In England, Department of Health rules do not allow doctors to prescribe medicines for six months at a time. The rules do not normally specify any particular period for prescriptions, as that decision is best made by the patient’s GP, taking into account her or his detailed knowledge of the patient’s medical history and current medical condition.

All of which seems fair. Most doctors would recognise that there are patients on stable long term therapy where a prescription covering up to three months would be appropriate, and times when a shorter period is much more sensible.

Yet all over England authorities are enforcing a “one-month only” rule. The reason put forward is that this is in the best interests of the patients, and saves money. Quite what the evidence is for either assertion is uncertain. Bandolier has been bombarded with demands from patients and professionals for the supporting evidence, and hasn’t found any.

First, it isn’t Bandolier’s fault; we think it’s daft too. Second, we could find no evidence from literature searching or asking folk who should know. The best information we have come across so far is that an old lady died and was found to have £18,000 worth of drugs in her cupboards. That may be so, but it is unclear that such heroic hoarding would have been aborted by monthly collections.

Now it is unusual for so many people to be so cross. The more they know about the impact the crosser they are. Patients are inconvenienced requesting and picking up prescriptions every month instead of every three, practice staff are frazzled, repeat prescription requests soar alongside dispensing costs. Adherence rates may be falling, and some patients are wondering why they are bothering.

So who has the evidence? What is its nature? Are the benefits in cost saving worth so much anger and hassle? How is this policy in the best interests of patients? Who decided it, and when?

**Switching statins**

When Bandolier departs its little ivory tower (fake, of course) and tastes the real world, questions are never about esoteric issues of evidence. Rather, they are worldly issues of real import to everyday practice. Most often asked is whether switching from atorvastatin to simvastatin is really a good thing. A quick search for the evidence seemed useful.

**Cholesterol levels in trials**

When you look at cholesterol and cholesterol subfractions in trials of statins lasting 12 weeks or longer (91 trials and 43,000 patients [1]), two important findings stand out.

The first is that atorvastatin 10 mg and simvastatin 40 mg are virtually identical in terms of their average effect in lowering total cholesterol and LDL cholesterol (Figures 1 and 2). Both were some way better than lovastatin, pravastatin and fluvastatin. Both were less good than rosuvastatin 5 or 10 mg. However, there were 10 times more patients analysed for simvastatin than atorvastatin, and 20 times more than for rosuvastatin. The weight of evidence is with simvastatin.

The second point made was that these longer (>12 week) trials showed little in the way of a significant dose-response. This is different from trials of up to six weeks, when a highly significant dose response was seen for all statins. This observation may be important. Some clinicians insist that higher concordance rates are obtained and target cholesterol levels attained when statins are prescribed at lower doses or with careful upward titration, but there aren’t trials to show it.

**Figure 1: Percent reduction in total cholesterol from baseline in studies of at least 12 weeks. Numbers of patients in brackets**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Percent change from baseline</th>
<th>Numbers of patients in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin 10 mg (495)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 5 mg (510)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 10 mg (1107)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 40 mg (10952)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 40 mg (3743)</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg (8716)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 40 mg (376)</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

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Searching for studies of switching statins found only two. One was from a large institute in the USA, the other in primary care in the UK. Both showed it to be feasible and cost-effective.

**US study [2]**

Conducted at the Walter Reed Army Medical Centre in Washington, the study planned to change all the patients on statins to cerivastatin – at that time both licensed and the cheapest. It was done with a full consultation and an educational programme, and with a purposely-created clinic to arrange the change. The clinic was staffed by a full time pharmacist working to an agreed algorithm, an analyst, and a research administrator, all with clinical support.

In four months it saw 1,356 patients, 942 of whom agreed to be part of the efficacy and monitoring study. Their mean age was 68 years, and 60% were men.

Statins used changed from predominantly atorvastatin and pravastatin (86%) to predominantly cerivastatin (96%). There were small average improvements in LDL and HDL cholesterol, with the proportion at or below their target cholesterol rising from 65% to 75%. In the 942 patients who were monitored, 28 (3%) experienced minor adverse events, mainly of muscle origin.

Despite administration costs of almost $200,000, the conversion policy saved $115 per patient in the first year.

**UK study [3]**

Switching of statins in a UK primary care setting was monitored in a practice of 9,050 patients with an annual drug budget of £1.3 million. The aim was to switch patients being prescribed 10 mg or 20 mg atorvastatin to simvastatin. All those taking 20 mg atorvastatin were switched to 40 mg simvastatin.

Initially, 122 patients were identified. Of these, 43 were excluded by a pharmacist (cholesterol greater than 5 mmol/L on 10 mg, or greater than 4.6 mg on 20 mg atorvastatin; previous use of simvastatin failing to reduce to target, renal failure, transplantation, on warfarin or amiodarone). A further nine were excluded by their GP on medical, administrative, or social grounds.

The seventy remaining patients were contacted by letter; none refused. All were switched; one experienced an adverse event so was switched back.

The average total and HDL cholesterol values were the same before and 3-4 months after the switch. Before the switch three patients had total cholesterol above 5 mmol/L; after the switch six had total cholesterol above 5 mmol/L.

The total cost of switching was £2,000, with full year savings of £14,700, or just over 1% of the practice drug budget. The cost per patient switched was £213 per year.

**Comment**

There is one important difference between these studies, otherwise so similar in their success and cost savings. It is how the changes were made. At Walter Reed the initiative came from staff themselves, from a team of interested clinical specialists formed to plan and build support for the project. It was inclusive, and took account of some of the more complicated clinical areas. In the UK the practice was asked (euphemism for told, very often) by its Primary Care Trust to make the change.

The top-down method can be effective, but is not always so, so an interesting and important caveat is instructive. A corporate decision was made by a cardiology department in a UK hospital to give high dose statin (atorvastatin 40 mg or 80 mg) to patients after myocardial infarction or revascularisation. This was an evidence-based decision, and increasingly we know that getting LDL cholesterol below a certain target is beneficial, with substantial atheroma regression for lower LDL cholesterol and HDL cholesterol raised by more than 7.5% [4].

The administrative bosses (a group of Trusts) over-ruled the policy, limiting prescribing to simvastatin 20-40 mg. An audit over the same calendar period under successive policies provided some insight into the advisability of this [5]. As Figure 3 shows, the simvastatin policy resulted in more deaths, and cardiac and non-cardiac readmissions.
A note on costs

There is much discussion about cost savings, some of it quite sensible [6,7]. When properly done in primary care in the UK, the implication is that if a similar proportion of patients were switched successfully it would save £630 million to the NHS over the five-year period until atorvastatin comes off patent. This is worth saving.

But it is interesting that the rather limited evidence to support the switch came after the orders, and not before. In primary care, all seemed to work out well over the short term. The caveat is that we have no outcome data over the long term, and now a wake up call that all may not be as simple as it looked. The buyer might be saving on one budget, and spending on the other.

There is also a question here about responsibility, which no one is answering. If, as in the example above, an administrative order (request) results in patient harm, and the patient sues, who carries the can and is up before the beak?

References:

**STATIN ADHERENCE AND OUTCOMES**

Taking effective medicines is likely to produce better results than keeping them in the cupboard. An observational study might be expected to find that result. A potential problem with the simplistic interpretation might be that patients who are most concordant are different in some way from those who are least – what is known as the healthy adherer effect. A new study looks at this and indicates that benefits of statins are related to adherence alone [1].

**Study**

The study was a longitudinal observational study of 31,500 patients aged at least 66 years who survived a myocardial infarct between 1999 and 2003 in Ontario, and who filled at least one prescription for statin, beta-blocker, or calcium antagonist within three months. For inclusion, at least 15 months of follow up information had to be available.

Computerised prescription records allowed the proportion of days covered by each therapy to be calculated. High, intermediate, and low adherence were defined as ≥80%, 40-79%, and <40% of days covered by therapy. The outcome was mortality overall, stratified by adherence and initial disease severity (high, intermediary, and low mortality risk according to age, sex, and severity of cardiac disease).

**Results**

Statins were used at least once by 17,800 patients, with 24,300 using a beta-blocker and 9,200 a calcium antagonist. One year average adherence rates were 88%, 84%, and 79% respectively. The proportion of patients stopping their drugs entirely during the overall 2.4 years of follow up was very low, 1.1% for statins, 1.7% for beta-blockers, and 3.2% for calcium channel blockers. For all three drug classes, most patients had high adherence ≥80% (68% to 81%).

For statins, compared with high adherers, the risk of mortality was 12% higher with intermediate adherence and 25% higher with low adherence. The effects with different rates of adherence and initial mortality risk are shown in Figure 1. There was a small, just significant trend to higher mortality with lower adherence for beta-blockers, and no difference with calcium channel blockers.

**Comment**

Calcium channel blockers have no proven survival advantage after myocardial infarction, and there was no difference in mortality between high and low adherers. This forms a control to demonstrate that there was no special effect of high adherence per se, and that the effects seen with statins and beta-blockers, and especially with statins, were due to the drug classes used. So we can confidently say that, in this case, common sense rules. Keep taking the statins is the order of the day.

Reference:
PHARMACY CARE IN OLDER PATIENTS

We know that many people do not take medicines prescribed for them, and that adherence rates are often low. We also know that older people have problems with their medicines, often because they are prescribed many medicines, to be taken at different times of the day. Finally, we know that major influences on admission to hospital with adverse drug reactions include older age, being a woman, and having lots of tablets to take.

It does not need a brain the size of planet to see that there are some problems here needing to be solved. A trial from the USA [1] suggests that extremely good adherence results can be had from some simple interventions from pharmacists that help older people understand and manage their medicines.

Trial

This is an interesting example of a randomised withdrawal trial design outlined in Figure 1.

1 All patients entered a two-month run in period used to ascertain baseline adherence, and measure blood pressure and cholesterol.
2 After this, all patients entered an intervention phase, during which they received their drugs individualised in blister packs with tablets labelled for time of day. This was supplemented with individualised education visits, and follow up with a pharmacist every two months. These visits taught patients about their drugs, their names and indication, strengths, adverse events and usage instructions.
3 After six months, patients were randomised to continuing the intervention or usual care.

Adherence, blood pressure, and cholesterol were measured during the run in period and at the end of each six-month period.

Figure 1: Randomised withdrawal design of study of pharmacy care in older patients with multiple health problems

<table>
<thead>
<tr>
<th>Month</th>
<th>Run in</th>
<th>Intervention</th>
<th>Usual care</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Median adherence (%)</td>
<td>62</td>
<td>99</td>
<td>68</td>
<td>96</td>
</tr>
<tr>
<td>&gt;80% adherence to all medicines</td>
<td>5</td>
<td>99</td>
<td>22</td>
<td>97</td>
</tr>
</tbody>
</table>

Results

Initially 200 patients entered the run in period, and 159 were eventually randomised. Their average age was 78 years (minimum 65 years), 77% were men, 57% had four or more health problems, with an average of nine chronic medications. There were high levels of use of statins and blood pressure medicines.

Results for adherence are shown in Table 1. The pharmacy care programme resulted in a large increase in adherence, with the proportion of patients more than 80% adherent to all medicines increasing from just 5% in the run in period to 99%. After randomisation, the intervention group maintained these high levels of adherence, while return to usual care resulted in a large decrease in adherence, approaching rates seen in the run in period.

Increased adherence resulted in large reductions in systolic and diastolic blood pressure during the intervention period; For LDL-cholesterol there useful reductions in both groups maintained after randomisation, with no significant difference between them.

Comment

This is a very important study, which shows that to achieve high adherence in older people with multiple health problems and medications, continuing intervention is needed. The paper, and especially the thoughtful discussion, should be read by anyone wanting to do better.

The benefits of high adherence are potentially large, given the generally low adherence usually seen in these circumstances, and given that low adherence is associated with increased rates of hospital admission. This is not a simple answer to a simple problem, but an indication that with insightful pragmatic action much better outcomes can result.

After all, the pills are better in the patient than in a bottle. If the latter we pay twice, in unused medicine and more healthcare costs. Given the acknowledged size of the problem, the implication is that this is a topic area that requires some sensible research and action.

Reference:

1 JK Lee et al. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol. A randomized controlled trial. JAMA 2006 296: 2563-2571.

Table 1: Median adherence (% of all tablets taken) and percentage of patients taking at least 80% of all medicines
PREVALENCE OF ASPIRIN RESISTANCE

Aspirin probably works by irreversibly inactivating cyclooxygenase-1 in platelets, which means that they cannot produce thromboxane A₂ with a consequent reduction in aggregation. It is worth noting that while NSAIDs also inhibit cyclooxygenase-1, this inhibition is reversible, and so any effect wanes as drug levels diminish, with only a transient reduction, if any, in platelet aggregation.

Aspirin resistance is a simple description of a complex phenomenon, namely the persistence of platelet aggregation despite use of aspirin. That simple statement is deceptive, however, because there is no agreed definition of aspirin resistance. A variety of laboratory tests are used to measure aspirin resistance.

So a moment’s reflection demonstrates that trying to measure the prevalence of aspirin resistance is not going to be straightforward. Apart from differences between individuals (due to pharmacokinetic or genomic issues), there will be issues of dose of aspirin, co-medication, medical condition, as well as method of measurement and definition of resistance to contribute to differences in measured prevalence. All of which is made plain by a systematic review [1] that tries to pull some of this together.

Systematic review

The systematic review used a heroic series of searches to find studies. To be included a study had to report the prevalence of aspirin resistance from a survey or cohort study with consecutive patients, have a clear definition of aspirin resistance, in well described patients using aspirin for secondary prevention of cardiovascular events.

Stratified analyses were planned by dose of aspirin and laboratory method used to measure aspirin resistance, according to the populations studied (post myocardial infarction, stroke or TIA, and revascularisation, or other).

Results

The review included 34 full articles and eight abstracts, but we are not told the number of patients studied in total, the number of patients in each study, nor the prevalence in each study. All we have is a series of results of pooled analyses, and it is clear that some individual studies must have reported on more than one group of patients, dose of aspirin, and method of analysis.

Overall aspirin resistance was 24%, with prevalence in individual studies ranging from 0% to 57%. Figure 1 shows the 95% confidence intervals for prevalence of aspirin resistance according to aspirin dose, after some statistical adjustments. There was little difference in aspirin resistance prevalence between different patient groups, or by different methods of measurement, with one exception. Five studies using arachidonic acid as an agonist in light transmission aggregometry reported lower prevalence values of 1% to 12% (average 6%).

Comment

It is a bit of a shame that there is some opaqueness about the review, and this is one of the times to bemoan the lack of accompanying tables with information on the individual studies. If they were there, we might do some sums of our own without retrieving 42 papers and starting from the beginning.

But that is a quibble stemming from the importance of the paper. The authors do their weighting based on patient numbers.

Perhaps the take-home message is that a prevalence of aspirin resistance of 1 person in 4 might be a worst-case scenario. For instance, we have the problems of definition and method, and it may well be that more conservative definitions and defined methods would reduce rather than increase the prevalence. Again, we have no idea about compliance: we know from other sources that compliance with daily aspirin is often poor, and that would certainly contribute to higher apparent aspirin resistance.

These are details that will be sorted out in due course. What we can be pleased about is that this should be the first step on the path of individualising therapy (perhaps measuring resistance after starting at very low doses of aspirin) and improving cardiovascular outcomes.

Reference:


Figure 1: Prevalence of aspirin resistance (failure to inhibit platelet aggregation) with daily aspirin dose

![Figure 1: Prevalence of aspirin resistance (failure to inhibit platelet aggregation) with daily aspirin dose](image-url)
GENES AND AGE-RELATED MACULAR DEGENERATION

Bandolier continues its journey into ever-harder tasks by trying to get its neurone wrapped around a genetics paper. In the usual course of events our neurone may have given up, except for the importance of the topic, age related macular degeneration (AMD). The paper includes both a meta-analysis and interactions with lifestyle factors [1] that makes it worth pursuing.

Study

Participants in two major US epidemiological studies were involved – the US Nurses Study and the Health professionals Follow Up Study, which between them originally enrolled about 170,000 healthcare professionals for long-term follow up. About 50,000 of these who had provided blood samples were used as the study base. Briefly, participants were asked about a diagnosis of AMD, with permission to review medical records. A diagnosis of AMD was confirmed by standard methods. For each case two or three controls were selected, within one year of age and with an eye examination within the previous two years.

DNA assays were used to explore for one known gene (CFH Y402H) and one locus for a hypothetical, but unknown, gene (LOC387715 A69S).

Results

The study group had 457 cases of AMD (293 dry AMD, 164 neovascular AMD) and 1,071 controls. AMD cases were associated with higher rates of obesity, smoking, and alcohol consumption, and lower intake of fruit and vegetables.

Interactions with lifestyle factors

Having a BMI ≥30 and being a current smoker doubled the risk of AMD for all most all genotypes of both genes. The most important lifestyle interactions with genetics were obesity and smoking for high risk homozygotes. For instance, for high risk homozygotes of CFH Y402H genotype, being overweight trebled the risk, and current smoking doubled it. For high risk homozygotes of LOC387715 A69S genotype current smoking quadrupled the risk.

Comment

Bandolier is fully aware that any gene jockeys reading this poor account of some stupendous work might fume at the inadequate treatment of their arcane arts. It is not an easy paper to read. But the message is important, and in the end simple.

If you happen to be one of the folk with two copies of the high risk variant of each of the two genes, your risk of AMD developing is very much higher than the average in the population. But the message is also that the risk is multiplied even more by an unhealthy lifestyle. For those at risk, lifestyle is the most important thing. This you can change: you can’t change your genes.

For those who moan that we don’t know if we have the high risk genotype, or who are prepared to gamble on not having it, Bandolier reminds you that an unhealthy lifestyle is stupid for any number of other reasons.

It is an interesting example of how genetics and environment conspire to produce very bad results in some people - the why me? Question answered.

Reference:
MINDSTRETCHER: ANALYSING OBSERVATIONAL STUDIES

Haven’t you always wanted to know what goes on in those statistical shenanigans found in so many observational studies, where raw results are “adjusted” for a whole range of criteria that may affect the results, from age and sex to inside leg measurement. No, it’s not sad, but important.

Usually all this is opaque to us, and probably ever will be, but a study of the difference that different methods make, and related to results of randomised trials [1] and an accompanying editorial [2] at least provide an indication of the magnitude of the changes adjusting methods can make.

Study

The study was of 122,000 Medicare patients in the USA aged 65-84, admitted with acute myocardial infarction, and eligible for cardiac catheterisation. Follow up for over seven years allowed investigation of the association between long-term survival and having cardiac catheterisation.

There was a rich set of data on each patient, and this allowed a number of different methods of adjusting raw results for various characteristics to be made.

Results

Of the 122,000 patients, 73,000 received cardiac catheterisation within 30 days. These tended to be younger, to be men, with less severe infarctions, and were more likely to be admitted to high-volume hospitals.

Table 1 shows the results. Without adjusting for differences between those given cardiac catheterisation and those not, the intervention looks very useful, with a very low relative mortality rate. Adjusting for the different risk factors reduced the apparent benefit, with a 64% apparent reduction in mortality falling to approximately 45% reduction in mortality with cardiac catheterisation for most methods, though only a 16% reduction with one method (Table 1). The method of adjusting the crude results obviously had a major impact on the apparent benefits of the intervention.

Table 1: Relative mortality rate (cardiac catheterisation vs no catheterisation) in a large observational study with unadjusted results and results adjusted to take account of imbalances in the two populations

<table>
<thead>
<tr>
<th>Risk adjustment method</th>
<th>Relative mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted survival model</td>
<td>0.36</td>
</tr>
<tr>
<td>Multivariate survival model with 65 covariates</td>
<td>0.51</td>
</tr>
<tr>
<td>Survival model using propensity score</td>
<td>0.54</td>
</tr>
<tr>
<td>Survival model using complex propensity score</td>
<td>0.54</td>
</tr>
<tr>
<td>Survival model using propensity based matching cohort</td>
<td>0.54</td>
</tr>
<tr>
<td>Instrumental variable-adjusted method</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Comment

The original paper and accompanying editorial [2] are more of a minbreaker than a mindstretcher for ordinary mortals. The survival benefits of routine invasive care from randomised trials are between 8% and 21%, and the question here is whether these RCT results can be used as the gold-standard to judge the methods of adjusting results from the large observational study.

If so, clearly the instrumental variable method would seem to be best. If not, the implication is that we are all at sea on this one. The argument would be that as randomisation balances all the differences between patients, that balance allows us to see the true effect of the intervention. Yes, but; the buts might include the fact that randomised trials may not reflect every aspect of clinical practice, and that exclusions from trials might muddy the waters when interpreting it for clinical practice.

How gold is the gold standard?

For this example, the effect sizes used from two meta-analyses (8% and 21% benefit) as a gold standard may not be the right ones. For a start, one analysis was over about six months and the other 17 months – much shorter than the seven years (84 months) used in the observational study. Then there is the point that neither meta-analysis exactly mirrors what is going on in clinical practice. A third point is that it is possible to find benefit effects of about 50% in at least one outcome of the meta-analyses. A fourth point, and probably very important, is that the statistical benefits were derived from relatively small absolute benefits.

Implications for interpreting observational studies

Confused? Join the club. The bottom line is that adjusting results in observational studies can make a huge difference to apparent treatment effect, and that it isn’t an exact science. A subsidiary is that choosing a gold standard has to be done with care.

In this case, where even the most conservative method indicated a benefit, we can be relatively sanguine. Where observational studies show only a small benefit, or bare statistical significance, we need to be much more cautious about interpretation, and worry more about issues like confounding by indication, or unknown differences between groups that are not taken into account.

References:

ADVERSE EVENTS WITH PLACEBO: REPRESENTATIVE OF REAL LIFE?

Bandolier 115 examined evidence about non-drug adverse events from two studies that collected adverse event information in young people without any disease and taking no medicine. The duration was three days, and symptoms were indicated from proffered lists.

Given that these were young men and women in their 20s, what was astonishing was the frequency with which adverse events were noted, with fatigue particularly common, but others also, like headache, joint and muscle pain, sleepiness, and inability to concentrate appearing frequently. Only 17% noted no symptoms, and many had multiple symptoms.

Clinical trials record adverse events in a number of ways, and even though adverse events are not usually the prime interest of clinical trials, we pore over the data because adverse events often drive therapy. The most obvious is that adverse events are a major driver of lack of adherence, or switching therapy, or both.

A review examines adverse events in placebo groups from statin trials, and makes comparison with another survey of adverse events in an adult German population [1], and leads us again to question the reliability of adverse event rates captured by clinical trials.

Study

The review identified statin drug trials published between 1994 and 2003 with more than 100 subjects in a placebo arm. Adverse events in placebo were noted as all cause and drug related. Results from a representative sample of 2,500 German adults assessing 33 symptoms for the previous seven days were used for comparison.

Results

Discontinuation rates for any cause in placebo groups of seven trials with 17,535 patients lasting 16 weeks to five years (mostly one year or longer) ranged from 3 to 40% on an annualised basis, averaging 10% a year. Discontinuation rates because of adverse events averaged 7% a year. In trials lasting at least three years there was less variability, with annualised rates of all cause discontinuations with placebo of 6% and adverse event discontinuations 4%.

Particular symptoms regarded as possibly drug related usually varied by factors of 4:1 or greater between large trials with at least 400 patients given placebo. Symptoms occurring with placebo and independent of presumed cause also varied between trials. Moreover, the rates at which these occurred with placebo in trials was different from that occurring in the absence of a trial (Figure 1).

Comment

While in part this paper simply rehearses what is already known about the problems with adverse event measurement and interpretation in clinical trials, it still gives us much to chew over. Usually variability between trials is due to small numbers, but not here. Different methods of capturing adverse events and different populations are theoretical reasons for differences.

But trials and clinical practice are not always the same, with relatively low discontinuation rates with statins in trials contrasting with high discontinuation rates in practice. And there’s what happens without drugs. Again, it is instructive to see how many symptoms can be recorded without a trial, and why those symptoms are often so less frequent in trials.

There is much food for thought. Adverse event reporting, analysis, and interpretation is a topic that demands much more of our attention.

Reference:

Figure 1: Adverse events recorded with placebo in patients in placebo groups in statin trials, and over seven days in 2,552 German adults aged 16-99 years, mean age 48 years.