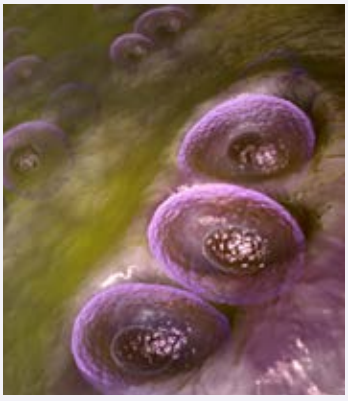
research update

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



MEDICAL RF.COM/SPL

From nose to knee

From this *Lancet* article I learn that the chondrocytes of the human nasal septum are of a higher quality than their sister cells in joints. "Compared with articular chondrocytes, chondrocytes derived from the nasal septum have superior and more reproducible capacity to generate hyaline-like cartilage tissues, with the plasticity to adapt to a joint environment. We aimed to assess whether engineered autologous nasal chondrocyte-based cartilage grafts allow safe and functional restoration of knee cartilage defects." The investigators at University Hospital Basel decided to try out laboratory enhanced nose cartilage to repair full thickness cartilage injuries in the knees of 10 patients. "No adverse reactions were recorded and self-assessed clinical scores for pain, knee function, and quality of life were improved significantly from before surgery to 24 months after surgery. Radiological assessments indicated variable degrees of defect filling and development of repair tissue approaching the composition of native cartilage." So another somewhat promising phase 1 trial of an orthopaedic technique. Now we'll just have to wait and see what bigger trials show.

Lancet 2016, doi:org/10.1016/S0140-6736(16)31658-0

Mending incisional hernias

Here is an observational study from Denmark on the five year outcomes after incisional hernia repair of the abdominal wall according to whether it was performed with or without mesh. I am afraid that I cannot pad out this section with any references to early Danish motets, or quotations from *Hamlet*. The simple fact is that mesh repair provided better early results but over five years the stuff can move about, become infected, or otherwise cause nuisance, partly offsetting its advantages. This is another surgical study that needs turning into a decision aid.

JAMA 2016, doi:10.1001/jama.2016.15217

Quality of outpatient care in the USA

Every now and again I dip back into the works of Avedis Donabedian, who published three books and a dozen key papers on the assessment of quality in medical care and refused to come up with any simple solution. How right he was. Here is a study that is supposed to describe how the quality of outpatient care has changed in the USA between 2002 and 2013. There were some small shifts in categories of "appropriateness" of treatment and advice about screening. Overall, nothing much changed. I suspect nothing much will ever change until a new medical workforce appears, taught from the start how to conduct better dialogues with patients and use their goals and experiences as the main metric for quality. This will probably be the work of two generations, and it's the greatest challenge for the medicine of our century. But, as Gandhi would have said, you can start right away with yourself.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.6217

Caffeine and heart failure

Needless to say I am writing with a mug of coffee by my side. If I developed heart failure would I need to give up this daily essential? Probably not, judging from a simple human experiment conducted in Brazil, still the largest producer of coffee in the world. Patients with systolic heart failure and at high risk of arrhythmia were recruited from a clinic in Porto Alegre and given 100mg of caffeine or placebo in addition to decaffeinated coffee every hour for five hours. During this time they were monitored for arrhythmias, and the experiment was repeated one week later. The high doses of caffeine provoked no arrhythmias in these high risk patients. I hope they were rewarded with many bags of real coffee beans.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.6374

Avoiding whole brain radiotherapy for lung cancer

Whole brain radiotherapy (WBRT) has predictable effects. Your hair falls out and you feel sick and lethargic while you're having it, and often for weeks afterwards. And then, in the case of the patients in the QUARTZ trial, you die: over half were dead within eight weeks, all but a handful by a year. They had non-small cell lung cancer with brain metastases. I must say I shuddered when I read this paper. It describes how, on the basis of observational evidence and one hopelessly inadequate trial with 49 patients from 1971, an entire population of dying patients has been exposed to unnecessary treatment for half a century. Not just that, but WBRT has undergone all sorts of futile refinements, which increasingly include neurosurgery, stereotactic radiosurgery, and systemic treatments. This trial, conducted in 69 centres in the UK and three in Australia, conclusively shows that dexamethasone alone provides exactly the same survival rates with or without WBRT. It wasn't until a Cochrane review in 2012 that people started to question the practice, which for all I know continues to be standard treatment. This is a horrible example that should be included in every lecture on evidence based medicine. Set against it should be the landmark paper (*New England Journal of Medicine* 2010;363:733-42) in which Temel et al found that "Among patients with metastatic non–small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival."

Lancet 2016, doi:org/10.1016/S0140-6736(16)30825-X

Low intensity ultrasound for fractures of the tibial shaft

ORIGINAL RESEARCH Population based cohort study using the UK Clinical Practice Research Datalink

Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST): randomised clinical trial

TRUST Investigators writing group; Busse JW, Bhandari M, Einhorn TA, et al

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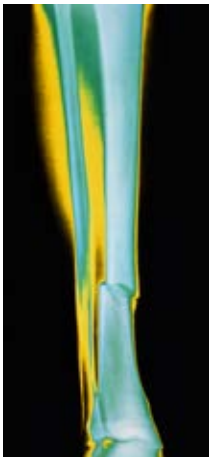
Find this at: http://dx.doi.org/10.1136/bmj.i5351

Study question Does low intensity pulsed ultrasound accelerate functional recovery and radiographic healing among patients with operatively managed tibial fractures?

Methods Concealed, randomised, blinded, sham controlled clinical trial with a parallel group design at 43 North American academic trauma centres. Between October 2008 and September 2012, 501 patients who underwent internal fixation with an intramedullary nail for tibial fracture were randomised 1:1 to self administer low intensity pulsed ultrasound (n=250) or to use a sham device identical in appearance (n=251) until their tibial fracture showed radiographic healing, or until one year after fixation. The primary registry specified outcome was time to radiographic healing within a year of fixation, and the secondary outcome was rate of non-union. Additional outcomes specified in the protocol included SF-36 physical component summary (SF-36 PCS) scores, return to work, return to household activities, return to at least 80% of function before injury, return to leisure activities, time to full weight bearing, scores on health utilities index, and adverse events related to the device.


SPL

Study answer and limitations SF-36 PCS data were available for 481/501 (96%) patients, with 2303/2886 (80%) observations. Radiographic healing data were available from 482/501 (96%) patients, of whom 82 were censored. There was no difference between the groups in SF-36 PCS scores (mean difference 0.55, 95% confidence interval −0.75 to 1.84, P=0.41, for the interaction between time and treatment; minimal important difference 3-5 points), other functional measures, time to radiographic healing (hazard ratio 1.07, 0.86 to 1.34; P=0.55), or safety outcomes. Though the trial failed to obtain 100% follow-up for the outcomes, multiple imputation led to similar estimates of treatment effects, providing reassurance that loss to follow-up was unlikely to have biased the results. Patient compliance was moderate, with only 73% of patients administering ≥50% of all recommended treatments. As the study devices were used by patients in an outpatient setting, this probably reflects use in routine clinical settings.

What this study adds Postoperative use of low intensity pulsed ultrasound after tibial fracture fixation does not accelerate radiographic healing and fails to improve functional recovery.

Funding, competing interests, data sharing This study was supported by grants from the Canadian Institutes of Health Research, and an industry grant from Smith & Nephew. Details of authors' competing interests can be found in the full paper on thebmj.com. Patient level data are available from the corresponding author.
Study registration ClinicalTrials.gov Identifier: NCT00667849.

COMMENTARY We now have sound evidence that it doesn't work

Busse and colleagues report findings from a trial of low intensity pulsed ultrasound (LIPUS) in tibial fracture healing. They are to be congratulated both for the rigour of the study and for their perseverance in bringing it to completion.

Previous randomised trials investigating the effectiveness of ultrasound treatment have had inconclusive results. Meta-analyses, which have attempted to pool these trial data, have consistently characterised a research topic comprising a few small trials reporting large positive effects.

Busse and colleagues report a randomised trial comparing self administered ultrasound with sham ultrasound in 501 US adults with fractures of the tibial shaft treated by internal fixation with an intramedullary nail. The authors found no significant differences between groups for any outcome. They conclude that ultrasound does not accelerate healing of tibial fractures or improve functional recovery.

It is time for us to make good use of their determination and abandon this ineffective treatment

On the face of it, this is a clear report of the clinical ineffectiveness of a commonly used treatment. Behind the report of the trial, however, is the story of these investigators' determination to bring their study to a successful conclusion.

The initial design focused around a functional primary outcome reported by patients. This protocol was first developed and submitted to a funding body in 2006. Subsequently, the US Food and Drug Administration asked the authors to switch their primary outcome to radiographic healing. In the end, radiographic healing was added as a co-primary outcome. Assessments of radiographic healing are notoriously unreliable and are, at best, only a proxy for successful outcomes as reported by patients.

Further complications occurred when the industry sponsor conducted an unplanned interim analysis in late 2012, which prompted a decision in March 2013 to terminate the study early on the grounds of futility. This meant that 73 participants were unable to fully complete the follow-up schedule. Three years of negotiation followed between the sponsor and the investigators—which the authors say included requests for multiple unplanned subgroup analyses—until finally we are able to read the full report of this study in a peer reviewed journal.

Fortunately for patients, clinicians, and clinical guideline groups, the results were clear, despite these influences. Busse and colleagues report important patient centred outcomes with a precise estimate, showing that low intensity pulsed ultrasound is of no benefit to adults with tibial fractures treated with an intramedullary nail. It is time for us to make good use of their determination and abandon this ineffective treatment.

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Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography

Dewey M, Rief M, Martus P, et al

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Study question Should invasive coronary angiography or computed tomography (CT) be performed in patients with an intermediate probability of coronary artery disease?

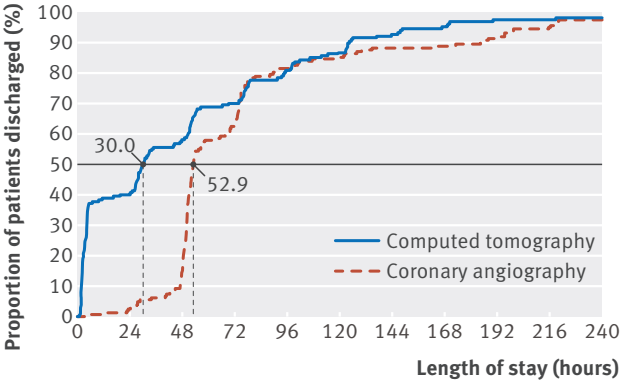
Methods This was a randomised single centre trial in patients with suspected coronary artery disease and a clinical indication for coronary angiography based on atypical angina or chest pain. Allocation could not be blinded and blinded independent investigators assessed outcomes. The primary outcome measure was major procedural complications.

Study answers and limitations CT reduced the need for angiography from 100% to 14% (95% confidence interval 9% to 20%, P<0.001) and was associated with a significantly greater diagnostic yield of angiography: 75% (53% to 90%) *v* 15% (10% to 22%), P<0.001. Major procedural complications were uncommon (0.3%) and similar across the groups. Minor procedural complications were less common in the CT group than in the angiography group: 3.6% (1% to 8%) *v* 10.5% (6% to 16%), P=0.014. CT shortened the median length of stay in the angiography group from 52.9 hours (interquartile range 49.5-76.4 hours) to 30.0 hours (3.5-77.3 hours, P<0.001). Median exposure to radiation was similar between the CT group and angiography group: 5.0 mSv (4.2-8.7 mSv) *v* 6.4 mSv (3.4-10.7 mSv), P=0.45. After a median follow-up of 3.3 years, major adverse cardiovascular events had occurred in seven of 167 patients in the CT group (4.2%) and six of 162 (3.7%) in the angiography group (adjusted hazard ratio 0.90, 95% confidence interval 0.30 to 2.69; P=0.86). 79% of patients stated that they would prefer CT for subsequent testing. Performance of CT may be different in clinical routine practice and the study was underpowered for the primary outcome.

What this study adds CT increased the diagnostic yield and was a safe gatekeeper for coronary angiography with no increase in long term events. The length of stay was shortened by 22.9 hours using CT and patients preferred this procedure.

Funding, competing interests, data sharing Funded by the Heisenberg programme of the German Research Foundation. The researchers are independent of the funding bodies. MD has relationships with Bayer, Bracco, Cardiac MR Academy, European Commission, European Regional Development Fund, German Foundation of Heart Research, German Federal Ministry of Education and Research, GE Healthcare, Guerbet, Springer, and Toshiba; BH has relationships with Bayer, Bracco, GE, Guerbet, Philips, Siemens, and Toshiba. Requests for patient level data will be considered by the CAD-Man trial group.

Trial registration ClinicalTrials.gov NCT00844220.



No of patients for outpatient evaluation or in hospital

Computed tomography	167	100	71	50	32	22	12	8	4	4	3
Coronary angiography	162	158	136	61	30	24	19	18	14	8	4

Reduction in length of stay using computed tomography instead of invasive coronary angiography

RAGUET H/BSIP/ALAMY

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CONSORT 2010 statement

Eldridge SM, Chan CL, Campbell MJ, et al

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In the literature there are a large and growing number of studies that authors describe as feasibility or pilot studies. Many of these studies are conducted in preparation for a future definitive randomised controlled trial (RCT) that aims to assess the effect of an intervention. Research has shown that such pilot and feasibility studies are often of poor quality and not well reported.

The Consolidated Standards of Reporting Trials (CONSORT) statement is a guideline (checklist with explanation and elaboration) designed to improve the transparency and quality of the reporting of RCTs. The authors of this paper developed an extension to the 2010 CONSORT statement, to apply to randomised pilot and feasibility studies that are in preparation for a future definitive RCT. The extension applies to any such randomised studies regardless of the terminology authors use to describe them, including, for example, those described as randomised feasibility studies, and pilot trials (if randomised).

The aims and objectives of pilot and feasibility studies should not be the same as for definitive RCTs. This is because, in contrast with definitive RCTs which assess the effectiveness of an intervention, the focus of pilot and feasibility studies is the feasibility of a future definitive RCT. This fundamental distinction leads to key differences between the information to be reported and the appropriate interpretation of standard CONSORT reporting items in this CONSORT extension and in the main CONSORT statement. The authors' 26 item checklist retains some of the standard CONSORT items, but most have been adapted, some removed, and some new items added.

The authors also provide a separate checklist for the abstract for a randomised pilot or feasibility study, a template for a CONSORT flow chart for these studies, an explanation of the changes, and supporting examples. They believe that routine use of this extension to the CONSORT statement will result in improvements in the conduct and reporting of randomised pilot and feasibility trials.

CONSORT checklist of information to include when reporting a pilot trial

Section/topic and item No	Standard checklist item	Extension for pilot trials	Page No where item is reported
Title and abstract			
1a	Identification as a randomised trial in the title	Identification as a pilot or feasibility randomised trial in the title	
Introduction			
Background and objectives:			
2b	Specific objectives or hypotheses	Specific objectives or research questions for pilot trial	
Outcomes:			
6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	
6b	Any changes to trial outcomes after the trial commenced, with reasons	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	
6c		If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	
Analytical methods:			
12a	Statistical methods used to compare groups for primary and secondary outcomes	Methods used to address each pilot trial objective whether qualitative or quantitative	
Results			
Participant flow (a diagram is strongly recommended):			
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	
Numbers analysed:			
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	
Outcomes and estimation:			
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	
Interpretation:			
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	
22a		Implications for progression from pilot to future definitive trial, including any proposed amendments	

This table shows selected items in the CONSORT extension. These items are new or have been substantially adapted from the CONSORT 2010 to focus to a greater extent on the objectives of a pilot trial and how those objectives relate to methods, results, and interpretation. Other items have also been adapted but are not shown here.
*Here a pilot trial means any randomised study conducted in preparation for a future definitive RCT, where the main objective is to assess feasibility.