research update

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

Keeping a cool head during chemotherapy

SCALP is the acronym for a trial which tested the effectiveness of a scalp cooling device to prevent alopecia in women undergoing chemotherapy for breast cancer. Good. This is an interim analysis, but it shows that keeping a cool head during chemotherapy with anthracyclines or taxanes reduced the need for a wig or head wrap from 100% to 63%.

A similar trial looked at women with breast cancer receiving non-anthracycline chemotherapy. In both trials, scalp cooling to a chilly 3°C began 30 minutes before chemotherapy was administered and continued for 90-120 minutes afterwards. The results were the same as in SCALP: a useful 50% diminution in hair loss.

JAMA 2017, doi:10.1001/jama.2016.20939, doi:10.1001/jama.2016.21038

Subgroups and "precision medicine"

This paper poses the question "How often are subgroup claims reported in the abstracts of randomized clinical trials supported by a statistically significant interaction test result and corroborated by subsequent randomized clinical trials and meta-analyses?" This is not an anorak question but something all clinicians should worry about. Somebody should invent a term for the urban myths that spread so rapidly through medicine despite the best attempts of the evidence based medicine community. Hint that some new thing may perhaps be better for a certain group of patients and we all start trying it on them. This should never be the case. The article concludes that "Attempts to corroborate statistically significant subgroup differences are rare; when done, the initially observed subgroup differences are not reproduced." The study was based on 64 randomised controlled trials, which made a total of 117 subgroup claims in their abstracts.

JAMA Intern Med 2017, doi:10.1001/jamainternmed.2016.9125

Periviable infant outcomes

"Periviable" is a new word to me. For neonatologists, it refers to infants born on the borderline of viability at 22 to 24 weeks of gestation. In most developed countries, survival rates have improved for these extremely premature babies, but the current study looks at their associated neurodevelopmental outcomes too, using data on 4274 infants from 11 centres that participated in the National Institute of Child Health and Human Development Neonatal Research Network. Between 2000 and 2011, survival increased from 30% to 36%, but the percentage of infants who survived with neurodevelopmental impairment did not statistically significantly change. This means that even when cared for in a subset of America's leading academic centres, 43% of surviving periviable babies will show neurological damage in childhood.

N Engl J Med 2017, doi:10.1056/NEJMoa1605566

Waist-to-hip ratio

I'm old enough to remember when the body mass index was a new thing. You worked it out on a pocket calculator when you had weighed and measured your patient. Before that, you just looked at his or her middle. This is, in fact, a better indicator of risk, as people have been pointing out for decades. Best of all, you can do both, as in this study of nearly 120 000 people on the UK Biobank database. And then you can see how much of the risk seems to be genetic, as you have their full genome as well. The conclusion of this study is that "A genetic predisposition to higher waist-to-hip ratio adjusted for body mass index was associated with increased risk of type 2 diabetes and coronary heart disease. These results provide evidence supportive of a causal association between abdominal adiposity and these outcomes."

JAMA 2017, doi:10.1001/jama.2016.21042

Redoing joint replacement

Woo, here is culture change in action: "Our study used novel methodology to investigate and offer new insight into the importance of young age and risk of revision after total hip or knee replacement. Our evidence challenges the increasing trend for more total hip replacements and total knee replacements to be done in the younger patient group, and these data should be offered to patients as part of the shared decision making process." Offering data to patients as part of a shared decision making process? In orthopaedics? Political correctness gone mad. In my day you told the patient what operation he or she needed, and how many months it would take to get done on the NHS, and how many days it would be to get done privately. Next! This new study was based on the UK Clinical Practice Research Datalink and found that the lifetime risk of requiring revision surgery in patients who had total hip replacement or total knee replacement over the age of 70 years was about 5%, with no difference between the sexes. But for those who had surgery younger than 70 years, the lifetime risk of revision increased for younger patients—up to 35% for men in their early 50s—with large differences seen between male and female patients (15% lower for women in the same age group). Those are certainly figures that patients should know about.

Lancet 2017, doi:10.1016/S0140-6736(17)30059-4

Off-label prescribing of antidepressants

ORIGINAL RESEARCH
Descriptive study of prescriptions from an electronic prescribing system

Off-label indications for antidepressants in primary care

Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R

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Find this at: http://dx.doi.org/10.1136/bmj.j603

Study question What is the level of scientific evidence supporting antidepressant prescriptions for off-label indications?

Methods This descriptive study included antidepressant prescriptions written by primary care physicians in Quebec, Canada, using an indication based electronic prescribing system. Antidepressant prescriptions were included if they were written for patients aged 18 years and older, between 1 January 2003 and 30 September 2015. Study outcomes included the prevalence of off-label indications by class and drug. Among off-label antidepressant prescriptions, the study analysis also looked at the proportion of prescriptions in each of the following categories: strong evidence supporting use of the prescribed drug for the respective indication; no strong evidence for the prescribed drug but strong evidence supporting use of another drug in the same class for the indication; or no strong evidence supporting use of the prescribed drug and all other drugs in the same class for the indication.

Study answer and limitations A total of 106 850 antidepressant prescriptions were written by 174 physicians for 20 920 adults. Only 15.9% (95% confidence interval 13.0% to 19.3%) of all off-label antidepressant prescriptions were supported by strong evidence, yet for 39.6% (35.7% to 43.2%) there was another antidepressant in the same class with strong evidence for the respective indication. For the remaining 44.6% (40.2% to 49.0%) of off-label prescriptions, neither the prescribed drug nor any other drugs in the class had strong evidence for the indication. This study was limited by the inclusion of physicians and patients from only one Canadian province.

What this study adds When primary care physicians prescribe antidepressants for off-label indications, these indications may often be lacking strong evidence. There is an important need to generate more evidence evaluating off-label antidepressant use and provide physicians with this evidence to optimise prescribing decisions.

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COMMENTARY Strength of evidence matters more than presence or absence of a specific licence

In their paper, Wong and colleagues found that almost a third of antidepressants were prescribed for off-label indications, most commonly pain, insomnia, and migraine.[2]

Clinicians can legally prescribe off-label, and professional responsibility in these circumstances is fundamentally the same as for on-label prescribing. Although off-label prescribing may need more explicit justification, the evidence supporting prescribing is more important than the presence or absence of a specific licence.

Only 16% of the off-label prescribing identified by Wong and colleagues was directly supported by strong evidence, with a further 40% having indirect support from strong evidence for other drugs in the same class.[2] Although it may seem odd that off-label prescribing can have strong evidence, this often occurs when new indications for old drugs are evaluated in trials but pharmaceutical companies fail to alter existing marketing authorisations because the drug is off-patent and the process is complex and expensive.

Amitriptyline for chronic pain is an example of evidence based and guideline recommended off-label prescribing.[2 4 5] Extending the range of uses of long established medicines in this way is attractive for healthcare professionals and patients, because these drugs are perceived to have familiar safety profiles and are cheaper than drugs still under patent protection.

Off-label prescribing is common and is often poorly supported by evidence or relies heavily on extrapolating evidence from one situation to another

For all prescribing, patients (or their parents or carers) should be given enough information to allow them to make an informed decision whether to take a medicine. This should include whether the intended use is off-label, but more importantly prescribers should discuss the strength of the evidence base underlying their recommendation.[3] Off-label prescribing matters because it is usually (but not always) associated with substantial uncertainty about the balance of benefit and harm.[8] Prescribers should therefore be cautious when they prescribe off-label on the basis of extrapolated evidence from a different indication, a different patient group, or a substantially different dose or formulation.

Equally, however, on-label prescribing also often involves extrapolation, most commonly because the patient needing treatment is very different from the patients included in trials. For example, the evidence underpinning on-label use of antidepressants to treat depression comes from trials in people with more severe depression and less psychiatric and physical comorbidity than is typical in everyday practice.[9 10] Most people with well characterised major depressive disorder in everyday practice would be ineligible for these trials.[11] They are less likely to respond to antidepressants and more likely to experience adverse events.[12]

As Wong and colleagues show, off-label prescribing is common and is often poorly supported by evidence or relies heavily on extrapolating evidence from one situation to another. These pitfalls are not confined to off-label drugs, however. Patients and prescribers should be cautious about all extrapolations of evidence whether the proposed treatment is "on-label" or "off-label."

Daniel R Morales
Bruce Guthrie b.guthrie@dundee.ac.uk
See bmj.com for author details

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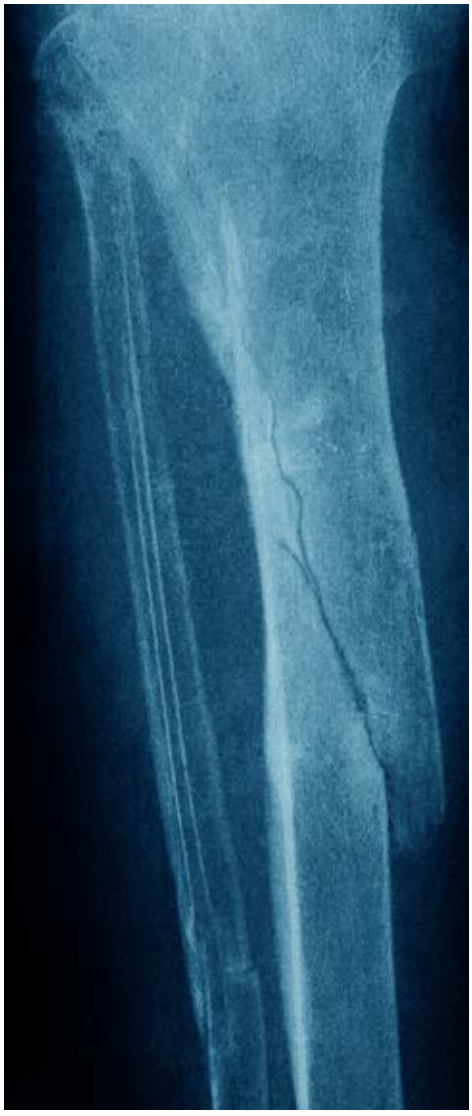
Low intensity pulsed ultrasound for bone healing



ORIGINAL RESEARCH

Systematic review of randomised controlled trials

Schandelmaier S, Kaushal A, Lytvyn L, et al

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Find this at: http://dx.doi.org/10.1136/bmj.j656

Study question Does low intensity pulsed ultrasound (LIPUS) improve bone healing?

Methods Systematic review and meta-analysis of randomised controlled trials comparing LIPUS with sham device or no device in patients with any fracture or osteotomy. Medical databases and trial registries searched until November 2016. Two reviewers identified studies, extracted data, and assessed risk of bias. A parallel guideline committee (*BMJ* Rapid Recommendation) advised the design and interpretation of the review, including selecting outcomes important to patients. GRADE was used to assess the quality of evidence.

Study answer and limitations 26 randomised controlled trials with a median sample size of 30 (range 8-501) were included. Compared with control, LIPUS did not reduce time to return to work or the number of subsequent operations. Effects for the outcomes days to full weight bearing, pain, and days to radiographic healing varied substantially between studies. Trials at high risk of bias suggested a benefit, whereas those at low risk of bias consistently showed no effect. The evidence applies directly to patients with fresh fractures. The applicability to other types of fracture or osteotomy is open to debate.

What this study adds Based on moderate to high quality evidence, mainly from studies in patients with fresh fracture, LIPUS does not improve outcomes important to patients and probably has no effect on radiographic bone healing.

Funding, competing interests, data sharing This study was unfunded. JWB, DHA, and GHG were co-authors of a clinical trial evaluating LIPUS, which was supported in part by an industry grant from Smith & Nephew, a manufacturer of LIPUS devices. There are no further data to share.
Systematic review registration PROSPERO CRD42016050965

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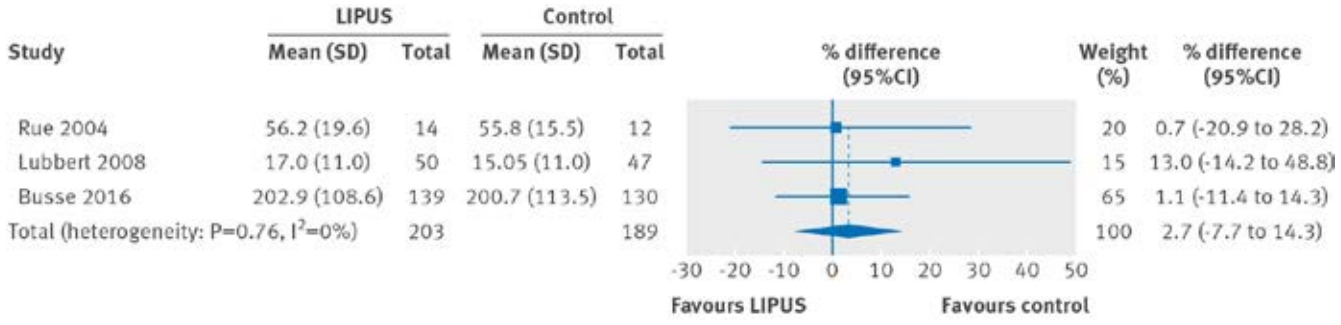

Difference in days to return to work after fracture treated with low intensity pulsed ultrasound (LIPUS) compared with sham device

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ORIGINAL RESEARCH Prospective controlled study with 10 years of follow-up

Risk of heart failure after community acquired pneumonia

Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR

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Study question What is the attributable risk of community acquired pneumonia on incidence of heart failure throughout the age range of affected patients and severity of the infection?

Methods Between 2000 and 2002, 4988 adults with community acquired pneumonia and no history of heart failure were recruited and matched on age, sex, and treatment setting with up to five controls without heart failure or pneumonia (n=23 060). Patients were then followed until 2012 and the risk of hospital admission for heart failure was evaluated after accounting for numerous patient characteristics.

Study answer and limitations The data suggest that the 10 year risk of developing new heart failure after a pneumonia event is approximately 12% and compared with age-sex matched controls, there was more than a 50% relative increase in the risk of new heart failure, irrespective of age or severity of the initial pneumonia (adjusted hazard ratio 1.61, 95% confidence interval 1.44 to 1.81). Patients with pneumonia aged 65 or less had the lowest absolute increase (but greatest relative risk) of heart failure compared with controls (4.8% *v* 2.2%; adjusted hazard ratio 1.98, 95% confidence interval 1.5 to 2.53), whereas patients with pneumonia aged more than 65 had the highest absolute increase (but lowest relative risk) of heart failure (24.8% *v* 18.9%; adjusted hazard ratio 1.55, 1.36 to 1.77). Given the observational nature of the study, the authors are unable to examine whether pneumonia causes heart failure in itself or whether heart failure is simply the final outcome in the cardiac cascade triggered by an acute pneumonia event. Other factors that are common to both community acquired pneumonia and heart failure are also likely to play a part, including advanced age, reduced renal function, and the presence of other major comorbidities.

What this study adds Pneumonia is statistically significantly associated with an increased risk of heart failure across the range of ages and regardless of the severity of the pneumonia episode. This should be considered when formulating post-discharge care plans and strategies to prevent recurrent pneumonia, and assessing downstream episodes of dyspnoea.

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ORIGINAL RESEARCH Propensity weighted nationwide cohort study

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation

Nielsen PB, Skjøth F, Søgaard M, et al

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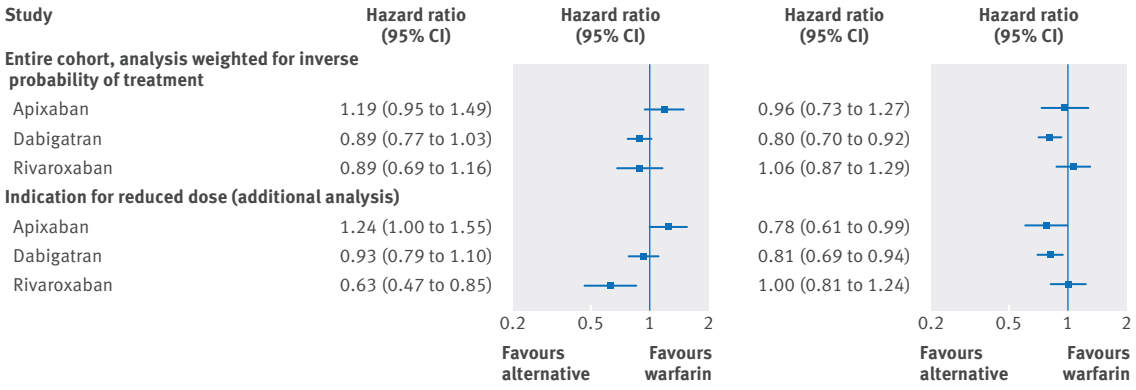
Study question How effective and safe are reduced dose non-vitamin K oral anticoagulants (NOACs) compared with warfarin in patients with atrial fibrillation who had not previously received an oral anticoagulant?

Methods This propensity weighted nationwide cohort study used individual linked data from three nationwide registries in Denmark, August 2011 to February 2016. The study population had not previously received anticoagulant treatment. Patients who started treatment with a reduced dose NOAC were compared with those who were treated with warfarin with respect to effectiveness and safety outcomes.

Study answers and limitations The 55 644 included patients were distributed according to treatment: 38 893 received warfarin (2.5 mg dose adjusted), 8875 received dabigatran (110 mg twice a day), 3476 received rivaroxaban (15 mg once a day), and 4400 received apixaban (2.5 mg twice a day). During one year of follow-up, dabigatran and rivaroxaban were associated with trends towards lower rates of ischaemic stroke/systemic embolism compared with warfarin (hazard ratios 0.89 (95% confidence interval 0.77 to 1.03) and 0.89 (0.69 to 1.16), respectively). Apixaban had a trend towards higher rates compared with warfarin (1.19, 0.95 to 1.49). Compared with warfarin, rates of bleeding with apixaban and rivaroxaban were similar (0.96 (0.73 to 1.27) and 1.06 (0.87 to 1.29), respectively), while rates with dabigatran were lower (0.80, 0.70 to 0.92). Bias from unobserved residual confounding and selective prescribing behaviour cannot be ruled out. Extensive sensitivity analysis, however, did not change the conclusions of the study.

What this study adds In patients with atrial fibrillation, apixaban 2.5 mg twice a day was associated with a trend towards higher rates of ischaemic stroke or systemic embolism compared with warfarin. Thromboembolic rates with dabigatran 110 mg twice a day and rivaroxaban 15 mg once a day were lower. The results, however, were not significant.



Outcomes at one year follow-up in patients with atrial fibrillation according to initiated treatment. SE=systemic embolism

Funding, competing interests, data sharing This study was funded partly by the Obel Family Foundation. Several authors have links with various pharmaceutical companies. Full details are on bmj.com. Data sharing is not possible.