concern is that without age and sex related “normal” ranges (and perhaps ethnic ranges, too), there could be a huge increase in unnecessary investigations and inappropriate referrals. The problem is not whether eGFR is a useful result, but rather about the judgement of when and in whom it is useful.

Most would agree that a GFR above about 60 mL/minute was pretty good in everyone, and that one of below 30 mL/minute was probably not so good, with more concern with even lower results than this. It is the grey area between 30 and 60 mL/minute that is the problem. At its crudest, the argument would be that a GFR value of 50 mL/minute would be worrying in a young man, while one of 40 mL/minute might not be in an otherwise healthy woman of 80 years. It should be noted, though, that others would not recognise this argument at all.

Table 1: Classification of kidney disease according to eGFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR (mL/minute/1.73 sq m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>≥90</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage with normal or raised GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild reduced GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduced GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduced GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

A further element of the problem relates to the circumstances in which blood samples are taken. After a meat meal (hospital canteen rather than trenchermon heroes) serum creatinine is increased and eGFR decreased (Figure 1) [2]. In the 32 participants in this little experiment, 12 would have fallen by at least one stage shown in Table 1, and in 11 from stages 1 or 2 to 3.

It is also the case that the original eGFR equation required calibration of the serum creatinine measurement to the laboratory that developed the equation. The calculations have recently been re-expressed using a standardised assay [3].

eGFR and age

GFR in healthy young men and women is about 130 and 120 mL/minute/1.73 sq m respectively (following this, for clarity, we drop the 1.73 sq m, so it has to be assumed). After the age of 40 years GFR drops by 1 mL/minute per year. So the incidence of low GFR should rise with age.

Figure 2 shows the percentage of men and women with eGFR below 60 mL/minute in an Italian population of 4,500 people from a single town [4]. Surveys in the USA tend to show somewhat higher rates, and the largest survey there involved 2.5 million veterans [5].
In Italians with eGFR <60 mL/minute, disorders associated with kidney disease were more common than in those with higher eGFR. In men, hypertension, high serum urate, high potassium and low calcium, and cardiovascular disease were significantly more common, while in women significantly more common were high serum urate, high potassium and low calcium, cardiovascular disease, and anaemia. With lower eGFR, the number of these associated conditions increased, to over two per patient when eGFR was below 40 mL/minute.

In US veterans [5], 20% of the whole cohort had eGFR of <60 mL/minute, with half of these having moderate reductions in the range of 50-59 mL/minute. Very low eGFR of <30 mL/minute was rare, and usually below 5% even in the cohort of 53,000 people aged 85 to 100 years old.

In patients with stable repeat creatinine measurements, and adjusting the risk of death for age, race, sex, and various chronic diseases, there was no increased risk of death at any age when eGFR was 50-59 mL/minute compared with patients in whom it was ≥60 mL/minute.

When eGFR was 40-49 mL/minute there was a significant increased risk of death in patients below 75 years, but not older. When eGFR was below 40 mL/minute, risk of death was significantly increased at all ages.

In patients with diabetes, and adjusting the risk of death for age, race, sex, and various chronic diseases, there was no increased risk of death at any age when eGFR was 50-59 mL/minute compared with patients in whom it was ≥60 mL/minute.

eGFR and diabetes

About 27% of 7,600 diabetic subjects in Manchester had eGFR of below 60 mL/minute (Figure 7), but only a tenth of these were below 30 mL/minute [7]. A similar pattern was seen in a survey of 3,300 diabetics in Teeside [8] and 4,300 in Wolverhampton [9]. In all these surveys only 2% or less of diabetics had eGFR below 30 mL/minute.

The Teeside study [8] had a 10-year follow up in which 36% of the cohort died. It was able to examine death rates over that time according to eGFR. The 10-year chance of death from any cause was much higher in those with the lowest eGFR (Table 3).

The presence of low eGFR in patients with diabetes may be important. In 269 diabetic patients who were asymptomatic...
for coronary heart disease, all cardiac events were recorded over a 2.3 year period [10]. It transpired that 29% (77) had an eGFR below 60 mL/minute at baseline; these patients were older, had a longer duration of diabetes, and a higher prevalence of albuminuria (though 35% had normal albumin excretion).

In these 77 patients, 25% had some cardiac event (nonfatal MI, unstable angina, percutaneous coronary intervention, or coronary artery bypass surgery) That was significantly higher than the 13% rate in the 192 with eGFR of 60 mL/minute or more.

### eGFR, heart failure, and MI

A systematic review of the prevalence of renal impairment in heart failure patients [11] assembled information on over 80,000 patients. Renal function was determined by a number of methods, but showed that any renal impairment was present in 63% of these patients, and moderate or severe impairment in 29%.

With greater impairment in renal function comes greater risk of mortality, especially in older patients. In a retrospective cohort of 57,000 patients (mean age 78 years) admitted to hospital with heart failure and 44,000 patients admitted with myocardial infarction who were followed up for one year [12], mortality was higher with lower eGFR, at about two or more times greater at lowest level of eGFR (60+%) compared with highest level (about 20-25%).

### Comment

Using estimated GFR is complex. There are concerns over different equations for the calculations, methods of creatinine measurement, muscle mass, alcohol, and cooked meat ingestion that all serve to muddy the waters to an extent. Most of these are important, but represent for the most part the sort of squabbles that academics undertake for valid reasons, though most of the time we ordinary mortals don’t need to trouble our neurone over it.

Estimated GFR will pick up impaired renal function. Most of what it does pick up tends to be in older patients with comorbidities. In most cases, the response is control of blood
Do statins reduce cholesterol and mortality? Of course they do, although not everyone is happy to agree about the exact mechanism providing the benefit, with argument still going on about cholesterol lowering and anti-inflammatory effects. We have a large number of large randomised trials that tell us so, with detailed pooled analysis of those trials to back it up. Trials run independently of pharmaceutical companies give the same answers as those run by the companies.

Even so, there are always those who are concerned that clinical trials are not the same as clinical practice. Clinical practice is populated by hosts of patients who wouldn’t get into any clinical trial, and the real world is complicated by such issues of compliance and comorbidity that would make trialists shudder. So an observational study of statins in clinical practice [1] is worth a few moments of our time.

**Study**

The study was a data mining exercise using a US veterans database with demographic, laboratory test, vital sign, drugs prescribed, outpatient visits, hospital admissions, and disease classifications on about 1.5 million patients, 95% of whom were men. Those with a prescription for any statin were identified, and relevant information collated on the 229,000 statin users and 1,262,000 nonusers.

The study looked at the effect of statin use on overall death. To examine the influence of statin use according to different levels of risk, a seven-point (0-6) risk score was used, scoring one point each for:

- Age ≥70 years
- Diabetes
- Previous myocardial infarction
- Hypertension
- High LDL cholesterol (≥2.6 mmol/L; 10 mg/dL)
- Current smoking

**Results**

Statins were rarely aged less than 50 years (6%), but almost half (46%) were aged 70 years or more. Almost 90% had used a statin for at least one year, and about half for three years or more. Simvastatin was most commonly used, even in almost 80%.

Statins users were very different from nonusers. They were much more likely to have hypertension, diabetes, and coronary artery disease, be depressed, or be current smokers. They were much more likely to be treated with drugs like beta-blockers, ACE inhibitors, calcium channel blockers, or aspirin.

Statins users had initially higher levels of total and LDL cholesterol and triglycerides than nonusers. After treatment, they had lower levels of total and LDL cholesterol, and triglyceride concentrations were the same.
Use of statin had a highly significant negative association with death in a statistical model, with a mean age at death two years older than for those not using statins. The distribution of age at death was somewhat different in statin users, with fewer dying very young (<45 years) or very old (>90 years). Statin use was associated with a statistically significant reduced risk of death when risk scores were 1 or above (Figure 1).

Comment

By any standard, the patients prescribed a statin in this observational study were not a good bet. Nearly 80% had hypertension, and 40% diabetes, with a mean initial total cholesterol of about 5.3 mmol/L. Half were taking antihypertensives or aspirin, and almost all were men. Yet they lived two years longer than their lower risk contemporaries.

This large and important study shows that the expected benefits from clinical trials are found in clinical practice. It also demonstrates that finding and treating higher risk patients in primary care is a sensible and useful process. Whatever the mechanism, this is useful background evidence away from clinical trials, and provides encouragement in these cold and dark Northern mornings.

Reference: