research update

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

CPR with or without breaks

Cardiopulmonary resuscitation for cardiac arrest outside hospital carries a mortality risk of more than 90%. It is usually assumed that the death rate would otherwise be 100%, but trials of CPR don't ever include a non-intervention arm, so we don't really know. In this huge US trial, emergency medical service groups were cluster randomised to give either continuous chest compressions without breaks for ventilation, or to have a ventilation break after every 30 compressions. There was no significant difference in outcome: 9-9.7% of patients survived to be discharged from hospital and 7-7.7% had "favourable neurologic function" at discharge.

N Engl J Med 2015, doi:10.1056/NEJMoa1509139

Another new drug does nothing

The easiest way to test a new drug for heart failure is to see what it does to levels of B type natriuretic peptide. Measured in a single individual, readings will shoot around all over the place, but measured in a group, the mean level will give you some idea if your agent is helping to relieve ventricular strain. Vericiguat is a soluble guanylate cyclase stimulator, which theoretically might help to stabilise worsening heart failure. "Among patients with worsening chronic HF and reduced LVEF, compared with placebo, vericiguat did not have a statistically significant effect on change in NT-proBNP level at 12 weeks but was well-tolerated. Further clinical trials of vericiguat based on the dose-response relationship in this study are needed to determine the potential role of this drug for patients with worsening chronic HF." I wouldn't hold your breath: this initial study, called SOCRATES-REDUCED, recruited 456 patients across three continents and managed to lose nearly a quarter of them over 12 weeks, all for no discernible effect. If I were Socrates, I might be asking some questions at this point.

JAMA 2015, doi:10.1001/jama.2015.15734

Metformin in T1DM

Metformin is an old drug with an untarnished reputation. It was probably worth doing a trial to see if it improved glucose control in overweight or obese adolescents with type 1 diabetes, even though it didn't, over a six month period. In some of the kids, it allowed a reduction in insulin dose, and in 24% of them it led to a major reduction in BMI, compared with 7% of those given placebo. Inevitably, it caused more gastrointestinal adverse effects. While the trial doesn't define a universal role for metformin in this group, it certainly doesn't rule out benefit in a substantial number.

JAMA 2015, doi:10.1001/jama.2015.16174

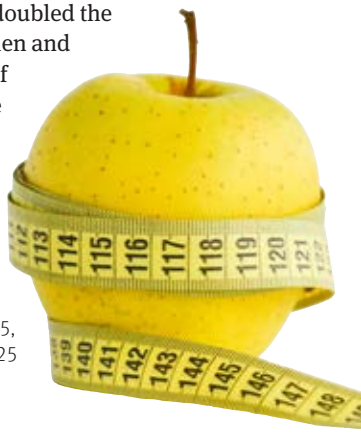
Stillbirth and obesity in Sweden

More than 30% of women in Sweden are either overweight (BMI 25 to <30) or obese (BMI ≥30) during early pregnancy. I must confess that I have never visited Sweden, so my Swedish stereotypes come from Wallander and a tweet from Trish Greenhalgh earlier this year, asking why everybody around her is slim and beautiful. Clearly, we have got this wrong. This whole population study looks at changes in BMI in relation to stillbirth and infant mortality. "Compared with women with a stable BMI (change between −1 kg/m^2 and <1 kg/m^2) between pregnancies, the adjusted RRs for women who gained at least 4 BMI units between pregnancies were 1.55 (95% CI 1.23–1.96) for stillbirth and 1.29 (1.00–1.67) for infant mortality. Stillbirth risks increased linearly with increased BMI gain." So here we have a potentially modifiable risk factor, although I'm not aware that anyone has an effective intervention for it. In my stereotype version of Sweden, small portions of fermented fish on crispbread would be delivered by weary members of the police force to every pregnant woman, leading to inappropriate emotional attachments and the uncovering of people-smuggling drug dealers who kill babies.

Lancet 2015, doi:http://dx.doi.org/10.1016/S0140-6736(15)00990-3

Big tummy+thin limbs=big risk

There are two main ways to assess "obesity": the body mass index and the waist to hip ratio (WHR). The commonest cause for an increased WHR is central fat deposition ("central obesity"), although I guess there can be other causes such as ascites or organomegaly. Every so often the National Health and Nutrition Examination Survey picks out a cohort of typical US citizens and measures such things for several years. Looking at data from 15 184 adults (52.3% women) aged 18 to 90 years in NHANES III, investigators confirm the paradox that having a normal BMI but an increased WHR confers a worse prognosis than being obese by the criterion of BMI alone. And this is no borderline effect: compared with simple obesity, it doubled the mortality risk in men and increased it by half in women over the 14 year follow-up period. Most of this added risk is due to cardiovascular factors.



Ann Intern Med 2015, doi:10.7326/M14-2525

Cite this as: *BMJ* 2015;351:h6638

CBT or antidepressants for acute depression?

ORIGINAL RESEARCH Systematic review and meta-analysis

Comparative benefits and harms of second generation antidepressants and CBTs in initial treatment of major depressive disorder

Amick HR, Gartlehner G, Gaynes BN, et al

Cite this as: *BMJ* 2015;351:h6019

Study question What are the benefits and harms of second generation antidepressants and cognitive behavioural therapies (CBTs) in the initial treatment of a current episode of major depressive disorder in adults?

Methods This was a systematic review including qualitative assessment and meta-analyses using random and fixed effects models. Medline, Embase, the Cochrane Library, the Allied and Complementary Medicine Database, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature were searched from January 1990 through January 2015. The 11 randomised controlled trials included compared a second generation antidepressant with CBT. Ten trials compared antidepressant monotherapy with CBT alone; three compared antidepressant monotherapy with antidepressant plus CBT.

ALFRED PASIEKA/SPL

Summary answer and limitations Meta-analyses found no statistically significant difference in effectiveness between second generation antidepressants and CBT for response (risk ratio 0.91, 0.77 to 1.07), remission (0.98, 0.73 to 1.32), or change in 17 item Hamilton Rating Scale for Depression score (weighted mean difference, −0.38, −2.87 to 2.10). Similarly, no significant differences were found in rates of overall study discontinuation (risk ratio 0.90, 0.49 to 1.65) or discontinuation attributable to lack of efficacy (0.40, 0.05 to 2.91). Although more patients treated with a second generation antidepressant than receiving CBT withdrew from studies because of adverse events, the difference was not statistically significant (risk ratio 3.29, 0.42 to 25.72). No conclusions could be drawn about other outcomes because of lack of evidence. Results should be interpreted cautiously given the low strength of evidence for most outcomes. The scope of this review was limited to trials that enrolled adult patients with major depressive disorder and compared a second generation antidepressant with CBT, and many of the included trials had methodological shortcomings that may limit confidence in some of the findings.

What this study adds Second generation antidepressants and CBT have evidence bases of benefits and harms in major depressive disorder. Available evidence suggests no difference in treatment effects of second generation antidepressants and CBT, either alone or in combination, although small numbers may preclude detection of small but clinically meaningful differences.

Funding, competing interests, data sharing This project was funded under contract from the Agency for Healthcare Research and Quality by the RTI-UNC Evidence-based Practice Center. Detailed methods and additional information are available in the full report, available at http://effectivehealthcare.ahrq.gov/.

COMMENTARY Both options look equally effective, although evidence is limited

Depression is an important and under-appreciated cause of global morbidity and mortality. Although reported point prevalence rates for major depressive disorder in primary care are close to 10%,[4] the literature is unclear about which treatments are most effective.

Amick and colleagues' systematic review and meta-analysis found no substantial differences in short term efficacy and tolerability between second generation antidepressants and cognitive behaviour therapy (CBT). Despite its methodological rigour, however, the review includes only 11 trials and 1511 patients. The authors' evaluation of remission and response—both key outcomes—are based on data from just three and five trials respectively; they judge that existing evidence comparing these two treatments is of low to moderate strength.

Ultimately, the results of this analysis should be simultaneously reassuring and disappointing for patients and their doctors. Reassuring because if only one of these two treatments is available, affordable, or preferred, choosing that option is unlikely to affect a patient's chances of improvement, remission, or tolerance of treatment. Disappointing because there is such a limited evidence base to evaluate treatments for a ubiquitous and often devastating condition. The relative paucity of good comparative evidence is in part because psychotherapy trials are more labour intensive for both patients and researchers. It is also because no one stands to profit substantially from expensive psychotherapy trials, in contrast to the financial rewards to pharmaceutical companies that often follow positive trials of new drugs.

One recent study identified a biomarker that might help to identify patients more likely to respond to CBT than to escitalopram.[10] Although the study was small, short term, and at high risk of bias, we must hope that bigger and better studies of biomarkers will lead eventually to improved targeting of treatments.

> The results of this analysis should be simultaneously reassuring and disappointing for patients and their doctors

Meanwhile, policy makers must acknowledge the World Health Organization's projection that major depressive disorder will be the leading cause of disease burden worldwide by 2030 by taking more meaningful steps towards primary prevention.[11] These steps should include efforts to correct social antecedents of depression such as poverty and lack of education, along with improved mental health curriculums in schools. Ultimately, such efforts could decrease the financial, personal, and interpersonal burden of this important illness while freeing up resources for other mental health services and treatments.

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Please see the editorial on thebmj.com for author details

Overtesting of adults with type 2 diabetes

ORIGINAL RESEARCH Observational population based study

HbA_{1c} overtesting and overtreatment among US adults with controlled type 2 diabetes, 2001-13

McCoy RG, Van Houten HK, Ross JS, Montori VM, Shah ND
Cite this as: *BMJ* 2015;351:h6138

Study question What is the extent and effect of excessive testing for glycated haemoglobin (HbA_{1c}) among adults with controlled type 2 diabetes?

Methods A retrospective analysis of data from a national administrative claims database included commercially insured individuals in the USA, 2001-13. Study patients were aged 18 years or older, had type 2 diabetes with stable glycaemic control (two consecutive tests showing HbA_{1c}<7.0% within 24 months), did not use insulin, had no history of severe hypoglycaemia or hyperglycaemia, and were not pregnant. HbA_{1c} testing frequency was measured within 24 months after the second (index) HbA_{1c} test, and classified as guideline recommended (≤2 times/year), frequent (3-4 times/year), and excessive (≥5 times/year). Changes in treatment regimen were ascertained within three months of the index test.

Study answer and limitations Of 31 545 patients in the study cohort (mean age 58 years; mean index HbA_{1c} 6.2%), HbA_{1c} testing frequency was excessive in 6% and frequent in 55%. Despite good glycaemic control at baseline, treatment was further intensified by addition of glucose lowering drugs or insulin in 8.4% of patients (comprising 13%, 9%, and 7% of those tested excessively, frequently, and per guidelines, respectively; P<0.001). Compared with guideline recommended testing, excessive testing was associated with treatment intensification (odds ratio 1.35 (95% confidence interval 1.22 to 1.50)). Excessive testing rates remained unchanged in 2001-08, but fell significantly after 2009. The odds of excessive testing was 46% lower in 2011 than in 2001-02. The study population is not representative of all US patients with type 2 diabetes because it was restricted to commercially insured adults with stable and controlled diabetes not receiving insulin treatment. The study design did not capture the underuse of HbA_{1c} testing.

What this study adds In this US cohort of adults with stable and controlled type 2 diabetes, more than 60% received too many HbA_{1c} tests, a practice associated with potential overtreatment with hypoglycaemic drugs. Excessive testing contributes to the growing problem of waste in healthcare and increased patient burden in diabetes management.

Funding, competing interests, data sharing NDS and RGM are funded partly by the Agency for Healthcare Research and Quality (R18HS18339) and AcademyHealth Delivery System Science Fellowship (2013), respectively. No competing interests declared.

COMMENTARY Our fondness for treating numbers is harming patients

Improvement in diabetes care is a medical success story, but increasing evidence suggests that overly aggressive treatment is an under-appreciated problem. McCoy and colleagues' results are yet another example of how prone we are to taking useful tests and treatments to excess. The common belief that there is "no harm in looking" continues to result in not just waste, but also palpable patient harm. The temptation to treat suboptimal numbers too often overrules more judicious judgments based on a careful assessment of risks and benefits.

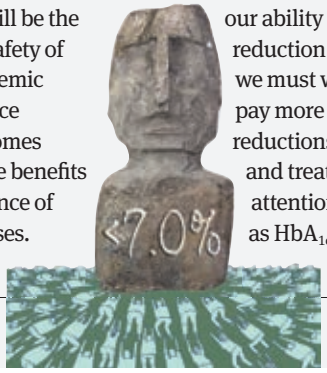
> Our fascination with numbers, in the form of surrogate outcomes, has been compared with idolatry

The desire to treat the numbers extends even to practice guidelines for HbA_{1c} targets, which have changed little since the days 25 years ago when end stage diabetes complications were rampant. This war on hyperglycaemia is increasingly difficult to justify. The many patients with end stage type 2 diabetes we saw back then often spent years with poor control of both glycaemia and blood pressure. They had no access to metformin, home blood glucose monitoring, angiotensin converting enzyme inhibitors, calcium channel blockers, and a host of other modern interventions. Each of these interventions now substantially reduces disease progression and has an even larger effect on end stage complications.[3] We should not be surprised that intensive glycaemic control has a small extra absolute effect on end stage complications for most patients. The law of diminishing returns predicts it.

When aggregated, the results of three large trials conducted in the modern era of blood pressure and lipid treatment suggest that for most patients over 50 years old with HbA_{1c} below 8.5%, additional treatment to improve control will be highly preference sensitive at best.[3] The most important factor will be the side effects, nuisance, and safety of treatment. Most newer glycaemic treatments have little evidence supporting safety.[5] This becomes increasingly important as the benefits of treatment fall and the chance of harm outweighing benefit rises.

I speak only of the patients with type 2 diabetes who are older, have at least moderate glycaemic control, good blood pressure control, and take a statin. There is certainly an important minority of patients who continue to be at substantial risk of diabetes related morbidity and mortality—namely, those with poor glycaemic control or those with early disease onset.[3] We should devote more attention and resources to this important subgroup, while promoting more discretion and shared decision making for older patients who have already achieved at least moderate control.

Our fascination with numbers, in the form of surrogate outcomes, has been compared with idolatry.[6] I will forgo speculation about why we are prone to treating numbers and not individuals, and just emphasise that our ability to estimate absolute risk reduction has never been greater.[7] If we must worship numbers, we should pay more attention to the absolute risk reductions likely to follow from tests and treatments and pay much less attention to isolated measures such as HbA_{1c}.



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ORIGINAL RESEARCH Retrospective cohort analysis

Association between concurrent use of warfarin and common sulfonylureas and serious hypoglycaemic events

Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A

Cite this as: *BMJ* 2015;351:h6223

Study question Is warfarin use associated with an increased risk of serious hypoglycaemic events among older people treated with the sulfonylureas glipizide and glimepiride?

Methods This was a retrospective cohort analysis of pharmacy and medical claims from a 20% random sample of Medicare fee for service beneficiaries aged 65 years or older. It included 465 918 beneficiaries with diabetes who filled a prescription for glipizide or glimepiride between 2006 and 2011 (4 355 418 person quarters); 71 895 (15.4%) patients also filled a prescription for warfarin (416 479 person quarters with warfarin use). The main outcome measure was emergency department visit or hospital admission with a primary diagnosis of hypoglycaemia in person quarters with concurrent fills of warfarin and glipizide/glimepiride compared with the rates in quarters with glipizide/glimepiride fills only. Multivariable logistic regression was used to adjust for individual characteristics. Secondary outcomes included fall related fracture and altered consciousness/mental status.

Summary answer and limitations In quarters with glipizide/glimepiride use, hospital admissions or emergency department visits for hypoglycaemia were more common in person quarters with concurrent warfarin use compared with quarters without warfarin use (294/416 479 *v* 1903/3 938 939; adjusted odds ratio 1.22, 95% confidence interval 1.05 to 1.42). The risk of hypoglycaemia associated with concurrent use was higher among people using warfarin for the first time, as well as in those aged 65-74 years. Concurrent use of warfarin and glipizide/glimepiride was also associated with hospital admission or emergency department visit for fall related fractures (3919/416 479 *v* 20 759/3 938 939; adjusted odds ratio 1.47, 1.41 to 1.54) and altered consciousness/mental status (2490/416 479 *v* 14 414/3 938 939; adjusted odds ratio 1.22, 1.16 to 1.29). Unmeasured factors could be correlated with both warfarin use and serious hypoglycaemic events, leading to confounding. The findings may not generalise beyond the elderly Medicare population.

What this study adds A substantial positive association was seen between use of warfarin with glipizide/glimepiride and hospital admission/emergency department visits for hypoglycaemia and related diagnoses, particularly in patients starting warfarin. The findings suggest the possibility of a significant drug interaction between these medications.

Funding, competing interests, data sharing JAR and DPG receive support from the National Institute on Aging, the Commonwealth Fund, and the Leonard D Schaeffer Center for Health Policy and Economics at the University of Southern California. ABJ receives support from the NIH Office of the Director. No additional data are available.

ORIGINAL RESEARCH Retrospective cohort analysis

Length of hospital stay after hip fracture and risk of early mortality after discharge in New York state

Nikkel LE, Kates SL, Schreck M, Maceroli M, Mahmood B, Elfar JC

Cite this as: *BMJ* 2015;351:h6246

Study question Can the length of hospital stay for hip fracture affect a patient's risk of death 30 days after discharge?

Methods In a retrospective cohort study, population based registry data from the New York Statewide Planning and Research Cooperative System (SPARCS) were used to investigate 188 208 patients admitted to hospital for hip fracture in New York state from 2000 to 2011. Patients were aged 50 years and older, and received surgical or non-surgical treatment. The main outcome measure was the mortality rate at 30 days after hospital discharge.

Study answer and limitations Hospital stays of 11-14 days for hip fracture were associated with a 32% increased odds of death 30 days after discharge, compared with stays lasting one to five days (odds ratio 1.32 (95% confidence interval 1.19 to 1.47)). These odds increased to 103% for stays longer than 14 days (2.03 (1.84 to 2.24)). Other risk factors associated with early mortality included discharge to a hospice facility, older age, metastatic disease, and non-surgical management. The 30 day mortality rate after discharge was 4.5% for surgically treated patients and 10.7% for non-surgically treated patients. These findings might not be generalisable to populations in other US states or in other countries. The administrative claims data used could have been incomplete or include inaccurate coding of diagnoses and comorbid conditions. The database also did not include patient socioeconomic status, which could affect access to care to a greater extent in New York state than in European countries. Specific cause of death was not available because few autopsies are performed in this population.

What this study adds By contrast with recent findings in Sweden, decreased length of hospital stay for hip fracture was associated with reduced rates of early mortality in a US cohort in New York state. This could reflect critical system differences in the treatment of hip fractures between Europe and the USA.

Funding, competing interests, data sharing University of Rochester grant from the Clinical Translational Science Institute for statistical analyses used in this work (National Institutes of Health (UL1 TR000042)) and the National Institutes of Health (K-08 AR060164-01A). No competing interests declared. Data may be obtained through SPARCS at https://www.health.ny.gov/statistics/sparcs/access/.