research update

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

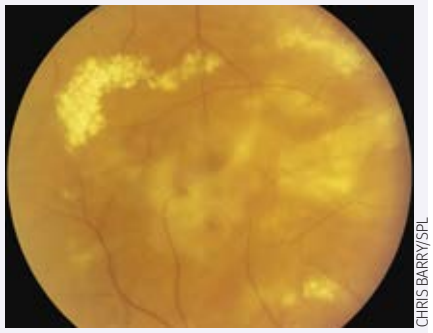
PCSK9 inhibitorzzzzz

The future of cardiology happened at 1300 GMT on Friday 17 March 2017. This was when the results of the FOURIER trial of evolocumab for the prevention of cardiovascular events were presented at the American College of Cardiology. The BBC immediately declared a massive breakthrough. All my American commentator friends sprang into action. In this new era, it would take, er, $2m (£1.6m) or more to avoid one event in a high risk population over two years. The effect on all-cause mortality would be, er, zero or worse. They had seen the future and it was, er, pants. Pants that cost $15 000 per person per year. As ever, I was awestruck by the mastery of the commentaries and data synthesis produced within hours by Harlan Krumholz, Larry Husten, Gary Schwitzer, James McCormack, and Vinay Prasad. By evening, the future had become the familiar past. We need longer trials. We need to look at how drugs are priced. We need to look beyond lipid lowering if we are to reduce cardiovascular disease further.

So, what were we actually looking at here? You will, I imagine, have heard of PCSK9 inhibitors and their remarkable ability to lower low density lipid cholesterol by binding to proprotein convertase subtilisin-kexin type 9 in the liver. Three antibodies were developed to achieve this: evolocumab, alirocumab, and bococizumab. The first two are fully human antibodies and are rarely treated as foreigners by the immune system. But bococizumab is a humanised rather than a human antibody: it contains 3% mouse material and—sadly for its manufacturers—this is sufficient to induce counter antibodies in most people. This is described in a report of the SPIRE trials, which were duly discontinued.

Evolocumab and alirocumab will continue to stumble on expensively. I imagine their main use will be to treat the more severe forms of hereditary hypercholesterolaemia. Expect more hyping of the "statin intolerance" concept too, as this will create another market sector. If you want more detail, look up the superb commentaries I mentioned. And if you want a new lipid lowering horse to put your money on, there's now inclisiran. It's a chemically synthesised small interfering RNA designed to target—you guessed it—PCSK9 messenger RNA. Could be transformational. Needs big phase 3 trials. Might end up costing a lot. Could transform preventive cardiology. Might bomb. You just never know.

- *N Engl J Med* 2017, doi: 10.1056/NEJMoa1615664
- *N Engl J Med* 2017, doi: 10.1056/NEJMoa1614062
- *N Engl J Med* 2017, doi:10.1056/NEJMoa1615758



CHRIS BARRY/SPL

Stem cells for age related macular degeneration

For people with age related macular degeneration hoping for a stem cell cure, this week's *New England Journal of Medicine* brings bad news. It comes in a case report that shows zero improvement after transplanting a sheet of retinal pigment epithelial cells differentiated from induced pluripotent stem cells in a patient with neovascular age related macular degeneration. The 41 authors of this paper took the utmost care to test the material, which they then implanted under the retina of one patient, after removing all neovascular membrane. At one year after surgery, the transplanted sheet remained intact, best corrected visual acuity had not improved or worsened, and cystoid macular oedema was present.

- *N Engl J Med* 2017, doi:10.1056/NEJMoa1609583

Our statin war correspondent writes

I know some people like to watch a good fight, but for me the statin wars between the *Lancet* and *The BMJ* seemed endlessly tiresome and pointless. Even now, the two central lessons don't seem to have emerged clearly: firstly, taking a statin is an individual choice, not a herd intervention; and, secondly, the effect is not a herd effect at all but accrues maximally to a few individuals while leaving most with no benefit at all. But in this overheated argument, the issue has been depicted as a moral crusade to make people take pills for their own good and tell them that any adverse effects they experience must be in their imagination. Many months after the *Lancet* published a review by Rory Collins, which was to settle the matter, the journal publishes responses from dissenters, including *The BMJ* authors whose article triggered the war and Fiona Godlee, who stood by them. She writes: "So despite Horton and Collins and colleagues wanting to shut down the discussion and award themselves the final word, the debate about statins in primary prevention is alive and kicking. It is a debate that needs to be resolved as thoughtfully, objectively, and openly as possible, and not by eminence based narrative reviews, however extensive, based on meta-analysis of data that only Collins, his fellow trialists, and industry sponsors have seen. This absence of independence and transparency is not unusual in medicine—indeed it is sadly still very much the norm." Bravissima! And praise to the *Lancet* for printing this. Can we look forward to calm and good sense from now on?

- *Lancet* 2017, doi:10.1016/S0140-6736(17)30721-3

Testing fails to predict preterm birth

Spontaneous labour is preceded by lengthening of the cervix and an increase in vaginal levels of fetal pronectin. So perhaps by measuring these things, one might be able to predict premature labour, ran the hypothesis. But a study of 9410 nulliparous women with singleton pregnancies showed that this combination predicted less than a quarter of preterm onset of labour, and is not fit for clinical use.

- *JAMA* 2017,doi:10.1001/jama.2017.1373

Alcohol and cardiovascular disease

ORIGINAL RESEARCH Population based cohort study using linked health records

Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases

Bell S, Daskalopoulou M, Rapsomaniki E, et al

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Find this at: http://dx.doi.org/10.1136/bmj.j909

Study question Is the association between alcohol consumption and cardiovascular disease consistent across a broad range of disease subtypes?

Methods A population based cohort study of 1 937 360 adults (51% women, aged ≥30, and free from cardiovascular disease at baseline) was constructed with linked electronic health records covering primary care, hospital admissions, and mortality for 1997-2010. Patients were categorised into non-drinkers and former, occasional, moderate (consumption within contemporaneous UK weekly/daily guidelines of 21/3 and 14/2 units for men and women, respectively), or heavy drinkers (exceeding guidelines) from clinically recorded alcohol consumption data.The authors then investigated whether, compared with moderate drinkers, other drinking categories were associated with a different risk of the initial lifetime presentation of 12 cardiaovascular diseases, including chronic stable angina, unstable angina, myocardial infarction, death from unheralded coronary heart disease, heart failure, sudden coronary death/cardiac arrest, transient ischaemic attack, ischaemic stroke, intracerebral and subarachnoid haemorrhage, peripheral arterial disease, and abdominal aortic aneurysm.

Study answer and limitations Heterogeneous associations exist between level of alcohol consumption and the initial presentation of different cardiovascular diseases. For example, non-drinking was associated with an increased risk of myocardial infarction (hazard ratio 1.32, 95% confidence interval 1.24 to 1.41), abdominal aortic aneurysm (1.32, 1.17 to 1.49), and ischaemic stroke (1.12, 1.01 to 1.24), but not cardiac arrest, or intracerebral or subarachnoid haemorrhage. Heavy drinking, however, conferred an increased risk of intracerebral haemorrhage (1.37, 1.16 to 1.62), cardiac arrest (1.50, 1.26 to 1.77), heart failure (1.22, 1.08 to 1.37), unheralded coronary death (1.21, 1.08 to 1.35), and peripheral arterial disease (1.35, 1.23 to 1.48), but a lower risk of myocardial infarction (0.88, 0.79 to 1.00) or stable angina (0.93, 0.86 to 1.00). This study did not account for differences in risk by drinking pattern, beverage type, or changes in drinking.

What this study adds In adults without cardiovascular disease, moderate drinking is associated with a lower risk of initial presentation of several, but not all, cardiovascular diseases. This has implications for patient counselling, public health communication, and clinical research.

Funding, competing interests, data sharing
See bmj.com or at www.caliberresearch.org.
Study registration ClinicalTrials.gov (NCT01864031).

COMMENTARY Big data put the link between moderate drinking and lower risk under the microscope

Over four decades ago, Klatsky and his colleagues published perhaps the first carefully conducted epidemiological investigation of alcohol consumption and risk of myocardial infarction,[1] a case-control study nested within the health records of the Kaiser Foundation Health Plan in California. Among non-smokers, the odds of myocardial infarction were about twice as high among non-drinkers as among drinkers, raising the possibility that alcohol consumption could lower risk of coronary heart disease.[1]

In subsequent analyses, Klatsky and colleagues went on to show that alcohol consumption has diverse associations with various forms of cardiovascular disease and its risk factors, including a roughly inverse association with coronary heart disease, a U shaped association with ischaemic stroke, and roughly direct associations with hypertension and haemorrhagic stroke.[2-5]

In a linked article, Bell and colleagues have now extended Klatsky's work in two directions.[6] The first leap forward is the

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The passive approach enables studies of massive sample size

estimation of a patient's actual alcohol consumption from clinical data, rather than from structured assessment tools like those applied in Kaiser-Permanente. Unfortunately, as the authors' examples illustrate, this requires creative extrapolation and will not be easy to export to settings outside the UK. The passive approach enables studies of massive sample size, overcoming random misclassification of alcohol consumption. Systematic error is more pernicious and contributed to both by intentional under-reporting by patients and by difficult classification choices forced by imperfect clinical information. Equally problematic, information on alcohol consumption was missing in 43% of the overall sample, with the potential for bias in any direction.

The second step forward is that Bell and colleagues examined a large and diverse set of endpoints that would be difficult to study with precision in smaller cohorts.[6]

This work fits into a burgeoning new generation of studies that adapt classic cohort designs to general practice settings by using data collected in electronic health records and large registries. These studies, which rely on advances in the information technology infrastructure embedded in healthcare settings, represent a promising convergence between medicine, public health, and research.

The new study does not offer a materially new view of the associations between alcohol consumed within recommended limits and risk of cardiovascular disease. The authors report lower rates of essentially every meaningful cardiovascular outcome, except haemorrhagic stroke, among moderate drinkers than among abstainers. Four decades of epidemiological studies have largely found the same. This work, however, sets the stage for ever larger and more sophisticated studies that will attempt to harness the flood of big data into a stream of useful, reliable, and unbiased findings that can inform public health, clinical care, and the direction of future research.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j1340

Dairy consumption, systolic blood pressure, and risk of hypertension

Ding M, Huang T, Bergholdt HKM, Nordestgaard BG, Ellervik C, Qi L, on behalf of the CHARGE Consortium

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Find this at: http://dx.doi.org/10.1136/bmj.j1000

Study question Are the observed inverse associations of dairy intake with systolic blood pressure and risk of hypertension causal?

Methods In this Mendelian randomisation study the authors used the single nucleotide polymorphism rs4988235 related to lactase persistence as an instrumental variable. Data were collected from 22 studies with 171 213 participants, and 10 published prospective cohort studies with 26 119 participants were additionally included in the observational analysis. The instrumental variable estimation was conducted using the ratio of coefficients approach. The authors further summarised eight published randomised clinical trials on association of dairy consumption with systolic blood pressure.

Study answer and limitations

Compared with the CC genotype (associated with complete lactase deficiency), the CT/TT genotype (associated with lactose persistence, and with certain lactase deficiency, respectively) of rs4988235 was associated with higher dairy consumption (0.23 (about 55 g/day), 95% confidence interval 0.17 to 0.29) serving/day; P<0.001) and was not associated with systolic blood pressure (0.31, 95% confidence interval −0.05 to 0.68 mm Hg; P=0.09) or risk of hypertension (odds ratio 1.01, 95% confidence interval 0.97 to 1.05; P=0.27). Using rs4988235 as the instrumental variable, genetically determined dairy consumption was not associated with systolic blood pressure (β=1.35, 95% confidence interval −0.28 to 2.97 mm Hg for each serving/day) or risk of hypertension (odds ratio 1.04, 0.88 to 1.24). Meta-analysis of the published clinical trials showed that higher dairy intake has no significant effect on change in systolic blood pressure for interventions over one month to 12 months. In observational analysis, each serving/day increase in dairy consumption was associated with −0.11 (95% confidence interval −0.20 to −0.02 mm Hg; P=0.02) lower systolic blood pressure but not risk of hypertension (odds ratio 0.98, 0.97 to 1.00; P=0.11). Dairy intake was self reported and measurement error might therefore exist.

What this study adds The weak inverse association between dairy intake and systolic blood pressure in observational studies was not supported by a comprehensive instrumental variable analysis and systematic review of existing randomised clinical trials. Using a Mendelian randomisation approach, the authors found that genetically determined dairy consumption was not associated with systolic blood pressure or risk of hypertension.

Funding, competing interests, data sharing LQ is a recipient of the American Heart Association scientist development award (07 30094N) for the Mendelian randomisation study. No additional data are available. The authors have no competing interests.

Stratified analysis on causal estimates of dairy consumption (serving/day) with systolic blood pressure (mm Hg) and risk of hypertension. Values are serving/day for dairy intake, mm Hg for SBP, and odds ratio for hypertension unless stated otherwise

		Instrumental variable		SBP		Hypertension	
Variables	No of studies	SNP rs4988235 with dairy intake	I^2 (%) (P value)	SNP rs4988235 with SBP	Dairy intake with SBP, instrumental variable estimation	SNP rs4988235 with risk of hypertension	Dairy intake with risk of hypertension, instrumental variable estimation
CC genotype frequency *:							
≤12%	14	0.27 (0.22 to 0.31)	34.4 (0.10)	0.27 (−0.14 to 0.67)	1.00 (−0.51 to 2.51)	0.99 (0.93 to 1.04)	0.96 (0.78 to 1.19)
>12%	9	0.21 (0.08 to 0.34)	87.4 (<0.001)	0.30 (−0.55 to 1.15)	1.43 (−2.71 to 5.57)	1.03 (0.95 to 1.11)	1.15 (0.79 to 1.68)
Region or country†:							
Northern Europe	10	0.28 (0.23 to 0.33)	10.5 (0.31)	0.37 (−0.13 to 0.87)	1.32 (−0.48 to 3.12)	0.96 (0.89 to 1.03)	0.86 (0.67 to 1.12)
Southern Europe	3	−0.01 (−0.14 to 0.11)	5.2 (0.08)	NA	NA	NA	NA
US	10	0.25 (0.16 to 0.34)	51.5 (<0.001)	0.01 (−0.59 to 0.62)	0.04 (−2.38 to 2.46)	1.01 (0.96 to 1.07)	1.04 (0.84 to 1.29)

SNP=single nucleotide polymorphism; NA=not available.
*One study excluded owing to extremely low frequency of CC (2%).
†Study conducted in Australia was not included.

ORIGINAL RESEARCH Cohort study

Risk of serious infections associated with use of immunosuppressive agents in pregnant women with autoimmune inflammatory conditions

Desai RJ, Bateman BT, Huybrechts KF, et al

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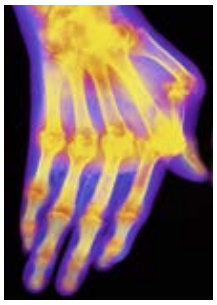
Find this at: http://dx.doi.org/10.1136/bmj.j895

Study question Does the risk of serious infections differ in pregnant women with autoimmune inflammatory conditions treated with different classes of immunosuppressive drugs?

Methods An observational cohort study was conducted among 4961 pregnant women with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, or inflammatory bowel disease identified from US public (Medicaid) or commercial health insurance databases. Exposure was classified into steroid, non-biological, or tumour necrosis factor α (TNF) inhibitors on first filled prescription during pregnancy. The outcome of serious infections was defined by hospital admission for bacterial or opportunistic infections and was assessed throughout pregnancy. Hazard ratios for comparative infection risk were derived using Cox proportional hazard regression models after adjustment for confounding with propensity score fine stratification. A logistic regression model was used to conduct a dose-response analysis among women filling at least one steroid prescription.



Study answer and limitations 71 out of 4961 pregnant women (0.2%) treated with immunosuppressives experienced serious infections. This risk of serious infections was similar (crude incidence rates per 100 person years: 3.4 (95% confidence interval 2.5 to 4.7) among 2598 steroid users, 2.3 (1.5 to 3.5) among 1587 non-biological users, and 1.5 (0.7 to 3.0) among 776 TNF inhibitors users. However, in the dose-response analysis, high dose steroid use was found to be an independent risk factor of serious infections in pregnancy (coefficient for each unit increase in average prednisone equivalent mg daily dose=0.019, P=0.02). As measures of disease activity were not explicitly recorded in the data sources, the study may be subject to residual confounding.

What this study adds In pregnant women with systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease, use of steroids, non-biologicals, and TNF inhibitors is associated with similar risk of serious infections. Steroid dose is an independent risk factor for serious infections in pregnancy. Pregnant women using high dose steroids should be monitored closely for development of serious infections.

Funding, competing interests, data sharing This study was not funded by any external institutions. Patient level data are not available to protect patient confidentiality in accordance with the authors' data use agreement.

RESEARCH METHODS AND REPORTING Interaction of patient characteristics

Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach?

Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF

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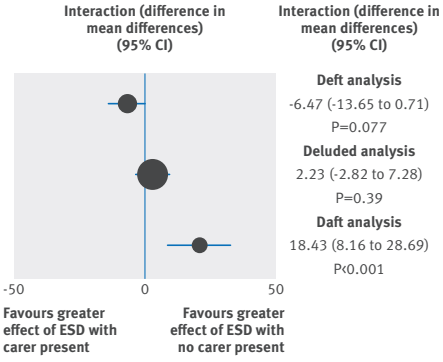
Identifying who will benefit most from treatments or other interventions underpins personalised medicine. Meta-analysis provides greater power than a single trial for exploring whether participant characteristics, such as age or severity of disease, determine an individual's response to treatment. However, assessing such interactions in meta-analysis raises additional complications, often overlooked, that affect neither single trial interaction analyses nor meta-analyses of main effects. The authors describe three main analytical approaches, derived from two independent quantities referred to in recent literature on individual participant data as "across-trial" and "within-trial" interactions. They refer to estimation of the across-trial interaction alone as daft (meaning absurd or preposterous), to a conflation of both as deluded (misleading or deceiving), and to estimation of the within-trial interaction alone as deft (demonstrating skill or cleverness). As their "monikers" suggest, daft and (to a lesser extent) deluded approaches are at risk of bias, whereas deft approaches are not.

To highlight the issues, the authors use a published meta-analysis of individual participant data comparing early supported hospital discharge with conventional arrangements after acute stroke. In this review, early supported hospital discharge reduced the mean duration of initial hospital stay; the authors investigated whether there was an interaction between this effect and the presence of a carer. As the figure shows, a deft approach suggests that presence of a carer is associated with a further reduction in the duration of hospital stay with early supported hospital discharge compared with standard care, whereas a daft approach would indicate the opposite. A deluded approach, meanwhile, would suggest negligible interaction.

The authors' systematic review of methods for analysing and presenting participant level interactions in recently published meta-analyses of individual participant data shows that, most commonly, deluded approaches are used or the methods are inadequately described. Where the reported data allowed for reanalyse, the authors found that deluded results are more likely to be statistically significant at the 5% level than equivalent deft results. Hence, the choice of approach might have an effect on the conclusions of systematic reviews and thus affect clinical decision making. The authors advocate that deft analysis and presentation become standard practice.



How the effect of an early supported hospital discharge (ESD) strategy on duration of hospital stay (days) may vary by whether a carer is present, according to deft, deluded, and daft analyses. Sizing of circles is in proportion to the inverse of the variance of the estimates