research update

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

Heavy water hype

Not long ago, I read Diana Preston's account of the history of nuclear physics from *Curie to Hiroshima, Before The Fall-Out* (2005). As war loomed and the military potential of nuclear fission became clear, all the combatants suddenly became interested in heavy water, or deuterium oxide. Mighty acts of derring-do punctuated the years from 1939-45: commando raids in Norway, secret convoys from Paris to North Africa, a final submarine load travelling thousands of miles from defeated Japan. All this centred on preserving, capturing, or destroying the heavy isotope of hydrogen, because it moderates neutrons sufficiently to allow controlled nuclear fission.

Nowadays, anyone can buy heavy water online at $1000 a litre. And pharma companies are starting to use it as a fashion accessory to replace good old hydrogen, which comes from water costing one cent a litre. The logic is that it "attenuates CYP2D6 metabolism and increases active metabolite half-lives and may therefore lead to stable systemic exposure while preserving key pharmacological activity."

Yeah, right, so you can take your pill twice a day instead of three times? That's about the sum of it, in a 12 week pilot study of deuterium-substituted tetrabenazine to reduce chorea in people with Huntington's disease. But no, hang on, we don't even know that, because the deutetrabenazine was compared with placebo, not ordinary tetrabenazine. The editorial on the trial (doi:10.1001/jama.2016.801) states, "Assuming deutetrabenazine is not priced to be significantly more expensive than tetrabenazine, the favorable profile of deutetrabenazine would offer an additional option for patients and clinicians." Great sense of humour.

JAMA 2016, doi:10.1001/jama.2016.8655

Wealth and diabetes outcomes

Let's go to a wealthy developed country with universal health coverage, low social inequality, and low levels of obesity. Is this the UK? No. Is this America? It certainly is not. It's Sweden, and even here socioeconomic status is a powerful predictor of all cause and cardiovascular mortality in people with type 2 diabetes. Strangely, the risk was much lower for non-Western immigrants with diabetes. The best way to improve your diabetes outcomes is to earn more money than other people. We need a new metric for this, with units called Marmots.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.2940

DON RYAN/AP/PA

Charlene Andrews, left, who is terminally ill with cancer, holds hands with Julie McMurchie, whose mother used Oregon's assisted suicide law to end her life, after it was announced that the U.S. Supreme Court upheld the state's assisted suicide law.

Doctors helping dying patients to die

"Attitudes and Practices of Euthanasia and Physician-Assisted Suicide in the United States, Canada, and Europe" is a really useful summary of the evidence, which concludes that "Euthanasia and physician-assisted suicide are increasingly being legalized, remain relatively rare, and primarily involve patients with cancer. Existing data do not indicate widespread abuse of these practices." The wonder is that its first author is Zeke Emanuel, who in the past has expressed his opposition to doctors helping dying patients to die at a time and place of their choosing. Anyway, here again is the bottom-line message of this open access review: "Between 0.3% to 4.6% of all deaths are reported as euthanasia or physician-assisted suicide in jurisdictions where they are legal. The frequency of these deaths increased after legalization. More than 70% of cases involved patients with cancer. Typical patients are older, white, and well-educated. Pain is mostly not reported as the primary motivation. In no jurisdiction was there evidence that vulnerable patients have been receiving euthanasia or physician-assisted suicide at rates higher than those in the general population."

JAMA 2016, doi:10.1001/jama.2016.8499

The theology of eating fat

Priests have often dictated matters of diet to their followers, and the priesthood of public health is certainly no exception. Two articles on the *JAMA Internal Medicine* website discuss the current theology of fat intake. The first is based on two familiar cohorts of US health professionals: the 83 349 women from the Nurses' Health Study, and the 42 884 men from the Health Professionals Follow-up Study. These nurses and doctors kept food diaries from time to time, and these entries can be used to calculate fifths of intake for various kinds of fat. Comparing the bottom fifth with the top fifth has become something of a fashion in the literature, so here are the hazard ratios for overall mortality: 1.08 for saturated fatty acid, 0.81 for polyunsaturated fatty acid, 0.89 for monounsaturated fatty acid, and 1.13 for trans fatty acid. Add a bit of leeway for confounding and this comparison of extremes doesn't provide the priesthood with very much to preach about, in my opinion.

The second study looks at the fatty acids that are regarded with greatest favour by most priests and their followers. You can actually measure intake in free-living populations by using biomarkers of seafood derived eicosapentaenoic acid (20:5ω-3), docosapentaenoic acid (DPA; 22:5ω-3), and docosahexaenoic acid (DHA; 22:6ω-3), and plant derived α linolenic acid (ALA; 18:3ω-3). By pooling 19 cohort studies, the authors were able to detect a weak (typically <10%) reduction in fatal coronary events in those with the highest level of ω-3 biomarkers ALA, DPA, and DHA. But when you next think of dinner, I would leave these papers behind.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.2417; doi:10.1001/jamainternmed.2016.2925

Drug safety in patients with type 2 diabetes

ORIGINAL RESEARCH Cohort study in primary care

Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality

Hippisley-Cox J, Coupland C

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Study question What are the risks of cardiovascular disease, heart failure, and all cause mortality associated with prescribed diabetes drugs, alone and in combination, in people with type 2 diabetes?

Methods In an open cohort study, 469 688 people with type 2 diabetes aged 25-84 years were followed up between 2007 and 2015, using the QResearch primary care database linked to hospital and mortality records. The authors assessed the risk of cardiovascular disease, heart failure, and all cause mortality in patients prescribed different diabetes drugs (thiazolidinediones (glitazones), gliptins, metformin, sulphonylureas, insulin, other) alone and in combination, adjusting for confounding variables.

Study answer and limitations Compared with no current treatment, there were no significant associations between monotherapy with gliptins and risk of any of the three outcomes. Dual treatment with gliptins and metformin was associated with a decreased risk of all three outcomes (reductions of 38% for heart failure, 33% for cardiovascular disease, and 48% for all cause mortality). Triple treatment with metformin, sulphonylureas, and gliptins was associated with a decreased risk of all three outcomes (reductions of 40% for heart failure, 30% for cardiovascular disease, and 51% for all cause mortality). Compared with no current treatment, monotherapy with glitazones was associated with a 50% decreased risk of heart failure; dual treatment with glitazones and metformin was associated with a decreased risk of all three outcomes (reductions of 50% for heart failure, 54% for cardiovascular disease, and 45% for all cause mortality); dual treatment with glitazones and sulphonylureas was associated with risk reductions of 35% for heart failure and 25% for cardiovascular disease; triple treatment with metformin, sulphonylureas, and glitazones was associated with decreased risks of all three outcomes (46% for heart failure; 41% for cardiovascular disease, and 56% for all cause mortality).

Adjusted hazard ratio (95% confidence intervals) for each outcome by use of glitazones and gliptins alone and in combinations

Outcomes by treatment	Adjusted hazard ratio (95% CI)		
	Heart failure	Cardiovascular disease	All cause mortality
No current treatment (reference)	1.00	1.00	1.00
Monotherapy:			
Glitazones	0.50 (0.26 to 0.97*)	0.79 (0.53 to 1.18)†	0.89 (0.67 to 1.18)†
Gliptins	0.87 (0.58 to 1.31)†	1.14 (0.85 to 1.54)†	1.20 (1.00 to 1.44)†
Dual treatment:			
Metformin and glitazones	0.50 (0.40 to 0.63)*	0.46 (0.39 to 0.54)*	0.55 (0.47 to 0.64)*
Metformin and gliptins	0.62 (0.52 to 0.75)*	0.67 (0.59 to 0.75)*	0.52 (0.46 to 0.59)*
Sulphonylureas and glitazones	0.65 (0.47 to 0.89)*	0.75 (0.58 to 0.98)*	0.96 (0.80 to 1.16)†
Sulphonylureas and gliptins	0.88 (0.66 to 1.17)†	0.97 (0.76 to 1.22)†	0.92 (0.79 to 1.08)†
Triple treatment:			
Metformin, sulphonylureas, and glitazones	0.54 (0.45 to 0.64)*	0.59 (0.53 to 0.66)*	0.44 (0.38 to 0.50)*
Metformin, sulphonylureas, and gliptins	0.60 (0.52 to 0.70)*	0.70 (0.63 to 0.78)*	0.49 (0.44 to 0.55)*

*Significantly decreased.
†Non-significant.
Hazard ratios adjusted for: sex; age; calendar year; duration since diagnosis of diabetes; ethnicity; Townsend deprivation score; smoking status; use of other diabetes drugs, other drugs, previous complications (blindness, hyperglycaemia, hypoglycaemia, amputation, severe kidney failure); comorbidities (hypertension; cardiovascular disease; atrial fibrillation; chronic renal disease; rheumatoid arthritis; valvular heart disease; peripheral vascular disease), clinical values (body mass index; systolic blood pressure; haemoglobin A1c; serum creatinine level; cholesterol to high density lipoprotein cholesterol ratio).

Although these results do not account for levels of adherence or dosage information and are subject to residual confounding by indication, they might have implications for prescribing of hypoglycaemic drugs.

What this study adds Clinically important differences in risk of cardiovascular disease, heart failure, and all cause mortality were found between different diabetes drugs alone and in combination.

Funding, competing interests, data sharing
No external funding. See www.qresearch.org for information on data sharing. JH-C is professor of clinical epidemiology at the University of Nottingham and codirector of QResearch, a not-for-profit organisation, which is a joint partnership between the University of Nottingham and Egton Medical Information Systems (leading commercial supplier of IT for 60% of general practices in the UK). JH-C is also a paid director of ClinRisk, which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. CC is professor of Medical Statistics in Primary Care at the University of Nottingham and a paid consultant statistician for ClinRisk.

ORIGINAL RESEARCH Population based cohort study

Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group

van Dalem J, Brouwers MCGJ, Stehouwer CDA, et al

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Study question What is the association between use of sulphonylureas and risk of hypoglycaemia in relation to renal function and different sulphonylureas in people with type 2 diabetes?

Methods The authors conducted a population based cohort study using data routinely collected from general practices in England (2004-12). New users (n=120 803) with at least one prescription for a non-insulin antidiabetic agent and aged 18 or more years were included. Participants were followed from the first prescription until the end of data collection, a record for hypoglycaemia, or a blood glucose level of less than 3.0 mmol/L. The associations between renal impairment and different sulphonylureas (with active or inactive metabolites) and the risk of hypoglycaemia were determined using Cox proportional hazard models.

Study answer and limitations The risk of hypoglycaemia was significantly increased in sulphonylurea users with severe renal impairment compared with metformin users (adjusted hazard ratio 4.96, 95% confidence interval 3.76 to 6.55). An increased risk of hypoglycaemic events was observed with use of all sulphonylureas (including gliclazide). Limitations of this study include the inability to distinguish severe from mild hypoglycaemic events and to identify patients with minor hypoglycaemic episodes that were corrected at home.

What this study adds The risk of a hypoglycaemic event is significantly increased in sulphonylurea users with severe renal impairment receiving general care, but did not differ between users of sulphonylureas with active metabolites and inactive metabolites. The study did not confirm current guidelines suggesting that gliclazide is superior to other sulphonylureas in reducing the risk of hypoglycaemia.

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Risk of hypoglycaemia in sulphonylurea users compared with metformin users; sulphonylurea users stratified by renal function and active versus inactive metabolites

Variables	Fully adjusted hazard ratio (95% CI)
Current metformin use	Reference
Current sulphonylurea use	2.50 (2.23 to 2.82)
Renal function <30 mL/min/1.73 m^2:	4.96 (3.76 to 6.55)
Sulphonylureas with active metabolites	1.48 (0.21 to 10.52)
Sulphonylureas with inactive metabolites	5.20 (3.94 to 6.88)
Renal function 30-59 mL/min/1.73 m^2:	2.69 (2.25 to 3.20)
Sulphonylureas with active metabolites	3.48 (2.15 to 5.64)
Sulphonylureas with inactive metabolites	2.60 (2.16 to 3.13)
Renal function ≥60 mL/min/1.73 m^2:	2.04 (1.73 to 2.41)
Sulphonylureas with active metabolites	2.46 (1.56 to 3.88)
Sulphonylureas with inactive metabolites	2.01 (1.69 to 2.39)
Unknown	2.63 (2.06 to 3.36)

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ORIGINAL RESEARCH National population based study with propensity matched comparative analysis

Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people

Paul S, Lee PC, Mao J, Isaacs AJ, Sedrakyan A

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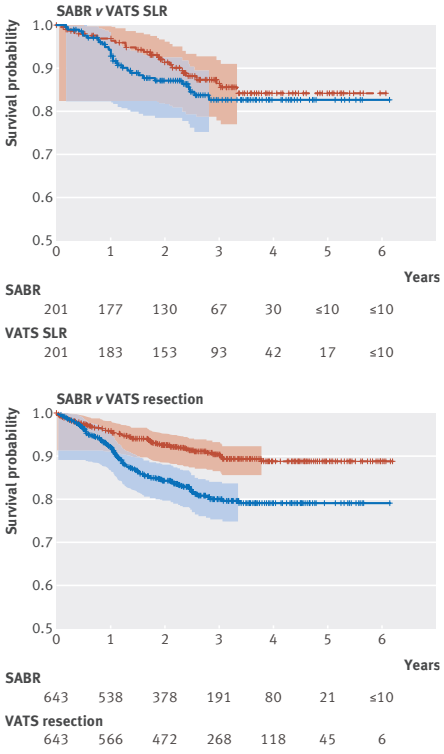
Study question Is survival after stereotactic ablative body radiotherapy (SABR) comparable with minimally invasive surgical resection in older patients with lung cancer?

Methods National Population based study using Surveillance, Epidemiology, and End Results (SEER) registry linked with the Medicare database (SEER-Medicare) in the United States. Patients with early stage lung cancer operated on from 1 October 2007 to 31 June 2012 were included and followed up through to 31 December 2013. SABR and thoracoscopic lung resection groups were propensity matched and compared regarding cancer specific survival.

Study answer and limitations Many patients, particularly those with large tumours, undergoing thoracoscopic surgical resection might have improved cancer specific survival compared with patients undergoing SABR. The average age of patients was 76. Follow-up of the entire cohort ranged from 0 to 6.25 years, with an average of three years. Estimated cancer specific survivals after SABR and thoracoscopic approach were 82.6% and 86.4%, respectively, for tumours sized ≤2 cm (non-significant difference) and 80.0% and 90.3%, respectively, for tumours sized ≤5 cm (significant difference). The study was limited by selection biases that cannot be completely accounted for with SEER Medicare data. This limitation, however, is similar to those of most studies in healthcare that look at non-surgical technologies compared with surgery using observational data. Most of the included patients were aged over 65 and underwent surgery in 2007-12. The results might not be generalisable to younger patients, who are in the minority among patients who undergo surgery for lung cancer in the US and western Europe.



Cancer specific survival for SABR v VATS SLR (video assisted thoracoscopic sublobar lung resection) for tumours sized ≤2 cm and SABR v VATS (video assisted thoracoscopic) resection for tumours sized ≤5 cm in propensity matched cohorts. Points shown with Hall-Wellner confidence bands

What this study adds Patients undergoing thoracoscopic resections might have improved cancer specific survival compared with those undergoing SABR for early stage non-small cell lung cancer, especially for those patients with larger tumours. This study argues that an adequately powered trial is needed to provide evidence for decision makers and clarity to the options for patients with early stage lung cancer.

Funding, competing interests, data sharing
The study received internal funding and leveraging MDEpiNet Science and Infrastructure Centre. The authors declared no competing interests. Data are available from SEER-Medicare.

ORIGINAL RESEARCH Nationwide cohort and nested case-control study

Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate

Abrahamsen B, Eiken P, Prieto-Alhambra D, Eastell R

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Study question Is there an association between long term (≥10 years) use of alendronate in people with osteoporosis and the risk of hip (expected benefit) and subtrochanteric/shaft femur (undesired effect) fracture(s)?

Methods Population based nationwide cohort study of all new users of alendronate in Denmark (1996-2007) aged 50-94 at the time they started treatment (n=61 990). Two nested case-control studies: hip (n=6784) and subtrochanteric/shaft (n=1428) fractures, matched to controls (obtained from the same cohort) by sex, age, and year of start of treatment. Incidence rates for both hip and subtrochanteric/shaft fracture over time were reported for the full cohort. Odds ratios from both case-control analyses were presented after adjustment for confounding.

Study answer and limitations Fracture rates were higher for hip (incidence rate 16.2/1000 person years, 95% confidence interval 15.8 to 16.6) than subtrochanteric/shaft (3.4/1000 person years, 3.2 to 3.6). As expected from randomised controlled trials and systematic reviews, risk of hip fracture was significantly lower (by almost 30%) among both compliant and long term users of alendronate. Reassuringly, there was no significant association between high compliance, current (compared with past), or long term (≥10 years) use of alendronate, and the risk of subtrochanteric/shaft fractures in our data.

What this study adds Long term adherent use of alendronate in excess of 10 dose years was associated with an adjusted 30% lower risk of hip fracture and no increase in the risk of fractures of the subtrochanteric femur or femoral shaft. These findings support a good benefit:risk profile of treatment with alendronate in terms of bone health for over 10 years of continuous use.

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