

research update

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

Behave yourself with antibiotics

Antibiotic prescribing for respiratory tract infections in primary care: I've covered this so many times I'm losing the will to live. This study comes from the United States, where antibiotic prescribing for respiratory tract infections is higher than in the United Kingdom and the proportion of resistant organisms is much higher. A cluster randomised trial included 47 practices on both coasts of the United States and used three behavioural interventions of proved value: firstly, suggested alternatives presented electronic order sets suggesting non-antibiotic treatments; secondly, accountable justification prompted clinicians to enter free text justifications for prescribing antibiotics into patients' electronic health records; and, finally, peer comparison sent emails to clinicians who compared their antibiotic prescribing rates with those of "top performers" (those with the lowest inappropriate prescribing rates). All of them worked.

● JAMA 2016, doi: 10.1001/jama.2016.0275



Biodegradable fashions

Models have swanked down the catwalks of Paris and Milan in dresses made out of biodegradables, and in outfits made of cobalt and chrome alloy (probably). It is the same in the fashion world of cardiology. Normal people can get bored with this quite quickly. In this meta-analysis, bioresorbable vascular scaffolds did not lead to different rates of composite patient oriented and device oriented adverse events at one year follow-up compared with cobalt-chromium everolimus eluting stents.

● Lancet 2016, doi: [http://dx.doi.org/10.1016/S0140-6736\(15\)01039-9](http://dx.doi.org/10.1016/S0140-6736(15)01039-9)

Stroke disappointments

I haven't commented quite so often on specialised rehabilitation programmes for stroke, but I've read Cochrane reviews of

several, and they generally report little or no difference from usual care. Sadly, that's the outcome of a trial comparing the efficacy of a structured, task oriented motor training programme with usual occupational therapy during stroke rehabilitation for upper limb motor deficits.

● JAMA 2016, doi: 10.1001/jama.2016.0276

Fingolimod failure

For nearly two decades I've been commenting on trials of drugs for relapsing-remitting multiple sclerosis, although I'm left with no idea about a clear winner. The Moving Finger writes; and, having writ, moves on. I know I have written about fingolimod, because I remember calling it thingummybob. Beyond that, I remember nothing. It has some effect on relapse-onset multiple sclerosis, attributed to its effect on the sphingosine 1-phosphate receptor. But primary progressive multiple sclerosis is a different and altogether nastier condition, and this trial shows that fingolimod makes no difference to progression. Nor does anything yet discovered.

● Lancet 2016, doi: [http://dx.doi.org/10.1016/S0140-6736\(15\)01314-8](http://dx.doi.org/10.1016/S0140-6736(15)01314-8)



The decline of Alzheimer's

Let's start off on a happy note and think about dementia. On Saturday morning the BBC News website ran a story about a new molecule tested on worms in Cambridge that could block the deterioration of brain cells. So there is hope—for the worms of Cambridge, if not for BBC journalists. And there is indeed hope for us all, according to a survey of 5205 adults aged 60 years or older followed up for three decades or more. "Among participants in the Framingham Heart Study, the incidence of dementia has



declined over the course of three decades. The factors contributing to this decline have not been completely identified." So the coming epidemic of dementia may not really happen at all, on the scale forecast by single issue lobbyists, regardless of any British breakthroughs that may happen in the coming days, weeks, or worms.

● N Engl J Med 2016, doi: 10.1056/NEJMoa1504327

Nearly there with polio

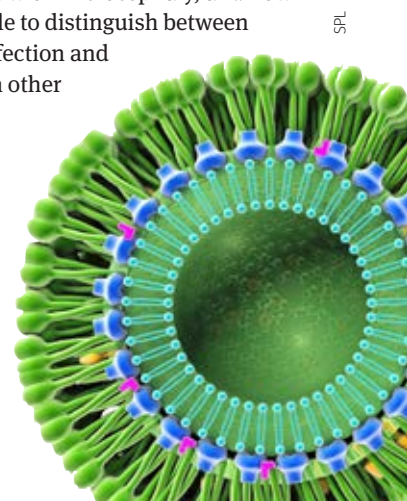
In 2015 there were just 72 reported cases of wild poliomyelitis in the world, all of them in Pakistan and Afghanistan. Type 2 wild poliovirus, one of three strains responsible for centuries of human paralysis and disfigurement, has been eradicated. It is almost time to rejoice, but this free Perspective piece describes the difficult endgame that must be got right before we can break open the champagne. Oral vaccines containing attenuated live type 2 virus need to be withdrawn because they are causing harm, whereas better vaccines against types 1 and 3 viruses need to be deployed universally until these strains also die out.

● N Engl J Med 2016, doi: 10.1056/NEJMp1514467

Nowhere near there with Zika

The virus of the moment is of course Zika. You will have read a lot about it—perhaps more than I have. But you may still want to read the short open access editorial on the *New England Journal of Medicine* website, which lists the problems we have yet to overcome in understanding how the virus may be linked with microcephaly, and how we may be able to distinguish between active Zika infection and infection with other flaviviruses.

● N Engl J Med 2016, doi: 10.1056/NEJMe1601862



Safety of incretin based drug treatments for type 2 diabetes

ORIGINAL RESEARCH International multicentre cohort study

Incretin based drugs and the risk of pancreatic cancer

Azoulay L, Filion KB, Platt RW, et al

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Find this at: <http://dx.doi.org/10.1136/bmj.i581>

Study question Are incretin based drugs associated with an increased risk of pancreatic cancer compared with sulfonylureas?



DR MARAZZI/ISPL

Methods This international, multicentre study combined the health records from six participating sites in Canada, the United States, and the United Kingdom. The cohorts consisted of patients initiating antidiabetic drugs between 1 January 2007 and 30 June 2013, with follow-up until 30 June 2014. Nested case-control analyses were done, where incident cases of pancreatic cancer were matched with up to 20 controls on sex, age, cohort entry date, duration of treated diabetes, and duration of follow-up. Hazard ratios and 95% confidence intervals for incident pancreatic cancer were estimated, comparing use of incretin based drugs with use of sulfonylureas.

Study answer and limitations In a cohort of 972 384 people with diabetes, the use of

incretin based drugs was not associated with an increased risk of incident pancreatic cancer (adjusted hazard ratio 1.02, 95% confidence interval 0.84 to 1.23). Given the observational nature of this study, residual confounding remains a possibility.

What this study adds This study provides some reassurance that incretin based drugs are not associated with an increased risk of pancreatic cancer in people with type 2 diabetes.

Funding, competing interests, data sharing The Canadian Network for Observational Drug Effect Studies, a collaborating centre of the Drug Safety and Effectiveness Network, is funded by the Canadian Institutes of Health Research (grant No DSE-111845). The sponsor had no influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; as well as preparation, review, or approval of the manuscript.

ORIGINAL RESEARCH Systematic review and meta-analysis of randomised and observational studies

Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes

Incretin Safety Study Investigators

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Find this at: <http://dx.doi.org/10.1136/bmj.i610>

Study question Do dipeptidyl peptidase-4 (DPP-4) inhibitors increase the risk of heart failure or hospital admission for heart failure in people with type 2 diabetes?

Methods Medline, Embase, CENTRAL, and ClinicalTrials.gov were searched for randomised controlled trials (RCTs) and observational studies that compared DPP-4 inhibitors with placebo, lifestyle modification, or active antidiabetic drugs in adults with type 2 diabetes, and reported heart failure or hospital admission for heart failure. RCTs and observational studies were pooled separately, and quality of evidence assessed by the GRADE approach.

Study answer and limitations Low quality evidence suggested no increase in the risk of heart failure with DPP-4 inhibitors versus control (38 trials, 42/15 701 v 33/12 591; odds ratio 0.97 (95% confidence interval 0.61 to 1.56); risk difference 2 fewer (19 fewer to 28 more) events per 1000 patients with type 2 diabetes over five years). Moderate quality evidence from RCTs showed an increased risk

of hospital admission for heart failure with DPP-4 inhibitors versus control (five trials, 622/18 554 v 552/18 474; 1.13 (1.00 to 1.26); 8 more (0 more to 16 more) events per 1000 patients with type 2 diabetes over five years). Effect estimates for observational studies were generally consistent with RCTs findings, but evidence was of low quality. Findings were limited owing to relatively short follow-up, potentially variable specification of outcomes, and small number of events from RCTs; and potential risk of bias in observational studies.

What this study adds DPP-4 inhibitors may increase the risk of hospital admission for heart failure, particularly in those with existing cardiovascular diseases or multiple risk factors for vascular diseases, compared with no use.

Funding, competing interests, data sharing The National Natural Science Foundation of China, "Thousand Youth Talents Plan" of China, and Young Investigator Award of Sichuan University funded the study; no competing interests; no additional data available.

Risk of heart failure or hospital admission for heart failure among people with type 2 diabetes receiving dipeptidyl peptidase-4 (DPP-4) inhibitors				
Comparison	No of studies	DPP-4 inhibitors (events/patients)	Control (events/patients)	Effect estimate (95%CI)
Heart failure				
Randomised controlled trials:				
DPP-4 inhibitors v control	38	42/15 701	33/12 591	Pooled odds ratio 0.97 (0.61 to 1.56)
Observational studies:				
DPP-4 inhibitors v sulfonylurea	1	Not reported	Not reported	Adjusted hazard ratio 1.10 (1.04 to 1.17)
Sitagliptin use v no use	1	—	—	Adjusted odds ratio 0.75 (0.38 to 1.46)
Hospital admission for heart failure				
Randomised controlled trials:				
DPP-4 inhibitors v placebo	5	622/18 554	522/18 474	Pooled odds ratio 1.13 (1.00 to 1.26)
Observational studies:				
DPP-4 inhibitors v active control	6	—	—	Pooled adjusted odds ratio 0.85 (0.74 to 0.97)
Sitagliptin use v no use	2	—	—	Pooled adjusted odds ratio 1.41 (0.95 to 2.09)

COMMENTARY Latest data are reassuring about pancreatic cancer, less so about heart failure

The incretin based drugs (dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists) are one of several options for glucose lowering in people with type 2 diabetes who are already taking (or unable to take) metformin.¹ As with other antidiabetic drugs, the long term safety of these drugs remains unclear. Studies by Azoulay and colleagues (doi:10.1136/bmj.i581) and Li and colleagues (doi:10.1136/bmj.i610) in this issue provide updated evidence about incretin based treatments and the risk of pancreatic cancer and heart failure.^{2,3}

Pancreatic cancer

In 2013 the Food and Drug Administration and European Medicines Agency undertook investigations of the possible link between incretin based treatments and pancreatic cancer owing to post-marketing reports suggesting higher rates of pancreatic cancer with these drugs,⁴ and a study suggesting abnormal pancreatic histology among users of incretin drugs versus non-users.⁵ These investigations revealed no clear causal role for incretin based drugs in the development of pancreatic cancer, and resulted in a call for more evidence to address this concern.⁴

Azoulay and colleagues assembled administrative and health record data from six sites in North America and the United Kingdom contributing to the Canadian Network for Observational Drug Effect Studies. Over a median of 1.3 to 2.8 years of follow-up, 1221 of 972 384 incident users of an antidiabetic drug were admitted to hospital with pancreatic cancer (incidence rate 0.60 per 1000 person years). Using a nested case-control design matching up to 20 controls (n=22 298) to each case (n=1221), the investigators reported no increase in risk of pancreatic cancer for users of glucagon-like peptide-1 receptor agonists and DPP-4 inhibitors compared with sulfonylurea users (adjusted hazard ratio 1.02, 95% confidence interval 0.84 to 1.23). The major issues limiting conclusions from this well planned study were the short duration of follow-up and potential interactions between drugs, especially since metformin has been associated with a decreased risk of cancer.⁶



Shared decision making that incorporates patient preferences continues to be especially critical as the options for antidiabetic drug treatments expand further

Heart failure

Although early preclinical data suggested that incretin based treatments might be beneficial for heart failure,⁷ results from two large placebo controlled trials (SAVOR-TIMI and a retrospective subgroup analysis from EXAMINE)^{8,9} suggested that DPP-4 inhibitors may increase the risk of hospital admission for heart failure. The FDA issued a safety warning in 2014¹⁰ calling for more evidence, and in 2015 the FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended changes to the saxagliptin and alogliptin labels to indicate the potential risk of heart failure with these agents.¹¹

Li and colleagues conducted a systematic review and meta-analysis of randomised trials and observational studies to update the evidence on the association between DPP-4 inhibitors and the risk of heart failure. Moderate quality evidence from five industry funded randomised controlled trials, including SAVOR-TIMI and EXAMINE,^{8,9} showed that DPP-4 inhibitors may increase the risk of hospital admission for heart failure among people with known cardiovascular disease (risk difference 8 events per 1000 over five years; odds ratio 1.13, 95% confidence interval 1.00 to 1.26). Evidence from the 38 industry funded randomised controlled trials evaluating risk of heart failure not limited to hospital admission was

of low quality as was the evidence from observational studies.

Overall, incretin based drugs do not seem to increase the short term risk of pancreatic cancer compared with sulfonylureas. As the use of incretin based drugs increases over time, longer term analyses of their use as monotherapy and in combination will provide more conclusive evidence. DPP-4 inhibitors do seem to increase the risk of hospital admission for heart failure among people with an increased cardiovascular risk. More evidence is needed to determine whether this risk is associated with all DPP-4 inhibitors and if it extends to patients without cardiovascular disease.

Patients and clinicians need to weigh up all potential risks and benefits when making decisions about different antidiabetic drugs. Both incretin based drug classes are associated with a low risk of hypoglycaemia and improvements in glucose control.¹² Clinicians and patients will be further informed by the results of these new studies, which report reassuring findings for incretin based treatments and risk of pancreatic cancer, but a likely increased risk of hospital admission for heart failure associated with DPP-4 inhibitors. A forthcoming report on the comparative effectiveness and safety of antidiabetic drugs published by the Agency for Healthcare Research and Quality will further inform discussions of the relative risks and benefits of these drugs.¹³ Shared decision making that incorporates patient preferences continues to be especially critical as the options for antidiabetic drug treatments expand further.

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Publication and reporting of clinical trial results

Chen R, Desai NR, Ross JS, et al

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Study question What are the rates of publication and reporting of results for completed clinical trials registered in ClinicalTrials.gov across leading academic medical centres (AMCs) in the United States?

Methods Using the Aggregate Analysis of ClinicalTrials.gov database and manual review, the authors identified all interventional clinical trials registered on ClinicalTrials.gov with a primary completion date between October 2007 and September 2010 and a lead investigator affiliated with an AMC in the USA. The study included all AMCs with 40 or more completed, registered interventional trials, a total of 4347 trials across 51 AMCs. The proportion of trials that disseminated results was determined; defined as publication or results reporting on ClinicalTrials.gov, overall and within 24 months of study completion.

Study answer and limitations AMCs disseminated results for 2892 (66%) trials; 1560 (36%) within 24 months of study completion (range 16% to 55% across individual AMCs). Only 1245 (29%)

completed trials were published within two years of study completion, and 547 (13%) reported results on ClinicalTrials.gov. The analysis was limited to trials completed by September 2010, to allow adequate time to assess publication and results reporting.

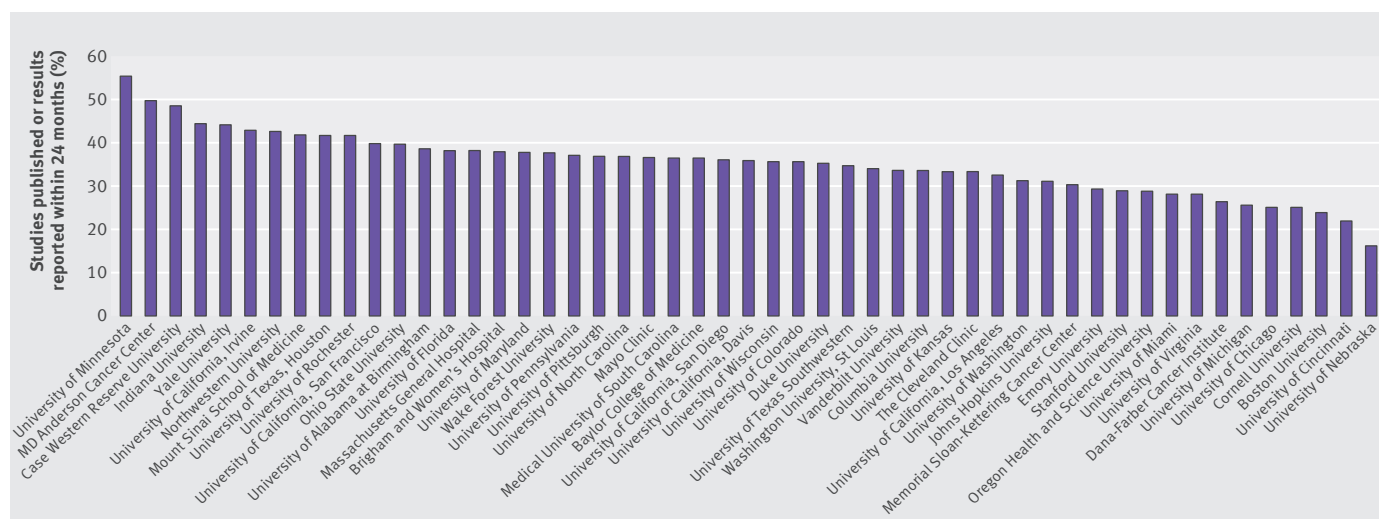
What this study adds Despite the ethical mandate and expressed values and mission of academic institutions, AMCs showed marked variation and poor

performance in the dissemination of clinical trial results.

Funding, competing interests, data sharing No specific funding or grant received from any agency in the public, commercial, or not for profit sectors. NRD, JSR, and HMK are supported by grants from the Agency for Healthcare Research and Quality, National Institute on Aging and American Federation for Aging Research, and the National Heart, Lung, and Blood Institute, respectively. Additional data are available from harlan.krumholz@yale.edu and the Dryad Digital Repository (datadryad.org).



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Rates of dissemination of clinical trial results (publication of results or reporting of results on ClinicalTrials.gov) within 24 months across academic institutions. Of 4347 completed clinical trials, this figure excludes trials without dissemination of results ($n=1455$) as well as those with publication date and results reporting date <0 ($n=216$)