All you need to read in the other general medical journals
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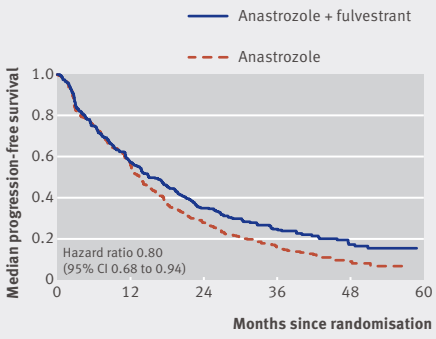
"The name of John Taylor will live forever in the annals of musical infamy, for he was the cataract surgeon who managed to blind Handel and kill J S Bach"
Richard Lehman's blog at www.bmj.com/blogs

Combination of drugs prolongs survival for women with metastatic breast cancer

Progression-free survival according to treatment



Adapted from *N Engl J Med* 2012;367:435-44

Compared with a regimen of giving anastrozole alone and exchanging it for fulvestrant if disease progresses, both drugs given together from the start improved progression-free survival by a month and a half and overall survival by six months in women with metastatic breast cancer.

Participants in this phase III trial were 694 postmenopausal women with hormone receptor positive metastatic breast cancer (oestrogen or progesterone receptor positive, or both). Anastrozole inhibits the synthesis of oestrogen and is taken orally each day, whereas fulvestrant acts at the oestrogen receptor and is given in monthly injections. None of the women had metastases in the central nervous system or had previously been treated for breast cancer, other than with tamoxifen.

In women who received the single drugs, median survival without disease progression was 13.5 months, compared with 15.0 months in women allocated combination treatment. For overall survival—a prespecified secondary outcome—these figures were 41.3 months and 47.7 months, respectively.

Three deaths that may have been associated with treatment occurred in the combination drug group, compared with none in the single drug arm. In the two groups, 11 and four patients, respectively, stopped treatment early because of toxic effects. Although severe adverse events were more common with combination treatment (46/346 *v* 38/332 with single drug treatment), the difference wasn't significant.
N Engl J Med 2012;367:435-44

VTE is most common in patients with cancer of the brain and pancreas

One in five deaths from venous thromboembolism (VTE) is in people with cancer. A systematic review of cohort studies quantified the risks associated with eight common types of cancer. Forty six papers that reported on 38 studies were eligible for inclusion. Participants in 31 studies were classified as high risk, because they had metastases or were receiving certain treatments, whereas participants in seven studies were considered to be at average risk.

The pooled incidence of venous thromboembolism for the high risk and average risk groups was estimated at 68 (95% CI 48 to 96) and 13 (7 to 23) per 1000 person years, respectively. However, the risks varied greatly with the type of cancer. In the high risk group, people with brain cancer had the highest risk of experiencing VTE over a year (20%), followed by those with pancreatic cancer (15.5%). Among people with average background risk, VTE was most common in those with pancreatic cancer (5.9% over a year) and brain cancer (4.8%). The lowest risk in the average risk group was for breast cancer (only 0.5%), but in women with breast cancer in the high background risk group, as many as 5.5% might experience venous thromboembolism within a year.

The authors call for a more evidence based approach to preventing thromboembolic events in people with cancer. Doctors should now have a better idea of whom to give prophylaxis and when.
PLoS Med 2012;9:e1001275

Obesity paradox holds in people who develop type 2 diabetes despite normal weight

We know that in some chronic diseases, such as heart failure and chronic kidney disease, people of normal weight die, on average, sooner than those who are overweight. The same has been shown for people whose body weight was normal at the time they were diagnosed as having type 2 diabetes.

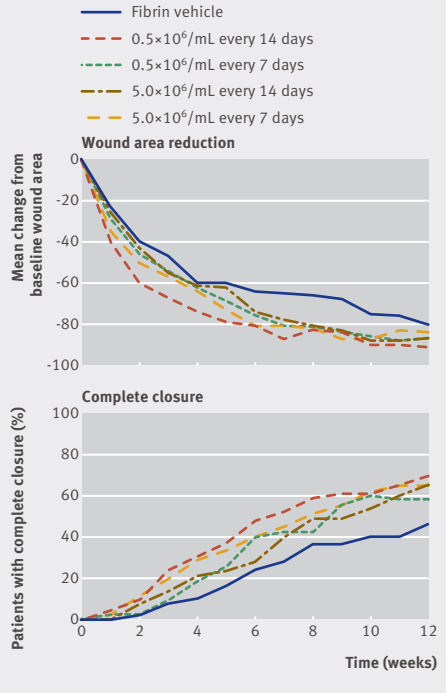
The data came from five large US cohort studies. Diabetes was newly detected in 2625 people, of whom 449 died during more than 27 000 person years of follow-up. Across studies, 9-21% (mean 12%) of people were of normal weight at the time of diagnosis. Mortality rates were consistently higher in these people than in participants with a body mass index of 25 or more. In people of normal weight, total mortality, cardiovascular mortality, and non-cardiovascular mortality were 284.8, 99.8, and 198.1 per 10 000 person years, respectively, compared with 152.1, 67.8, and 87.9 per 10 000 person years for those who were overweight or obese. After adjustment for demographic data and cardiovascular risks, people with normal weight had double the risk of dying of any cause, compared with those who were overweight or obese. Risks for cardiovascular and non-cardiovascular mortality were increased 1.5-fold and 2.3-fold, respectively.

Poor cardiorespiratory fitness and physical inactivity may pose a greater threat to health than obesity, write the editorialists (p 619).
JAMA 2012;308:581-90

A cell based spray shows promise for leg ulcers

A spray containing human keratinocytes and fibroblasts—derived from neonatal foreskin—was tested as a treatment for chronic venous

Effect of cells on healing of chronic leg ulcers



Adapted from *Lancet* 2012;doi:http://dx.doi.org/10.1016/S0140-6736(12)60644-8

leg ulcers in a phase II placebo controlled dose finding trial. The trial comprised 228 patients from 28 centres in the US and Canada. Participants had up to three leg ulcers that measured 2-12 cm^2 and had persisted for 6-104 weeks, despite standard compression treatment. As part of the study, all participants also received four layer compression bandages.

Of the four doses tested against vehicle, the lowest dose (0.5×10^6 cells/mL every 14 days) was most effective. With vehicle alone, 23 of 50 (46%) patients had ulcer closure at three months. For the most effective dose this was 32 of 46 (70%), with a 16% greater mean reduction in the wound area compared with vehicle alone. Adverse events, few of which were serious, were distributed evenly between the groups.

The treatment will probably be cost effective in the long term, and it could help with other types of chronic wounds, such as ischaemic or diabetic ulcers, write the editorialists (doi:http://dx.doi.org/10.1016/S0140-6736(12)61255-0).

Lancet 2012; doi:http://dx.doi.org/10.1016/S0140-6736(12)60644-8

Little evidence informs device regulation practices

A systematic review found only 20 studies that provide empirical evidence on which to base changes in how the US and the European Union regulate medical devices. These two markets are extremely lucrative for the industry, which has global revenues of more than $350bn (£225bn; €285bn) a year. Recent high profile recalls of devices such as artificial hips and breast implants have prompted calls for better approval practices as well as post-marketing surveillance.

Nine studies examined pre-market practices, four of which looked at the evidence on which devices are approved. It turns out that for two out of three devices, only a single, often small study is available, using only surrogate outcomes, and lacking a randomised comparison group. Only 14% of these studies were blinded. Major limitations were also found for post-marketing surveillance processes in a further eight studies that focused on recalls of devices. Finally, three surveys of manufacturers' views suggest approval processes in the EU are less stringent and less costly in terms of time and money than US practices.

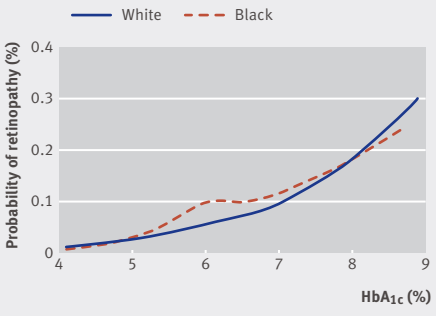
Few conclusions can be drawn from this sparse evidence base. In the US, the Food and Drug Administration needs to follow up on its promise to single out high risk devices and improve post-marketing surveillance, especially for devices that had been approved on particularly poor evidence. Relying on recalls to assess the safety of individual devices or classes of devices is fundamentally flawed, and a better system needs to be put in place. In the EU, greater transparency is needed, as well as post-marketing surveillance.

The systems will probably soon go through changes. These need to be accompanied by more and better quantitative research to guide further improvements in the years to come.

PLoS Med 2012;9:e1001276

No rationale for ethnicity specific HbA_{1c} cut offs in diagnosing diabetes

Association between HbA_{1c} and probability of retinopathy in black and white populations



Adapted from *Ann Intern Med* 2012;157:153-9

At any given concentration of blood glucose, black people will have higher levels of glycated haemoglobin (HbA_{1c}) than white people. Such observations have fuelled the proposals to raise the cut-off value at which diabetes is diagnosed in black people. However, the occurrence of diabetic retinopathy is considered the best criterion for comparing glycaemic measures, and it has been used to set the current cut off for diagnosing diabetes ($HbA_{1c}\geq6\%$ irrespective of ethnicity).

As it turns out, diabetic retinopathy occurs in black people at lower concentrations of HbA_{1c} than it does in white people. This was found in a series of US national health surveys, which contained data on 2804 white people and 1008 black people aged 40 years or more. For any value of HbA_{1c} between 5.0% and 7.0%, retinopathy was more common in black than in white people. Its prevalence was as common in black people with HbA_{1c} between 5.5% and 5.9% as it was in whites with HbA_{1c} between 6.0% and 6.4%.

It is not clear whether the results are due to a real biological difference, or possibly residual confounding by sociobehavioural factors, which might include access to care. The present analysis was adjusted only for age, sex, hypertension, body mass index, and family history of diabetes.

The researchers also estimated that, if the diagnostic cut off was lowered from the current 6.5% to 6.0%, an additional 1.8 million black and 7.6 million white US adults aged 40 or more would be diagnosed as having diabetes. To detect one additional case of retinopathy, nine new diagnoses of diabetes would be made.

Future studies should evaluate whether the diagnostic threshold for diabetes should be lower in black people. For now, however, the diagnostic criteria should not change.

Ann Intern Med 2012;157:153-9

The ethical identity of some doctors is well aligned with that of drug companies

That most industry sponsored drug trials are now headed by private doctors rather than their academic colleagues is not in itself a problem. However, the ethics of these doctors may be questionable.

Semi-structured interviews lasting on average 40 minutes were conducted in 25 private research clinics in two US cities. Participants were 12 primary investigators, 18 coordinators, and three recruiters, as well as seven non-physician staff, 14 trial participants, and nine people working for drug companies.

As might be expected, doctors cited extra revenue as the main reason for regularly doing industry sponsored drug trials. Research brings in more money than clinical work, and delegating work to other staff can save time. Although things such as intellectual rewards, higher professional status, and benefits to patients and the public were also mentioned, most doctors viewed conducting trials as a business rather than science. These doctors attended different conferences and sessions from those attended by academic doctors, generally business related ones rather than research or clinically related ones. None of the primary investigators participated in data analysis or writing up a report. Nine out of 11 stated they regularly headed trials in areas of medicine for which they didn't have specialty training.

Worryingly, when asked about ethics, none of the interviewed doctors thought to mention their responsibility to patients. Instead, they thought their responsibility was to drug companies to diligently follow the protocols. Moreover, they placed trust in the ethics of drug companies which, some doctors thought, must believe in what they are doing because of the investments they made.

Data collection for this study was done nearly a decade ago. Perhaps things have improved since then.

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