Our suggested randomised design to evaluate drugs courts has limitations. Offenders who enter no or a delayed plea (about 20%) are not eligible. How judges are chosen for the drugs court also matters when extrapolating from the randomised evidence-base: fewer, and perhaps more senior, judges may preside in a drugs court than in conventional courts, where either a judge or magistrates sit.

Medicines of proven efficacy are only provided to patients in the UK's National Health Service if the drugs are cost effective. UK justice needs equivalent appraisal in its use of public funds. Speedier and more effective sentencing in drugs courts—in terms of reduced recidivism—might offset greater organisational and judicial costs. Additionally, recovery from drug dependency may save injectors' lives or reduce claims for welfare benefits. The a-priori case for affordability, and hence for evaluation, would need to be determined and be explicit in the study protocol.

Finding out about effectiveness for recidivism would mean randomising 700–900 offenders to have 80% power to discern a reduction in 2-year recidivism from 70% to 60%, and ten times as many to discern even a one-third reduction in 2-year mortality from 3% to 2%. Assuming only 180 eligible randomised clients in each of the four jurisdictions where drugs courts are planned, one-third of them assigned to the drugs court, should give answers on 2-year recidivism well within 4 years; answers on mortality would take much longer.

Drugs-court evaluations need the discipline of a well-written protocol. Ministers cannot duck the mathematics of numbers needed to neutralise the play of chance. Criminal justice should stop playing at evaluation, and recognise evidential rigour.[12]

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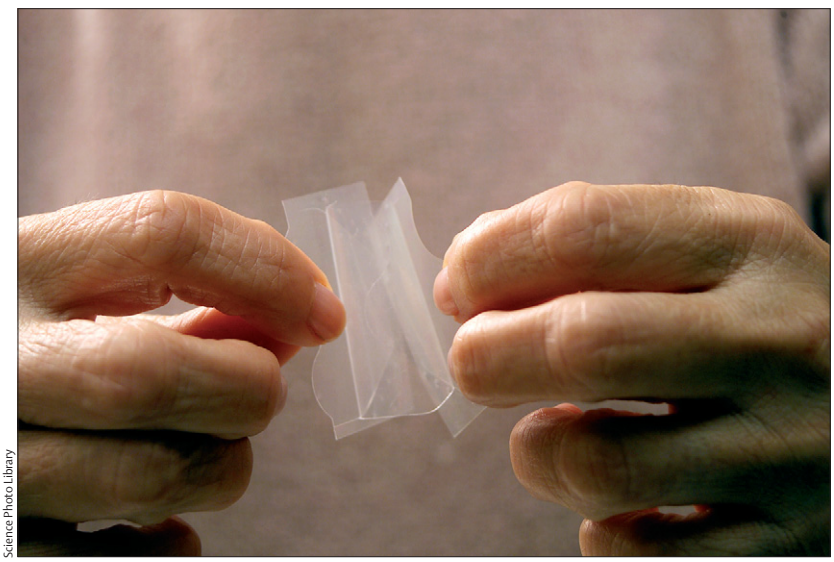
The HRT controversy: observational studies and RCTs fall in line

For several years, we witnessed a disarraying debate about the conflicting messages between observational studies and randomised trials on the effect of hormone replacement therapy (HRT) on coronary heart disease and breast cancer. HRT seemed protective for coronary heart disease in observational studies, but randomised trials found an increase of coronary heart disease in the first years of use.[1] For breast cancer, combined oestrogen-progestin showed a lesser risk in the large Women's Health Initiative randomised trial than in observational studies such as the Million Women Study.[2,3] Unopposed oestrogens had a smaller breast cancer risk than combined preparations in observational studies, but carried no risk in the trial.[4] Observational research suffered a credibility crisis.

Recent reanalyses have brought the results from observational and randomised studies into line. The results



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are surprising. Neither design held superior truth. The reasons for the discrepancies were rooted in the timing of HRT and not in differences in study design.

For coronary heart disease, the results of observational data and trials fell in line, mainly by analysing the data according to time since start of HRT.[1,5,6] For randomised trials, this is the natural analysis because therapy starts at randomisation. In the Women's Health Initiative and other trials, the first years of hormone replacement by combined oestrogen-progestin did increase coronary heart disease, which then waned. The analysis of the observational studies, however, had mostly been a contrast between current users at the time of enrolment to never users. Most current users were past the window wherein coronary heart disease risk was increased and were in a phase of decreased incidence. When cohort data from the observational part of the Women's Health Initiative were reanalysed according to time since start of therapy, the same pattern emerged of an initial increase in risk, followed by a decrease.[5] Thus nothing was intrinsically wrong with the observational data; what went wrong was an analysis that had not taken into account that the effect of HRT might be different over time. The piece of evidence that closes the case is the recent reanalysis of the Nurses Health Study on combined oestrogen-progestin and coronary heart disease, which finds the same pattern of an initial increase in risk by contrast with the original analysis which showed overall protection.[1] An array of comments followed.[7–12] Whether the decrease in coronary heart disease on continued use is due to deletion of susceptible individuals or a causal effect cannot be learned from these analyses.

For breast cancer, women in the randomised trials had on average been in menopause longer; in the observational study, the women had started HRT closer to menopause. Adjustment for previous use of hormones already increased the estimates in the trials, but the findings of observational and randomised studies fell in line when the reanalyses of the randomised trial data adjusted for the gap between menopause and treatment, showing a clear increase in risk for combined preparations and a slight increase for unopposed oestrogens.[2,4] The observational studies had picked up a true signal for the women closer to menopause. In the randomised trial, that signal was diluted because fewer women close to menopause were enrolled. The signal is important for daily practice, because HRT is usually started close to menopause. Again, the discrepancies were not due to differences in study design, but to the timing of start of treatment relative to menopause.

The randomised trials had it right for coronary heart disease but failed to sufficiently focus on women close to menopause for breast cancer. The main reasons for the discrepancies were changes of the effects of HRT over different times: time from start of therapy and time since menopause. In the reanalyses, adjustments for standard risk factors had some additional effects, but did not clinch the analyses as much as the two principal interactions with time. A lesser effect of time since menopause was also seen for coronary heart disease: longer time since menopause heightened the risk. For coronary heart disease the effects also differed for oestrogen alone and combined preparations.[6]

The results put an end to years of debate about HRT, coronary heart disease, and breast cancer, but also clarify the debate on the merits of randomised versus observational studies. They show that "observational-randomised discrepancies cannot be automatically attributed to randomisation itself".[1] Still, randomised trials will almost always be necessary to show whether the hoped-for benefit of a medical intervention exists. Our knowledge about HRT and coronary heart disease would be different, were it not for the randomised trials, even if on reanalysis the observational data carried the same message.[9] By contrast, observational research will often suffice to investigate adverse effects.[13] Rarely,

the same adverse effect for the same treatment can be investigated by observational research and in very large randomised trials,[14] as happened with breast cancer and HRT. These comparisons support the notion that observational studies may better reflect the true harm in real-life prescribing than selected populations enrolled in randomised trials.[14]

The resolution of the discrepancies between randomised and observational evidence is not just important for our insight into the merits of both types of research. It directly enlightens our knowledge about HRT by confirming that the cardiovascular risk is real, and slightly stronger in older women, while the breast cancer risk is equally real, and is stronger in women closer to menopause.[9] It was a long and difficult debate, but we owe a tribute to the persons who inspired and have led these reanalyses.

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Sirolimus to replace calcineurin inhibitors? Too early yet

Replacement of ciclosporin and mycophenolate mofetil with sirolimus has been associated with regression of Kaposi's sarcoma in renal transplant recipients on chronic immunosuppression. Disease development parallels reactivation of latent human herpesvirus 8 (HHV-8) or donor-to-recipient transfer of HHV-8-infected progenitor cells. Patrizia Barozzi and colleagues[1] recently reported nine patients with post-transplant Kaposi's sarcoma associated with a lack of HHV-8-specific T cells. In two patients who were switching from calcineurin inhibitors to sirolimus, disease recovery was paralleled by normalisation of the T-cell repertoire and recovery of both HHV-8 specific effector and memory T lymphocytes. Thus sirolimus might achieve remission of Kaposi's sarcoma by restoring a specific immune response against the tumour-associated virus.

Sirolimus is a macrolide with potent immunosuppressive and antiproliferative activity.[2] This drug suppresses interleukin-driven T-cell proliferation by blocking signal-transduction pathways required for the progression of cytokine-stimulated T cells from G_1 to S phase.[2] Early studies in animals showed that sirolimus, unlike calcineurin inhibitors, was devoid of intrinsic nephrotoxicity.[3] Consistently, renal transplant patients on 2-year sirolimus therapy had significantly lower concentrations of serum creatinine than controls on ciclosporin.[4] This attracted special attention to the use of this powerful immunosuppressant to replace ciclosporin and avoid the nephrotoxicity of chronic calcineurin inhibition.[2]

Enthusiasm faded, however, when the US Multicenter Trial showed that sirolimus-treated renal transplant recipients had significantly higher serum creatinine than ciclosporin-treated recipients, despite having fewer rejections.[5] Subsequent studies consistently showed that this effect, first attributed to exacerbation