research update

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

Waiting versus intervention for PSA-detected cancers

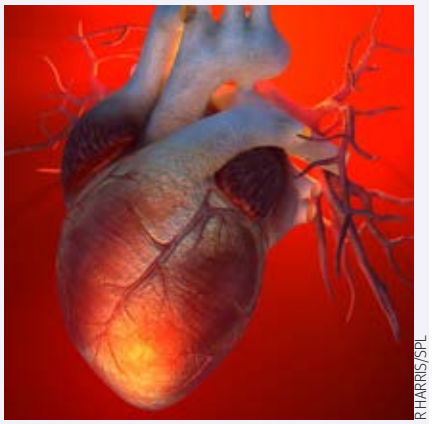
Everyone will by now be aware of this massively important British trial, which carried out prostate specific antigen tests on 82 429 men aged 50 to 69 years and randomised 1643 to active monitoring (545 men), surgery (n=553), or radiotherapy (n=545). "There were 17 prostate cancer specific deaths overall: 8 in the active-monitoring group, 5 in the surgery group and 4 in the radiotherapy group; the difference among the groups was not significant (P=0.48 for the overall comparison). In addition, no significant difference was seen among the groups in the number of deaths from any cause (169 deaths overall; P=0.87 for the comparison among the three groups)." So in the second week of September 2016, every urologist in the world knows that PSA screening detects very few cancers that are ever going to kill men, and that they will be equally alive at 10 years whether you watch them or operate or give them radiotherapy.

N Engl J Med 2016, doi:10.1056/NEJMoa1606220

Cardiac MRI to reduce angiography?

This week's *Journal of the American Medical Association* features two articles about cardiac care in the UK. This first one describes how a group of British investigators went about testing the hypothesis that among patients with suspected coronary heart disease, cardiovascular magnetic resonance (CMR) guided care is superior to National Institute for Health and Care Excellence guidelines directed care and myocardial perfusion scintigraphy guided care in reducing unnecessary angiography. To me, the most interesting thing is that it was a publicly funded trial that explicitly sets patient importance above public health importance, although it ended up informing both. "It remains a point of debate as to whether all of protocol-defined unnecessary angiograms in this study were clinically unnecessary; some would argue that negative tests are the 'price to pay' for not missing important disease in others. This assumes a population perspective, and our trial primary end point was derived after close consultation with patient and public representatives: from an individual patient perspective, an angiogram that does not change their treatment or their clinical outcome is considered by patients to have been unnecessary." Bravo. The pretest probability of the participants having occlusive coronary disease was nearly 50%. Having CMR resulted in fewer angiograms than following NICE guidance. The number of major adverse cardiovascular events was the same in all groups. I really like the way this trial was done and written up. It leaves lots of questions unanswered but it helpfully lists them all, and shows impressive thought and honesty throughout.

JAMA 2016, doi:10.1001/jama.2016.12680



R HARRIS/SPL

Sex differences in myocardial infarction

A sudden drop in temperatures reminds me that England is generally too cold, meaning that Norway must be basically uninhabitable. No wonder Norsemen plundered and settled every warm place they could find, from Sicily to North America. People in Norway get heart attacks, like people everywhere. And Norwegian women get fewer than Norwegian men, like women everywhere. Nobody knows why, and after this population based prospective study from Tromsø, Norway, we still don't. "The observed sex contrast in risk of MI cannot be explained by differences in established CHD risk factors. The gender gap persisted throughout life but declined with age as a result of a more pronounced flattening of risk level changes in middle-aged men."

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.5451

NSTEMI management in England and Wales

The *Journal of the American Medical Association* is also the place to find out about the management of non-ST elevation myocardial infarction (NSTEMI) in England and Wales between 2003 and 2013. This report is based on data on patients with NSTEMI in 247 hospitals in England and Wales obtained from the Myocardial Ischaemia National Audit Project. It's great that we had this audit going across so many centres, but I think the Scandinavians did even better when they set up the randomised FRISC trial at the same time, as I reported last week. Anyway, we are doing something right: "Among patients hospitalized with NSTEMI in England and Wales, improvements in all-cause mortality were observed between 2003 and 2013. This was significantly associated with use of an invasive coronary strategy and not entirely related to a decline in baseline clinical risk or increased use of pharmacological therapies."

JAMA 2016, doi:10.1001/jama.2016.10766

Malaria and mosquito trapping

Sometimes it is nice when a trial fails, even a malaria trial. Actually this one didn't exactly fail, but the investigators thought they had the right power for a definitive cluster randomised trial, and in that they were disappointed, because the incidence of malaria was so low during their study. The intervention was a solar powered odour baited mosquito trapping system. It doesn't sound all that effective to me: overall, 2660 trap nights of mosquito monitoring recorded 651 female Anopheles mosquitoes during the 100 week intervention period. Perhaps they should try a different fragrance. Still, the clusters with perfume machines installed had significantly lower malaria prevalence than those without them during the entire intervention period of 24 months. The authors conclude that "The unexpectedly low clinical incidence of malaria during roll-out led to an imprecise estimate of effectiveness from the clinical incidence data. The substantial effect on malaria prevalence is explained by reduction in densities of *Anopheles funestus*." It doesn't quite add up to me. I'm sure I've been in holiday rooms with at least 651 female mosquitoes in them.

Lancet 2016, doi:10.1016/S0140-6736(16)30445-7

Weight loss: are obesity genes just a distraction?

ORIGINAL RESEARCH Systematic review and meta-analysis

FTO genotype and weight loss

Livingstone KM, Celis-Morales C, Papandonatos GD, et al

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Find this at: http://dx.doi.org/10.1136/bmj.i4707

Study question What is the effect of the fat mass and obesity associated (FTO) genotype on weight loss after dietary, exercise, or drug based interventions in randomised controlled trials?

Methods The authors conducted a systematic review and random effects meta-analysis of individual participant data from randomised controlled trials. Ovid Medline, Scopus, Embase, and Cochrane were searched from inception to November 2015. Eligible trials were those in overweight or obese adults reporting reduction in body mass index, body weight, or waist circumference by FTO genotype (rs9939609 or a proxy) after dietary, physical activity or drug based interventions. Gene by treatment interaction models were fit to individual participant data from all studies included in this review, using allele dose coding for genetic effects and a common set of covariates. Study level interactions were combined using random effects models. Eight eligible trials were identified for the systematic review and meta-analysis (n=9563). Overall, differential changes in body mass index, body weight, and waist circumference in response to weight loss intervention were not significantly different between FTO genotypes.

Study answers and limitations Carriage of the FTO minor allele was not associated with differential change in adiposity after weight loss interventions. Body mass index decreased by an additional −0.02 (−0.13 to 0.09), body weight by −0.04 kg (−0.34 to 0.26), and waist circumference by −0.06 cm (−0.43 to 0.31) for each copy of the allele after weight loss intervention compared with that expected under naturalistic change in the control group. An important limitation is that the authors evaluated the effect of FTO genotype only and so the effect of other obesity related genes on weight loss in response to these interventions remains to be determined.

What this study adds Genetic predisposition to obesity associated with the FTO minor allele can be at least partly counteracted through dietary, physical activity, or drug based weight loss interventions.

Funding, competing interests, data sharing KML is funded by the Alfred Deakin postdoctoral research fellowship, CCM was supported by the UK Research Council in partnership with the Department of Health. The authors have no competing interests. No additional data are available.
Systematic review registration PROSPERO CRD42015015969.

COMMENTARY The causes of the obesity epidemic may have little to do with gene profiles

Many companies offer personalised weight loss plans tailored to our DNA, selling the idea that the effectiveness of dieting is predetermined. In reality, the extent to which genes determine the ability to lose weight remains unclear. The study by Livingstone et al[2] represents a substantial step towards answering this, at least for the FTO gene, the allele currently associated with the largest variance in body mass index.[3] Their systematic review and meta-analysis of data from almost 10 000 participants in randomised trials found no relation between the FTO gene and the ability to lose weight.

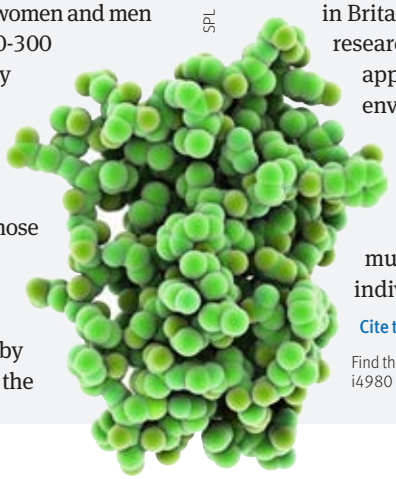
The authors acknowledge several limitations in their analysis, but the strength and clarity of the findings mean that, at least for FTO, genes do not appear to affect our ability to lose weight using standard interventions. Interactions of multiple obesity related genes might prove to have a bigger influence.[5]

Was it ever plausible that the FTO gene would have a noticeable influence on energy imbalance, and hence weight gain, compared with the influence of environmental factors such as food price, availability, and marketing? Evidence suggests that people who are homozygous for the FTO allele are on average 3 kg heavier than those not carrying the gene, possibly through reduced control of appetite.[6] In the analysis by Livingstone et al, the difference between participants with the FTO allele and those without was only 0.89 kg at baseline. These weight differences are minor compared with the degree of excess weight gain seen across populations, and equate to an estimated over consumption of just 525 kcal per year for 20 years. It is therefore hard to see the over-consumption driven by the FTO gene as a serious problem for public health.

Energy imbalances causing modern obesity are much larger. Public Health England estimates that women and men consume on average 200-300 kcals/day more than they need. This, and the level of excess weight seen across populations, implies much bigger effects are at play than those so far linked to the FTO gene. The causes of obesity are multiple and complex,[9] but the study by Livingstone et al adds to the evidence that environmental factors might dominate over at least common obesity linked genes.

Much bigger effects are at play than those so far linked to the FTO gene

An understanding of how diet and lifestyle interact with the genome might help some people, particularly those with rare conditions that cause devastating levels of weight gain in early life.[1] It is increasingly evident, however, that the idea that personalised interventions based on the genome will yield population benefit, might not pay off, at least in the short term. Given that obesity and poor diet are leading causes of morbidity in Britain,[14] a rebalancing of research towards whole systems approaches including environmental drivers may be of greater benefit to the population in the long term. The solutions to the obesity crisis must be societal, as well as individual.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Risk of erectile dysfunction associated with use of 5-α reductase inhibitors for benign prostatic hyperplasia or alopecia

Hagberg KW, Divan HA, Persson R, Nickel JC, Jick SS

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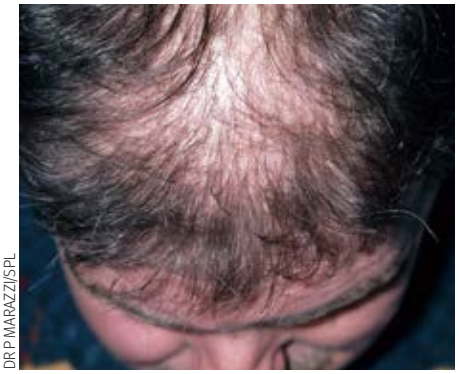
Study question Does use of 5-α reductase inhibitors to treat benign prostatic hyperplasia or alopecia increase the risk of erectile dysfunction?

Methods The authors conducted two cohort studies with nested case-control analyses using the Clinical Practice Research Datalink (CPRD). For the benign prostatic hyperplasia study, they identified men aged 40 or more with benign prostatic hyperplasia who received a prescription for a 5-α reductase inhibitor (finasteride or dutasteride) or α blocker, or both (n=71 849), and classified exposure as 5-α reductase inhibitor only, 5-α reductase inhibitor+α blocker, or α blocker only. In the alopecia study, they identified men aged 18-59 with alopecia (n=12 346) and classified exposure as finasteride 1 mg or no treatment. All men were free from risk factors for erectile dysfunction or treatment for erectile dysfunction before cohort entry. Cases were men who had a diagnosis for erectile dysfunction or treatment for erectile dysfunction (surgery or prescription for a phosphodiesterase type 5 inhibitor) during follow-up.

Study answer and limitations 5-α reductase inhibitors do not increase the risk of incident erectile dysfunction, regardless of indication for use. The risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia. The authors might have missed some cases of erectile dysfunction where phosphodiesterase type 5 inhibitors were prescribed outside of general practice because during the study period these drugs were available through private sources. Also, the CPRD does not capture information on severity of benign prostatic hyperplasia.

What this study adds The results of this study provide evidence that 5-α reductase inhibitors do not increase the risk of clinically meaningful incident erectile dysfunction in men who are free of sexual dysfunction and risk factors, regardless of indication for use (benign prostatic hyperplasia or alopecia). The risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia, independent of exposure category, which should be accounted for in the design of future studies evaluating the safety of 5-α reductase inhibitors.



DR P MARAZZI/SPL

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Results of case-control analyses evaluating use of 5-α reductase inhibitors and risk of erectile dysfunction

Exposure at index date	No (%) of cases	No (%) of controls	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Benign prostatic hyperplasia case-control study:	n=5768	n=23 060		
α blocker only	4624 (80.2)	18 699 (81.1)	1.0 (ref)	1.0 (ref)
5-α reductase inhibitor only	723 (12.5)	2844 (12.3)	1.03 (0.94 to 1.13)	0.94* (0.85 to 1.03)
5-α reductase inhibitor+α blocker	421 (7.3)	1517 (6.6)	1.13 (1.01 to 1.27)	0.92* (0.80 to 1.06)
Alopecia case-control study	n=547	n=2178		
No treatment	511 (93.4)	2021 (92.8)	1.0 (ref)	1.0 (ref)
Finasteride 1 mg	36 (6.6)	157 (7.2)	0.91 (0.62 to 1.33)	0.94† (0.64 to 1.40)

*Adjusted for body mass index, smoking status, non-erectile dysfunction sexual dysfunctions, Peyronie's disease, hypertension, diabetes, hyperlipidaemia, depression, orchitis, alcohol misuse, drug switcher, and duration of benign prostatic hyperplasia, conditional on matching factors.

†Adjusted for body mass index, smoking status, duration of benign prostatic hyperplasia, non-erectile dysfunction sexual dysfunctions, hypertension, diabetes, hyperlipidaemia, cardiovascular disease, liver disease, depression, alcohol misuse, drug misuse, and receipt of a prescription for β blockers within six months before the index date, conditional on matching factors.

β blockers and mortality after myocardial infarction in patients without heart failure

Puymirat E, Riant E, Aissoui N, et al

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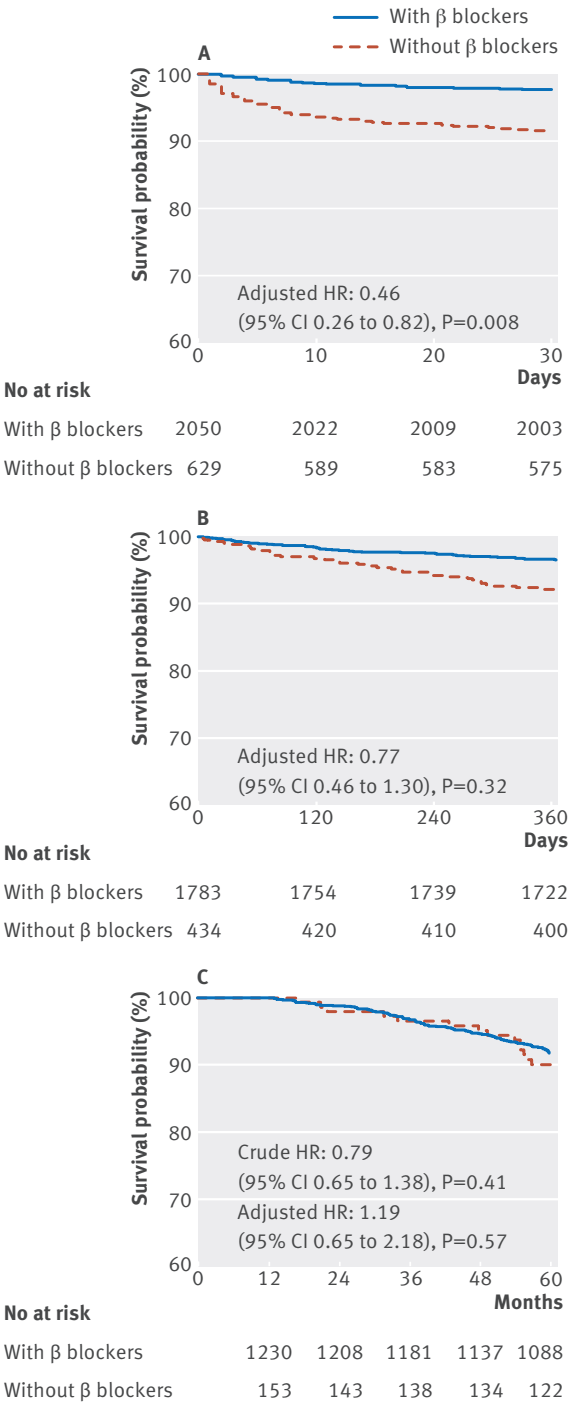
Study question What is the association between early and prolonged β blocker treatment and mortality after acute myocardial infarction in patients without heart failure?

Methods This study used data from a nationwide French registry (FAST-MI 2005), including consecutive patients with acute myocardial infarction in 223 centres; 2679 patients without heart failure or left ventricular dysfunction were included. Mortality was assessed at 30 days in relation to early use (≤48 hours of admission) of β blockers, at one year in relation to prescription at discharge, and at five years in relation to continued use at one year.

Study answer and limitations β blockers were used early in 77% (2050/2679) of patients, were prescribed at discharge in 80% (1783/2217), and were still being used in 89% (1230/1383) of those alive at one year. Thirty day mortality was lower in patients with early β blocker use (adjusted hazard ratio 0.46, 95% confidence interval 0.26 to 0.82), whereas the hazard ratio for one year mortality associated with β blockers at discharge was 0.77 (0.46 to 1.30). Persistence of β blockers at one year was not associated with lower five year mortality (hazard ratio 1.19, 0.65 to 2.18). As with all observational studies, the analysis is subject to potential bias.

What this study adds Early use of β blockers at the acute stage of myocardial infarction seems to be associated with a substantial decrease in 30 day mortality, whereas prolonged β blocker treatment beyond one year is unlikely to improve survival.

Funding, competing interests, data sharing FAST-MI is a registry of the French Society of Cardiology, supported by unrestricted grants from Pfizer and Servier. Additional support came from the French Caisse Nationale d'Assurance Maladie. See online paper for full competing interests. The authors commit to making the relevant anonymised patient level data available on reasonable request.
Study registration Clinicaltrials.govNCT00673036.



Survival according to ß blocker use. A: 30 day survival according to ß blocker use during the first 48 hours after admission in patients with no history of heart failure and no heart failure on admission.

B: one year survival according to ß blocker prescription at discharge in patients with no history of heart failure and no documented left ventricular dysfunction.

C: five year survival in patients discharged taking ß blockers, according to continuation of ß blocker treatment at one year. HR=hazard ratio; CI=confidence interval