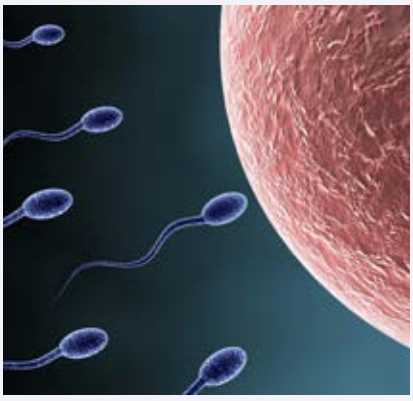
research update

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



Lifestyle change useless for infertility

This week the *New England Journal of Medicine* published a Dutch randomised trial of a lifestyle programme in obese infertile women. The intervention had no effect on overall fertility outcomes: in fact, at two years the frequency of vaginal births of healthy singletons at term was statistically significantly lower in the intervention group than in the control group, which received immediate fertility treatment. This is great news for millions of obese women around the world who are having trouble getting pregnant: they can skip being preached at and made to go on diets and bikes, and get straight on with treatment and having babies.

N Engl J Med 2016, doi:10.1056/NEJMoa1505297

Ventricular tachycardia ablation

Here is some serious cardiology for grown men. It so happens that in the United States, fewer than 10% of interventional cardiologists/electrophysiologists are women, suggesting that ablation therapy must bear some hidden resemblance to snooker or motor racing. Ventricular tachycardia ablation is a last ditch procedure, which can kill as well as cure: two cardiac perforations and three cases of major bleeding occurred in the ablation group of this 259 participant trial. But the alternative was escalated dose amiodarone which was worse and less effective: it was associated with two deaths from pulmonary toxic effects and one from hepatic dysfunction. So if you have survived myocardial infarction but still have recurrent ventricular tachycardia despite having an implantable cardioverter defibrillator, you might do best by submitting yourself to the manly ministrations of the guy with the blue hat.

N Engl J Med 2016, doi:10.1056/NEJMoa1513614

Prognosis in the ICU

Here's an open access paper about prognosis that both qualitatively and quantitatively explores how doctors and "surrogates" differ in their perception of prognosis in the intensive care unit and the reasons for this. Surrogates are the ones taking decisions on behalf of critically ill patients, and their estimates of prognosis are pretty good. The estimates of doctors are, however, even better. The reasons for discordance between the two groups are fascinating: they include hanging on to hope, religious belief, and belief in the hidden resilience of the patient. It's another terrific example of the mixed methods approach, which should be far, far more common than it is. "*Rerum cognoscere causas*" is the motto of Sheffield University—to know the causes of things. In medicine, you can often find out the causes of things much better by asking people than by counting numbers.

JAMA 2016, doi:10.1001/jama.2016.5351

Going to church delays going to heaven

American nurses who went to religious services between 1992 and the present are more likely to be alive than those who did not. This fact emerges from the Nurses' Health Study, leading the authors to conclude "Religion and spirituality may be an underappreciated resource that physicians could explore with their patients, as appropriate." I won't even attempt to guess what they have in mind.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.1615

People who say they are active get less cancer

For our next ride on the great Confounding Rollercoaster, let's match up rates of cancer and the amount of physical activity that people claim to do in their spare time. Unfortunately, these data have not been adjusted for church, mosque, or synagogue attendance, so there may be residual doubts. But the study says that exercise prevents cancer, so it must be correct.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.1548

Breasting the waves of uncertainty

I am a bit late coming to the important B-path study, which appeared on the *Annals of Internal Medicine* website two months ago. It's a study of histopathologists' levels of agreement in interpreting breast biopsy slides. For definite normals and definite cancers, agreement was over 90%. But for the kinds of change that are lumped as ductal carcinoma in situ (DCIS), concordance was fuzzier: 18.5% of samples were overinterpreted and 11.8% underinterpreted. And for "atypia," the figures were 53.6% and 8.6%, respectively. Almost all these biopsies were done as a result of mammography. The National Health Service still encourages women to have mammography by running an opt-out rather than opt-in system. It seems to me that it should now ensure that any biopsy reported as showing atypia or DCIS should be read by three histopathologists. But the fact is that we don't know the clinical course of these abnormalities so we'll still end up overdiagnosing a great number of women who would have done perfectly well without mastectomy, radiotherapy, chemotherapy, and hormone therapy.

Ann Intern Med 2016, doi:10.7326/M15-0964

Progesterone doesn't prevent preterm birth

OPPTIMUM is a rather vainglorious acronym for a trial, but for once I won't complain. This is just about as good as it gets. The trial was based in NHS hospitals with one Swedish outlier, and publicly funded. It was perfectly designed and powered to answer a simple and important clinical question, and here is the result: "Vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes, and had no long term benefit or harm on outcomes in children at 2 years of age." That's it.

Lancet 2016, doi:10.1016/S0140-6736(16)00350-0

Predicting cardiovascular disease

ORIGINAL RESEARCH Systematic review

Prediction models for cardiovascular disease risk in the general population

Damen JAAG, Hooft L, Schuit E, et al

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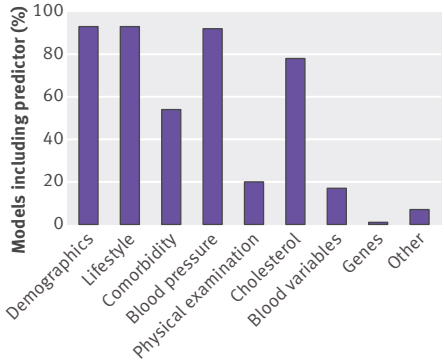
Find this at: http://dx.doi.org/10.1136/bmj.i2416

Study question What models for prediction of cardiovascular disease (CVD) in the general population exist, how many have been externally validated, and what are their predictive performances?

Methods The authors searched Medline and Embase until June 2013 for studies describing the development or external validation of a multivariable model for CVD risk prediction in the general population.

Study answer and limitations In 212 included articles, the development of 363 prediction models and 473 external validations were described. Most models were developed in Europe (n=167, 46%), predicted risk of coronary heart disease (n=118, 33%), and covered a 10 year period (n=209, 58%). The most common predictors were smoking (n=325, 90%) and age (n=321, 88%), and most of the models were sex specific (n=250, 69%). Substantial heterogeneity in predictor and outcome definitions was observed. For 92 models (25%) crucial information was missing to actually use the model for individual risk prediction. Only 132 models (36%) were externally validated. A limitation of this study was the exclusion of non-English articles, which might have affected the geographical representation.

What this study adds There is an excess of models predicting CVD in the general population and the usefulness of most models remains unclear owing to methodological shortcomings, incomplete presentation, and lack of external validation. Rather than developing yet another similar CVD risk prediction model, future research should focus on external validation and head-to-head comparisons of existing CVD risk models, tailoring these models to local settings, and investigating whether these models can be extended by the addition of new predictors.



Predictors included in developed models

Funding, competing interests, data sharing This study was supported by grants from The Netherlands Organization for Scientific Research, Dutch Heart Foundation, and Cochrane Collaboration, by MRC grant G1100513, and the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement No 279233. The authors have no competing interests. No additional data are available.

COMMENTARY An over-abundance of risk models offering few real benefits to patients

Cardiovascular disease remains a major global threat despite a progressively reducing incidence and case fatality for myocardial infarction and stroke. Development of preventive interventions led to a plethora of prediction models designed to identify those at risk and target interventions at those most likely to benefit. Existing models are summarised in the linked systematic review by Damen and colleagues.[1]

Too many models

They identified 363 models reported in 212 papers, and a high proportion contained methodological errors. Why are there so many? Risk prediction for CVD began in 1948 with the Framingham model from Massachusetts.[2,3] Over the years it became increasingly apparent that this model's performance was suboptimal in modern populations outside the USA. Dominated by white middle class males, the Framingham cohort was no longer sufficiently relevant to 21st century Europe. Globally, the growth of previously undeveloped market economies and the dispersal of peoples away from their regions of origin triggered further attempts either to modify existing algorithms for different regions or to start from scratch.

> CVD risk is an ideal condition on which to test new statistical techniques, whether or not there is any clinical justification

New risk factors were identified that were not included in the original Framingham model, and new modelling approaches became available. CVD events are generally discrete and well documented, so CVD risk is an ideal condition on which to test new statistical techniques, whether or not there is any clinical justification to do so. Other opportunities included new data sources, such as the large primary care population supporting the derivation of QRISK2.[4] The ability to link or combine separate data sources has enormously increased the power of observational research in a way unavailable to previous generations, to the benefit of CVD risk modelling.

Too little benefit

For some individuals, identification of CVD risk might trigger more healthy behaviour, or access to preventive drug treatment. For others, the identification of risk may represent a medicalisation of normality, which turns people into patients, adversely affects self image and life insurance premiums, and exposes large numbers of people to the side effects of drugs, for the benefit of just a few. Programmes aiming to assess systematically the CVD risk of healthy people have so far proved frustratingly ineffective at improving hard clinical outcomes such as CVD incidence.[6] Damen and colleagues conclude that head-to-head comparisons of promising algorithms would be more beneficial than deriving new ones, and that as novel risk factors are identified, researchers should evaluate what they add to existing models. Most importantly, we need to translate CVD risk recognition into tangible and measurable clinical benefit for patients and the public.

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Late mortality after sepsis

ORIGINAL RESEARCH
Propensity matched cohort study

Late mortality after sepsis

Prescott HC, Osterholzer JJ, Langa KM, Angus DA, Iwashyna TJ

Cite this as: *BMJ* 2016;353:i2375
Find this at: http://dx.doi.org/10.1136/bmj.i2375

Study question Is late mortality after sepsis driven predominantly by pre-existing comorbid disease or is it also the result of sepsis itself?

Methods In this observational cohort study, US Health and Retirement Study participants (1998-2010) with fee-for-service Medicare coverage who were admitted to hospital with sepsis were matched 1:1 by pre-illness state to 777 adults not currently in hospital, 788 patients admitted with non-sepsis infection, and 504 patients admitted with acute sterile inflammatory conditions. The primary outcome was late mortality (31 days to two years). We also measured odds of death at multiple intervals to determine how long excess mortality persists after sepsis.

Study answer and limitations Sepsis was associated with a 22.1% (95% confidence interval 17.5% to 26.7%) absolute increase in late mortality relative to adults not in hospital, a 10.4% (5.4% to 15.4%) absolute increase relative to patients admitted with non-sepsis infection, and a 16.2% (10.2% to 22.2%) absolute increase relative to patients admitted with sterile inflammatory conditions (P<0.001 for each comparison). Mortality remained higher for at least two years relative to adults not in hospital. Limitations were that patients aged <65 were excluded, and sepsis was ascertained from Medicare claims, representing the diagnosis used in clinical practice.

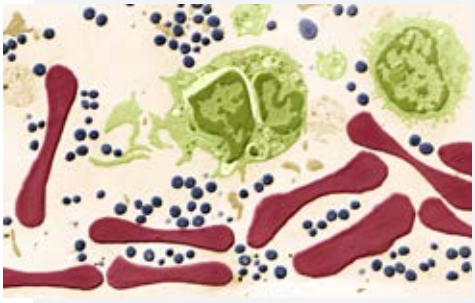
What this study adds More than one in five patients who survives sepsis has a late death not explained by health status before sepsis.

Funding, competing interests, data sharing This work was supported by grants from the National Institutes of Health and the US Department of Veterans Affairs Health Services Research and Development Service. The authors have no competing interests. Additional statistical code is available on request.

COMMENTARY
Downstream effects of sepsis include unexplained late deaths

Sepsis is an extreme manifestation of the body responding to a severe infection—in part adaptive and protective, but potentially maladaptive and life threatening. Prescott and colleagues report that patients who survive an episode of sepsis have a significant excess risk of mortality for a prolonged period of time.[4]

For substantial numbers of patients, leaving the intensive care unit does not represent the end of something, rather it represents the start of something else, often not anticipated by them or understood by others. Many studies have described the difficulties experienced by patients and their families including loss of muscle mass and strength,[5] cognitive dysfunction, anxiety and depression,[6] and post-traumatic stress.[7] Along with this come challenges, both medical and financial, for those who become informal caregivers.[8 9] In the UK this has been addressed, at least in ambition, with the publication of NICE guidelines for rehabilitation after critical illness.[10]



EYE OF SCIENCE/SPL

Bacterial infection can lead to sepsis

Prescott and colleagues identified an excess mortality associated with sepsis that persisted for the full two years of follow-up in some comparisons. Though it is always possible that some unidentified confounder has contributed to an inaccurate result, it is difficult to see how this particular research question could have been approached in an alternative or more rigorous way. Important unanswered questions remain, however. Does this apparent late mortality extend to patients aged under 65? What are the mechanisms? From what do people actually die? Finally, what could be done to ameliorate this excess risk? The paper contains some intriguing data on "terminal admissions," which seemed dominated by diagnoses related to infection; sepsis can reappear in people whose constitution has been eroded by previous critical illness.[11]

> Leaving the intensive care unit does not represent the end of something, rather it represents the start of something else

A long shadow

Those of us who follow up patients after a period in intensive care are often impressed by their resilience. However, we also see many people whose general robustness seems seriously diminished and who apparently lack the necessary strength to withstand any further major challenges to their health. Such individuals commonly require substantial amounts of assistance with activities of daily living, have a reduced quality of life, and do not seem to have the necessary capacity to recover their pre-illness functional status. The authors speculate that accelerated cardiovascular pathology could be a contributing factor. This is certainly plausible, as is the potential contribution of a persistent inflammatory (and possibly immunosuppressed) phenotype.[12]

What should we do with this new information? Perhaps we need to educate healthcare professionals in both primary and secondary care, along with patients and the wider public, about these downstream effects of sepsis, in a similar way to the educational efforts currently being expended on presentation and early treatment[2] (www.sepsistrust.org). Prescott and colleagues have done well to identify this issue from a system not prospectively designed for this purpose. With several "big data" initiatives developing, and the potential to link data on acute illness with future community healthcare information, we might soon be in a position to set up prospective registries of critical illnesses such as sepsis and hence understand the long term risks in more detail.

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ORIGINAL RESEARCH Cross sectional study

Regulatory approval of new medical devices

Marcus HJ, Payne CJ, Hughes-Hallett A, et al

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Find this at: http://dx.doi.org/10.1136/bmj.i2587

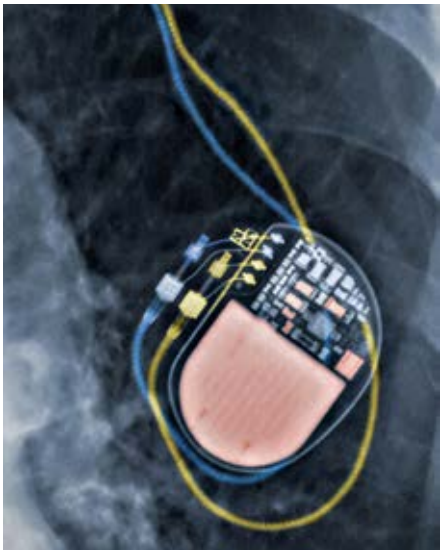
Study question How do new medical devices secure regulatory approval?

Methods In this cross sectional study, PubMed databases were searched between 1 January 2000 and 31 December 2004 for clinical studies of new medical devices. The authors then searched the medical device databases of the US Food and Drug Administration for clearance or approval relevant to these devices.

Study answer and limitations 5574 titles and abstracts were screened, 493 full text articles assessed for eligibility, and 218 clinical studies of new medical devices included. In all, 99/218 (45%) of the devices described in clinical studies ultimately received regulatory clearance or approval. These included 510(k) clearance for devices determined to be substantially equivalent to another legally marketed device (78/99; 79%), premarket approval for high risk devices (eg, heart pumps) (17/99; 17%), and others (4/99; 4%). Of these, 43 devices (43/99; 43%) were actually cleared or approved before a clinical study was published. This study has several limitations, including restriction of the analysis to clinical studies of new medical devices reported in the biomedical literature, and using only the FDA medical device databases.

What this study adds A multitude of new medical devices were identified in clinical studies, almost half of which received regulatory clearance or approval. The 510(k) pathway was most commonly used, and clearance often preceded the first published clinical study.

Funding, competing interests, data sharing HJM was supported by an Imperial College Wellcome Trust clinical fellowship, and CJP was supported by a Wates Foundation fellowship. The authors have no competing interests or additional data to share.



APOGEE/SPL

FDA PROCESSES

- **510(k)** A premarketing submission to demonstrate that a device is as safe and effective—that is, "substantially equivalent"—to a legally marketed device; for example, fetal heart monitor
- **Premarket approval (PMA)** Contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use or uses; for example, implantable cardiac defibrillator
- **Humanitarian device exemption (HDE)** Similar to premarket approval but with exemption from the effectiveness requirements; it is intended for devices that benefit patients with rare disease; for example, radioactive microspheres for cancer treatment

ORIGINAL RESEARCH New initiator cohort study

Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation

Wang SV, Franklin JM, Glynn RJ, Schneeweiss S, Eddings W, Gagne JJ

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Find this at: http://dx.doi.org/10.1136/bmj.i2607

Study question What are the expected rates of thromboembolism and major bleeding for a given patient if that patient were to initiate treatment with dabigatran or warfarin as part of routine care?

Methods A cohort study included 21 934 patients with atrial fibrillation who initiated dabigatran or warfarin. Information on these patients was taken from a commercial healthcare claims database in the United States (2009-13). Within this cohort, cross validated models were developed to predict rates of thromboembolism and major bleeding, based on risk factors included in $CHADS_2$ and HAS-BLED scores, respectively. Information on stratified event rates during relevant treatment was also extracted from publications of major randomized controlled trials.

Study answer and limitations Overall, annual event rates per 100 patients were 1.7 for thromboembolism and 4.6 for major bleeding. For thromboembolism, calibration of estimates from a randomized controlled trial was similar to calibration of model based predictions. However, trial estimates for major bleeding consistently underestimated the rate of bleeding among patients in routine care. This was particularly pronounced in warfarin initiators with high HAS-BLED scores (event rates underestimated by up to 4.0 major bleeds per 100 patient years). The study was limited by potential under-recording and inability to measure important clinical variables not typically captured in claims data, short average duration of treatment observed in routine care patients, as well as the small number of outcomes in dabigatran initiators during the study period.

What this study adds Accurate estimates of risk under alternative treatments can inform treatment choice. Models developed and validated using observational data performed as well as randomized controlled trials at predicting the rate of thromboembolism, and better than trials at predicting the rate of major bleeding among patients initiating dabigatran or warfarin as part of routine care.

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