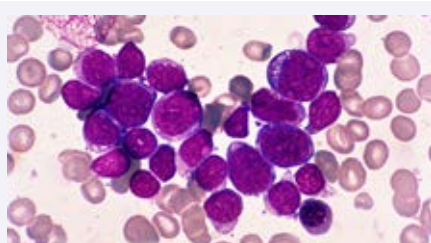


research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on <http://bmj.co/Lehman>



JEAN BONHOMME, ISM/SPL

All sorts of acute myeloid leukaemia

Ernest Rutherford (1871-1937), New Zealand's greatest son, said that physics is the only science, and the rest is just stamp collecting. Nowadays physics seems largely about making stuff up, so I feel safer with the stamp collectors. And what wonderful stamps they are finding every day! When you were a student with your medical school stamp album, there was just one Penny Black, called acute myeloid leukaemia (AML). Now the stamp collectors have looked at the watermarks and all that sort of thing and it turns out that there are 76 types of Penny Black or AML. And this, of course, matters a great deal if you happen to have one of them. Quarks, wormholes, and superstrings will or will not exist forever, whether or not you are alive, but if your AML doesn't get the right treatment you will soon cease to puzzle about such things and become part of the unknowable. Most people wish to postpone this. To get AML is a misfortune, but to get AML with chromatin-spliceosome and TP53-an euploidy is doubly so. You have a bad prognosis, and at the moment there is not a lot that can be done about it. In 10 years' time, there might be. Let's hope that in the meantime, the biggest obstacle to progress in oncology—completely unaffordable tests and treatments—will have been sorted out. An 1840 Penny Black will set you back about £2500 at current prices. That might buy you a couple of weeks' worth of combined chemo and monoclonal antibody treatment. So I read papers like this latest *NEJM* one about genuinely huge advances in our understanding of cancer with mixed feelings: will these patients genuinely benefit or will they become victims of the current “your money or your life” system of oncology drug development?

• *N Engl J Med* 2016, doi:10.1056/NEJMoa1516192

Wobbles in the US fat plateau

Obesity in American adults has just about plateaued. OK, it still isn't an attractive sight: a wobbling belly of a plateau, with 35% of men and 40% of women obese by the criterion of a body mass index greater than 30. And women are still tending to get a little fatter. This is an approximate summary of data obtained from the National Health and Nutrition Examination Survey over the nine years preceding 2014. This cannot be good, yet it isn't having the dire effects that the data might have predicted: type 2 diabetes is on a slight wane, and cardiovascular disease continues to drop.

• *JAMA* 2016, doi:10.1001/jama.2016.6458

Obesity in US kids

But what about the kids? Let me just give you the summary: “In this nationally representative study of US children and adolescents aged 2 to 19 years, the prevalence of obesity in 2011-2014 was 17.0% and extreme obesity was 5.8%. Between 1988-1994 and 2013-2014, the prevalence of obesity increased until 2003-2004 and then decreased in children aged 2 to 5 years, increased until 2007-2008 and then levelled off in children aged 6 to 11 years, and increased among adolescents aged 12 to 19 years.”

• *JAMA* 2016, doi:10.1001/jama.2016.6361

Early general anaesthesia and cognitive outcomes

Had general anaesthesia in human babies started off with animal experiments, it might never have caught on, since exposure of young mammals to commonly used anaesthetics causes neurotoxicity, including impaired neurocognitive function and abnormal behaviour. Fortunately that doesn't seem to apply to young humans with a single exposure to general anaesthesia in their first 36 months. Here's a neat long term study of 105 sibling pairs in which one received general anaesthesia (median duration 80 minutes) for inguinal hernia surgery before the age of 3. When assessed at the age of 10-11, no statistically significant

differences in mean scores were found between sibling pairs in memory/learning, motor/processing speed, visuospatial function, attention, executive function, language, or behaviour.

• *JAMA Intern Med* 2016, doi:10.1001/jama.2016.6967

Overtreating diabetes

It's five and a half years since I tagged along with John Yudkin on a short, life changing visit to Yale to talk diabetes with Harlan Krumholz. On that occasion I first met Joe Ross and Kasia Lipska, and the following year I met Victor Montori and Nilay Shah. Together they comprise most of the authors on this new paper assessing how many out of 31 542 people with type 2 diabetes on an insurance database were likely to be receiving too much treatment, and what effect this had on rates of hypoglycaemia. They conclude that over 20% of these people fall into the overtreated category, and that this nearly doubles their risk of hypoglycaemic episodes. You may say I like this study because I think that these friends are among the coolest people in medicine. This is true. It is also an important study. Someone needs to look at the UK figures.

• *JAMA Intern Med* 2016, doi:10.1001/jamainternmed.2016.2275

Fundamental choices

Haemorrhoids are swollen veins, and you can leave them alone or treat them with rubber bands. That is about as far as my understanding stretches. It had never occurred to me that where there are veins there must be an artery to feed them, and that one way to treat piles might be to ligate the haemorrhoidal artery. Apparently this procedure has caught on with proctologists. The British HubBLE trial sought to compare the rubber bands with arterial ligation in people with second and third degree haemorrhoids. They found that ligation is more expensive, has more complications, and is more painful. The humble rubber band is an article of great domestic value, although it has uses that you should not try out at home.

• *Lancet* 2016, doi:10.1016/S0140-6736(16)30584-0

Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation

Jaspers Focks J, Brouwer MA, Wojdyla DM, et al

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Find this at: <http://dx.doi.org/10.1136/bmj.i2868>

Study question Does the treatment effect of apixaban versus warfarin differ with increasing numbers of concomitant drugs used by patients with atrial fibrillation?

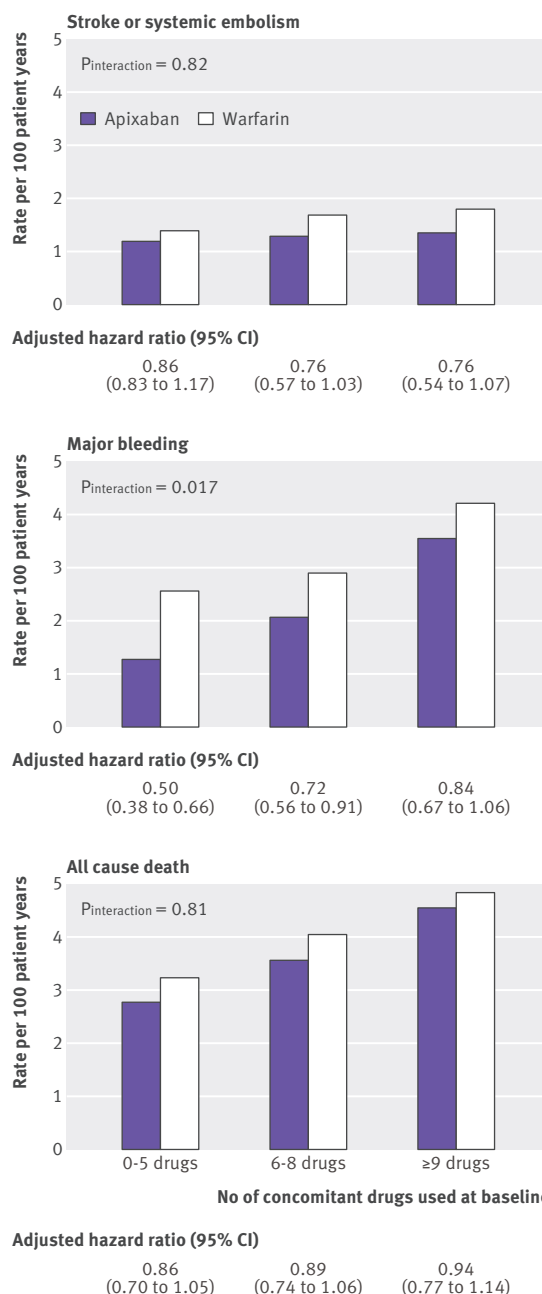
Methods In a post hoc analysis of results from the ARISTOTLE trial (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation), 18 201 participants were divided into groups according to the number of concomitant drug treatments used at baseline. Clinical outcomes and treatment effects of apixaban were compared with those of warfarin (adjusted for age, sex, and country), with a median follow-up of 1.8 years.

Study answer and limitations Increasing numbers of concomitant drugs resulted in increased comorbidity, and a raised risk of stroke and systemic embolism, major bleeding, and mortality. Patients with polypharmacy (n=13 932 (76.5%)) were older and more often from the United States. Relative risk reductions in stroke or systemic embolism between apixaban and warfarin were consistent ($P_{\text{interaction}}=0.82$), with lower event rates on apixaban regardless of the number of concomitant drugs. For major bleeding, the relative benefit of

apixaban over warfarin fell with increasing numbers of concomitant drugs used ($P_{\text{interaction}}=0.017$). Attenuation of the safety benefit was not explained by differences in use of interacting drugs, such as inhibitors of cytochrome P450 3A4 enzyme and P-glycoprotein, and warfarin potentiators. Although polypharmacy may cause a differential drug response to oral anticoagulation, this study was a post hoc analysis, looking at the baseline burden of medication and based on a trial population.

What this study adds Of the ARISTOTLE trial participants, three quarters had polypharmacy; this subgroup had greater comorbidity, more interacting drugs, increased mortality, and higher rates of thromboembolic and bleeding complications. In terms of a potential differential response to anticoagulation therapy in patients with atrial fibrillation and polypharmacy, apixaban was more effective than warfarin and at least as safe.

Funding, competing interests, data sharing The ARISTOTLE study was supported by Bristol-Myers Squibb and Pfizer. Competing interests are stated in full in the article on thebmj.com. No additional data available. Trial registration ARISTOTLE trial, ClinicalTrials.gov NCT00412984.



Association between randomised treatment and main outcomes, by number of concomitant drugs used at baseline by ARISTOTLE trial participants

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Pinpointing the health effects of alcohol

ORIGINAL RESEARCH Observational cohort study using differences in alcohol sales laws

Access to alcohol and heart disease among patients in hospital

Dukes JW, Dewland TA, Vittinghoff E, et al

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Find this at: <http://dx.doi.org/10.1136/bmj.i2714>

Study question What is the relation between alcohol consumption and heart disease, assessed using differences in county level alcohol sales laws as a natural experiment?

Methods This was an observational cohort study of hospital based healthcare encounters in Texas, USA. The study population was 1 106 968 patients aged 21 or older who were residents of “wet” (no alcohol restrictions) and “dry” (complete prohibition of alcohol

sales) counties and admitted to hospital between 2005 and 2010, identified using the Texas Inpatient Research Data File. Outcome measures were prevalent and incident alcohol misuse and alcoholic liver disease in the validation analyses and atrial fibrillation, acute myocardial infarction, and congestive heart failure in the main analyses.

Study answer and limitations Residents of wet counties had a greater prevalence and incidence of alcohol misuse and alcoholic liver disease than did those in dry counties. In the main analysis, greater access to alcohol was associated with more atrial fibrillation and less myocardial infarction and congestive heart failure, although an increased risk of congestive heart failure was seen shortly after alcohol sales

were liberalised. The principal limitation of this study is that it is an observational study using data from an administrative dataset, prohibiting proof of causal relations.

What this study adds Laws limiting alcohol sales have measurable public health effects, and increased access to alcohol is associated with more alcohol misuse, alcoholic liver disease, and atrial fibrillation, but fewer myocardial infarctions.

Funding, competing interests, data sharing Research reported in this publication was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health. The funders had no role in the design, analysis, interpretation, or writing of this study, and there are no other relevant competing interests for this work. No additional data are available.

COMMENTARY Fresh insights from health policy analysis, but more certainty needed

The possible health benefits of alcohol continue to cause controversy, chiefly because of the lack of experimental evidence that would put this question to rest. One observational approach is the ecological design, which compares alcohol consumption at the population level with various indicators of national cardiovascular disease burden.⁷

Ecological analyses have both advantages and disadvantages. For example, the problem of ex-drinkers⁸ is largely mitigated, because the national level of alcohol consumption is unlikely to be meaningfully influenced by that subset of abstainers. However, ecological analyses cannot link individual exposure with outcome, and the possibility of confounding by group level factors remains a serious concern.

Postcode lottery

One popular extension of the ecological approach, time series analysis, profits from the dynamic nature of alcohol policies in local communities. In the United States, a remarkably heterogeneous patchwork of alcohol policies exist at the state and community level, dating to the end of the Prohibition era in 1933.

The Texas Liquor Control Act of 1935 established a statewide commission to

All interested parties should press for a trial quickly and wholeheartedly

regulate the state's industry, with gradual easing of restrictions on alcohol sales on a local basis. In 2003, legal reform made it easier for local municipalities to change the legal status of alcohol sales, immediately leading to some 50-90 local referendums yearly across the state. These drives led to a striking patchwork of policies tilted toward legalization; of the state's 254 counties, seven currently prohibit alcohol sales throughout, 53 uniformly allow alcohol sales, and 194 contain mixed policies.

Dukes and colleagues adopt an inception cohort approach to evaluate the subset of “wet” and “dry” counties in Texas. Individuals admitted to hospital were examined cross sectionally and longitudinally to evaluate the presence of cardiovascular and other diagnoses in relation to the county's alcohol sales status, both across counties and, in the seven counties that changed their status.

Their analysis is not entirely ecological. But while outcomes were assessed at the individual level, alcohol consumption was not and hence it is impossible to tie individual consumption to any outcome. Moreover, “dry” Texas counties all occupy the state's north-central, socially conservative region,

whereas “wet” counties disproportionately lie along the state's Mexican border, leaving substantial opportunity for confounding. The time series analyses, which minimize this type of confounding but are susceptible to concurrent secular trends, were necessarily much smaller with limited follow-up and 95% confidence intervals that overlapped with the cross county findings.

What next?

How should readers use these results? Firstly, since they align broadly with the results from prospective cohorts, these findings provide some reassurance that alcohol may truly reduce the risk of coronary heart disease. Secondly, the results confirm that novel approaches have potential but limited practical value in the absence of individual level data.¹² Lastly, both proponents and skeptics of the hypothesis that alcohol consumption reduces cardiovascular risk should recognize that nothing short of a randomized trial of alcohol consumption will provide the quality of data necessary to answer this question. All interested parties should press for such a trial quickly and wholeheartedly. It is time to move forward.

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Whole grains and public health

ORIGINAL RESEARCH Systematic review and dose-response meta-analysis of prospective studies

Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality

Aune D, Keum N, Giovannucci E, et al

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Find this at: <http://dx.doi.org/10.1136/bmj.i2716>

Study question Is there an association between consumption of whole grains and the risk of cardiovascular disease, total cancer, and all cause and cause specific mortality?

Methods PubMed and Embase were searched up to 3 April 2016. Summary relative risks and 95% confidence intervals were calculated with a random effects model. Forty five studies (64 publications) were included.

Study answer and limitations Higher intake of whole grains was associated with a reduced risk of coronary heart disease, cardiovascular



disease, total cancer, all cause mortality, and mortality from respiratory disease, diabetes, infectious diseases, and all non-cardiovascular, non-cancer causes of death. Reductions in risk were observed up to an intake of 210-225 g a day (seven to seven and a half servings per day) for most of the outcomes. Three servings (90 g) is equivalent to two slices of bread and one bowl of cereal or one and a half pieces of pitta bread made from whole grains. There was little evidence of an association with refined grains,

white rice, total rice, or total grains. Included studies were heterogeneous, specifically with regard to classification of food items as whole grain.

What this study adds This meta-analysis suggests that a high intake of whole grains is associated with a reduced risk of heart disease and cancer and mortality from respiratory disease, diabetes, infectious diseases, and other causes of death. These findings support dietary guidelines that recommend increased intake of whole grains to reduce the risk of premature mortality.

Funding, competing interests, data sharing The project was funded by Olav og Gerd Meidel Raagholt's Stiftelse for Medisinsk forskning, the liaison committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) and the Imperial College National Institute for Health Research (NIHR) Biomedical Research Centre (BRC). The authors declare no competing interests, and no additional data are available.

COMMENTARY Small increases in population intake could bring substantial benefits

Whole grains consist of the entire grain, and, unlike refined grains, they still contain bran and germ, which are rich in dietary fibre and micronutrients. A large body of evidence on whole grains in relation to health outcomes has accumulated over the past 10 or 15 years.

Aune and colleagues report a meta-analysis of 45 cohort studies, showing that a higher intake of whole grains is associated with a lower risk of cardiovascular disease, total cancer, and all cause and disease specific mortality.² Several mechanisms could explain the association between intake and a lower risk of major diseases and death. Whole grains have beneficial effects on glucose-insulin homeostasis, blood lipids, and gastrointestinal health.³ The new meta-analysis, however, has several weaknesses, including poor information on the assessment of whole grain intake in many of the included studies and few studies for some endpoints such as mortality from diabetes and infectious diseases.

Future studies should improve the assessment of whole grain intake by

Authorities should take great care not to promote whole grain foods with high sugar and salt content

reporting intakes in a similar way,⁴ using biomarkers to track compliance in randomised trials, and using validated assessment methods in observational studies.⁵ We still need more and better research on the biological mechanisms of health effects and the contribution to health of different grain types. For instance, whole grain oats and rye might be more beneficial than whole grain wheat in relation to cardiovascular disease.⁶

The Scandinavian way

National guidance in Scandinavian countries recommends a whole grain intake of 75 g/day per 10 MJ.⁷ UK guidance is much less specific, with advice to choose "whole grain, brown or high fibre varieties whenever you can."⁸ Currently, the whole grain intake in the UK is far below the intake recommended in Scandinavian countries (see figure on bmj.com). Lessons can be learnt from Denmark, where the intake of whole grains has almost doubled over the past 10 years (figure), thanks

to the combined efforts of the food and health authorities, non-governmental organisations (NGOs), and industry.

If and when other countries set specific recommendations for whole food intake, the authorities should take great care not to promote whole grain foods with high sugar and salt content. In a recent study, children and adolescents with the highest intake of whole grains also had the highest intake of sugar,¹³ possibly because their primary source of whole grains was from breakfast cereals with added sugar.

Aune and colleagues report reductions in risk associated with whole grain intakes of up to 7.5 servings a day.² Even in Denmark, a country with one of the highest whole grain intakes in the world, only about 6% of people currently consume seven or more servings.⁹ The largest health benefit might be achieved simply by shifting people from low or no intake of whole grains to an intake of just one serving. These small individual improvements could have a relatively large effect across whole populations through reductions in both morbidity and mortality.

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