RESEARCH

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Should we monitor antiretroviral therapy in resource poor settings?

Getting life prolonging antiretroviral drugs into resource poor settings has been the priority; whether to and how to monitor the people taking them are questions that have received less attention. So far only one trial has investigated monitoring options, write Carlos de Rio and Wendy Armstrong (p 1127).

FRANCIS SHEEHAN/SPL

Their commentary accompanies a randomised controlled trial and cost effectiveness analysis of three monitoring strategies for 1096 people receiving ART in Uganda. Mermin and colleagues (p 1134) and Kahn and colleagues (p 1135) compare three strategies: clinical monitoring alone; clinical monitoring and quarterly CD4 count; and clinical monitoring, CD4 count, and viral load.

For UK readers, the contrast with monitoring regimes in the UK will be stark. WHO previously decided against monitoring treatment in resource poor settings, based on the results of the previous trial. But these new studies show that CD4 monitoring reduced adverse outcomes, and that the strategy was cost effective. The addition of viral load testing did not provide a statistically significant benefit over and above CD4 count; and at five times the cost of CD4 testing, the cost effectiveness study does not support its use.

Now policy makers are left to ponder whether antiretroviral therapy should be monitored in a resource poor setting, such as Uganda, or whether the money would be better spent on simply widening access to the drugs.

Evidence for cardiovascular biomarkers: does effect size vary with study design?

TEK IMAGE/SPL

"It is wrong to assume that a biomarker that is (causally) related to incidence of disease (aetiology) is necessarily (causally) related to progression (prognosis). Risk prediction models are easy to produce, hard to validate, and harder still to implement in clinical practice. And, thus far, evidence of impact on decision making or prognosis is nearly always lacking." So said Harry Hemingway and colleagues two years ago in the *BMJ* (2009;339:b4184), in an article that called for, among other things, "clarity over the strength of evidence required for prognostic biomarkers to be considered 'established' or 'useful'."

It's not just the strength of evidence that's up for scrutiny, so is the production of that evidence. Is it better to test the predictive power of biomarkers using observational (cohort and case-control) studies or data from randomised controlled trials? This isn't an esoteric question only for methodologists. It matters to clinicians and patients, because the wrong conclusions about biomarkers could lead to the wrong tests and even the wrong disease management.

Ioanna Tzoulaki and colleagues comprehensively reviewed meta-analyses of biomarkers that might predict cardiovascular disease, coronary heart disease, or cardiovascular mortality (p 1137). Eligible meta-analyses had to include at least one observational study and at least one randomised controlled trial. They found 31 such meta-analyses, and concluded that, on average, cardiovascular biomarkers have less promising results in the evidence derived from randomised controlled trials than from observational studies. In the full version of the paper on bmj.com the authors discuss why this matters; for instance, "If one considered only data from randomised controlled trials, probably neither Lp(a) lipoprotein nor C reactive protein would be considered good biomarkers." It's a cliche, but clearly, more research is needed. Tzoulaki and colleagues suggest that study registration and biobanking could be used to ensure that all datasets are assessed for each emerging biomarker, and not just those that are "in the fridge" of certain investigators. Editorialist Jan Vandenbroucke isn't convinced, however (p 1128)

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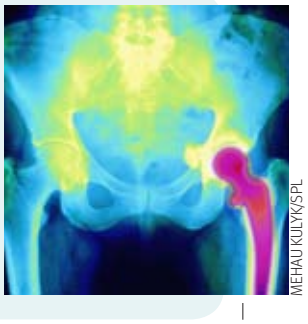
Comparative assessment of implantable hip devices with different bearing surfaces Art Sedrakyan and colleagues systematically appraised evidence about clinical outcomes after hip replacement with various bearing surfaces, including data from the US Food and Drug Administration (doi:10.1136/bmj.d7434).

Effectiveness of strategies incorporating training and support of traditional birth attendants on perinatal and maternal mortality Confirming the findings of randomised controlled trials, this meta-analysis by Amie Wilson and colleagues shows that in developing countries, perinatal and neonatal deaths are significantly reduced with strategies incorporating training and support of traditional birth attendants (doi:10.1136/bmj.d7102).

Statins and prevention of infections Findings of a meta-analysis by Hester van den Hoek and colleagues do not support the hypothesis that statins reduce the risk of infections, as suggested in observational studies (doi:10.1136/bmj.d7281).



MEHAU KULYK/SPL

Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial

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STUDY QUESTION

Does the addition of routine viral load and CD4 cell count monitoring provide clinical benefits to individuals receiving ART in sub-Saharan Africa, above that of providing ART with clinical monitoring alone?

SUMMARY ANSWER

Routine CD4 cell count monitoring was associated with improved health and survival compared with clinical monitoring alone.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Monitoring CD4 cell counts can improve survival in people receiving ART in sub-Saharan Africa. In this study examining whether there is an added benefit of providing viral load testing, there were no significant differences between those patients who received quarterly CD4 cell counts and those who received quarterly CD4 cell counts and viral load measurements.

Design

Adults with HIV and a CD4 count of <250 × 10^6cells/L or World Health Organization stage 3 or 4 were offered ART and randomised to one of three monitoring arms: a viral load arm (clinical monitoring, quarterly CD4 counts, and viral loads); a CD4 arm (clinical monitoring and CD4 counts); or clinical arm (clinical monitoring alone).

Participants and setting

We enrolled 1094 adults with HIV who were members of the AIDS Support Organisation in Tororo, Uganda. The median baseline CD4 count of participants was 129 cells × 10^6/L.

Primary outcome

The first episode of a new serious morbidity or death over a median of three years of follow-up.

Main results and the role of chance

In an intention to treat analysis, 47 people either had at least one serious morbid event or died in the viral load arm, 58 in the CD4 arm, and 72 in the clinical arm. In a Cox proportional hazards model adjusted for baseline age, sex, CD4 cell count, viral load, and body mass index, participants in the clinical arm were more likely to have at least one serious morbid event or die than participants in the viral load arm (7.6 *v* 4.8 per 100 person years; adjusted hazard ratio 1.83, 95% confidence interval 1.25 to 2.69) and the CD4 arm (7.6 *v* 6.0 per 100 person years; 1.49, 1.03 to 2.13). There was no significant difference in the risk of first serious morbid event or death between the CD4 arm and the viral load arm (1.23, 0.82 to 1.84).

Harms

There were no identified harms associated with study participation.

Bias, confounding, and other reasons for caution

The proportion of individuals who experienced two viral loads >500 copies/mL was lower (5.6%) than in most previous reports of ART programmes from sub-Saharan Africa. This could have reduced our ability to detect differences between the study arms.

Generalisability to other populations

This study is probably generalisable to other home based ART programmes in sub-Saharan Africa with a similar programme design. These results could provide reassurance to clinicians and patients in resource limited settings who have access to CD4 cell counts but not viral load testing and support the continued expansion of CD4 cell count monitoring as well as ART.

Study funding/potential competing interests

This study was funded by the US Centers for Disease Control and Prevention, the US Agency for International Development, and the President's Emergency Plan for AIDS Relief.

Trial registration number

Clinical Trials NCT00119093.

Morbidity and death in people with HIV receiving ART in Uganda according to monitoring arm during follow-up

Monitoring	Events/participants	Person years of follow-up	Rate per 100 person years	Adjusted hazard ratio (95% CI)	
				Compared with viral load arm	Compared with CD4 arm
Viral load arm	47/368	979.4	4.8	—	—
CD4 arm	58/371	971.6	6.0	1.23 (0.82 to 1.84)	—
Clinical arm	72/377	950.9	7.6	1.83 (1.25 to 2.69)	1.49 (1.03 to 2.13)

CD4 cell count and viral load monitoring in patients undergoing antiretroviral therapy in Uganda: cost effectiveness study

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EDITORIAL
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STUDY QUESTION

Is it cost effective to add routine monitoring of CD4 cell count and viral load for individuals receiving antiretroviral therapy (ART) in sub-Saharan Africa, compared with providing ART with clinical monitoring alone?

SUMMARY ANSWER

Routine CD4 cell count and clinical monitoring costs $174 (£109, €123) per disability adjusted life year (DALY) averted compared with clinical monitoring alone. Adding routine viral load monitoring costs at least $5000 per DALY averted compared with combined clinical and CD4 count monitoring. By comparison, the WHO standard for "very cost effective" is $500 per DALY averted in Uganda, and for "cost effective" is $1500.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

ART in sub-Saharan Africa costs $500 to $1000 per DALY averted. Previous estimates of the cost effectiveness of laboratory monitoring relied on computer simulation models and varied widely. This analysis based on data from a randomised controlled trial found that adding routine monitoring of CD4 count, by improving clinical outcomes and reducing switching to more expensive antiretroviral drugs, costs less per DALY averted than ART.

Main results

For 100 people starting ART, adding CD4 count monitoring compared with clinical monitoring alone increases costs by $20 458 and averts 117.3 DALYs (cost effectiveness ratio $174 per DALY). Adding viral load monitoring adds $142 458 and averts 27.5 DALYs ($5181 per DALY).

Design

Cost effectiveness analysis: net programme cost (adjusted for changes in medical care costs), divided by the reduction in disease burden (expressed as DALYs averted).

Sources of effectiveness

Clinical effects were derived from a randomised controlled trial of monitoring regimens for home based ART in rural Uganda, for 1094 adults with HIV and a median CD4 count of 129 $\times 10^6$ cells/L. This trial found that routine monitoring of CD4 cell counts improved health and survival compared with clinical monitoring alone, and that viral load monitoring had a small but non-significant clinical benefit.

Data sources

Resource use (personnel, drugs, test kits, other consumables, equipment, and other medical care) was estimated from the trial. Costs were estimated from the randomised controlled trial, local wage rate schedules, and international organisations involved in drug and test kit procurement and pricing. Outcomes were calculated for the three year study and projected 15 years into the future.

Results of sensitivity analysis

With clinical inputs based on the as treated analysis (from 90 days, when laboratory monitoring began), viral load monitoring is more expensive and less effective than other monitoring strategies. The favourable cost effectiveness ratio for clinical/CD4 is robust to uncertainties in individual inputs. For example, halving the cost of test kits decreases the ratio for CD4 counts to $117 and for viral load to $3316. Doubling the cost increases the ratios to $289 and $8911, respectively. Limiting the analysis to the three year trial, the ratio is $307 for clinical/CD4 and rises to $10 257for viral load. In 25% of probabilistic simulations, the clinical/CD4 strategy is less expensive and more effective than adding viral load.

Limitations

We had mortality data only during the three year trial and had to extrapolate for the remaining time horizon. We treated all observed clinical differences as real, even if statistically non-significant, thus assuming a benefit for viral load monitoring in the base case. The study population had high rates of adherence to ART and low rates of virological failure, making generalisation to low adherence populations uncertain.

Study funding /potential competing interests

This study was funded by US Centers for Disease Control and Prevention, Kenya, and US National Institute of Drug Abuse (R01 DA15612).

Incremental costs, DALYS, and cost effectiveness ratios for antiretroviral monitoring study, Tororo and Busia districts, Uganda, 2003-7

	Cost ($)	Incremental cost ($)	DALYs incurred	Incremental DALYs averted	ICER: $ per DALY averted
Clinical	606 260	—	466.4	—	—
Clinical/CD4	626 718	20 458	349.1	117.3	174
Clinical/CD4/viral load	769 177	142 458	321.6	27.5	5181

Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

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STUDY QUESTION

What are the benefits and harms of targeting intensive glycaemic control versus conventional glycaemic control in patients with type 2 diabetes?

SUMMARY ANSWER

Targeting intensive glycaemic control does not seem to reduce all cause mortality in patients with type 2 diabetes but increases the risk of severe hypoglycaemia.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Whether intensive glycaemic control reduces the risk of death, macrovascular disease, or microvascular disease in patients with type 2 diabetes is uncertain. Sufficient evidence exists for an absence of a 10% relative risk reduction in all cause mortality, as well as for a 30% increase in the risk of severe hypoglycaemia, with intensive versus conventional glycaemic control.

Selection criteria for studies

We included randomised clinical trials in patients with type 2 diabetes comparing targeting intensive glycaemic control versus conventional glycaemic control.

Primary outcome(s)

The main outcomes were all cause mortality and cardiovascular mortality in patients with type 2 diabetes.

Main results and role of chance

We included 14 clinical trials that randomised 28 614 participants with type 2 diabetes (15 269 to intensive control and 13 345 to conventional control). We found no significant effect on all cause mortality for intensive glycaemic control compared with conventional glycaemic control (relative risk 1.02, 95% confidence interval 0.91 to 1.13; P=0.74). Trial sequential analysis (TSA) adjusting for sparse number of randomised patients and repetitive testing showed that only 28 149 of the heterogeneity adjusted required information size of 46 677 patients were accrued. Meta-analysis of 12 trials did not show a statistically significant effect of intensive glycaemic control on cardiovascular mortality (relative risk 1.11, 0.92 to 1.35; P=0.27). TSA showed that only 22% of the heterogeneity adjusted required information size to detect or reject a 10% relative risk reduction was actually accrued. Intensive glycaemic control may reduce the risk of non-fatal myocardial infarction (0.85, 0.76 to 0.95; P=0.004), but TSA did not confirm this finding. Intensive glycaemic control led to a reduction in the composite microvascular outcome (0.88, 0.79 to 0.97; P=0.01), but TSA showed that sufficient evidence was not reached. Intensive glycaemic control significantly increased the risk of severe hypoglycaemia (2.39, 1.71 to 3.34; P<0.001), although heterogeneity was substantial (I^2=73%; P=0.005). TSA showed sufficient evidence for a 30% increase in relative risk of severe hypoglycaemia when intensive glycaemic control is targeted.

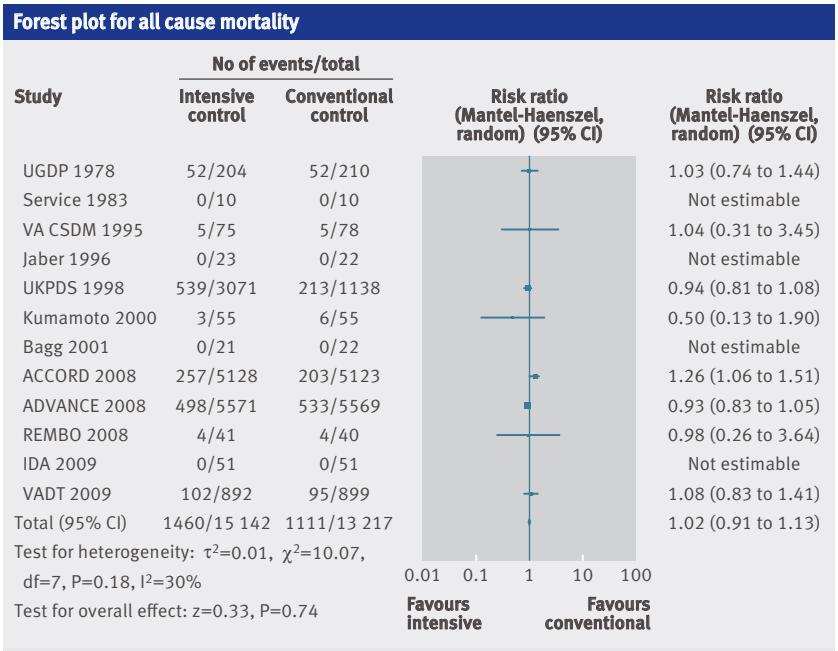
Bias, confounding, and other reasons for caution

Six of the 14 included trials were classified as having a low risk of bias on the basis of sequence generation, allocation concealment, and blinding. Seven of the trials had risks of selective outcome reporting bias. Differences existed between the glycaemic targets as well as the anti-diabetes interventions used to achieve the target in the trials. The participants in the included trials were heterogeneous.

Study funding/potential competing interests

The study was funded by the Copenhagen Trial Unit, Rigshospitalet, Denmark; the Cochrane Metabolic and Endocrine Disorders Group, Germany; and the Copenhagen Insulin and Metformin Therapy Group. SSL, AV, and TA have reported equity in Novo Nordisk A/S. SSL and AV have received fees from Novo Nordisk A/S for speaking. TA is employed at Steno Diabetes Center, Gentofte, Denmark, as were AV and SSL at the time the review was written. Steno Diabetes Center is an academic institution owned by Novo Nordisk A/S. CH has been employed at Novo Nordisk after completion of the data extraction.

Forest plot for all cause mortality



Prognostic effect size of cardiovascular biomarkers in datasets from observational studies versus randomised trials: meta-epidemiology study

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EDITORIAL by Vandenbroucke

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STUDY QUESTION

Do the reported effect sizes of cardiovascular biomarkers differ between datasets from observational studies and those from randomised controlled trials?

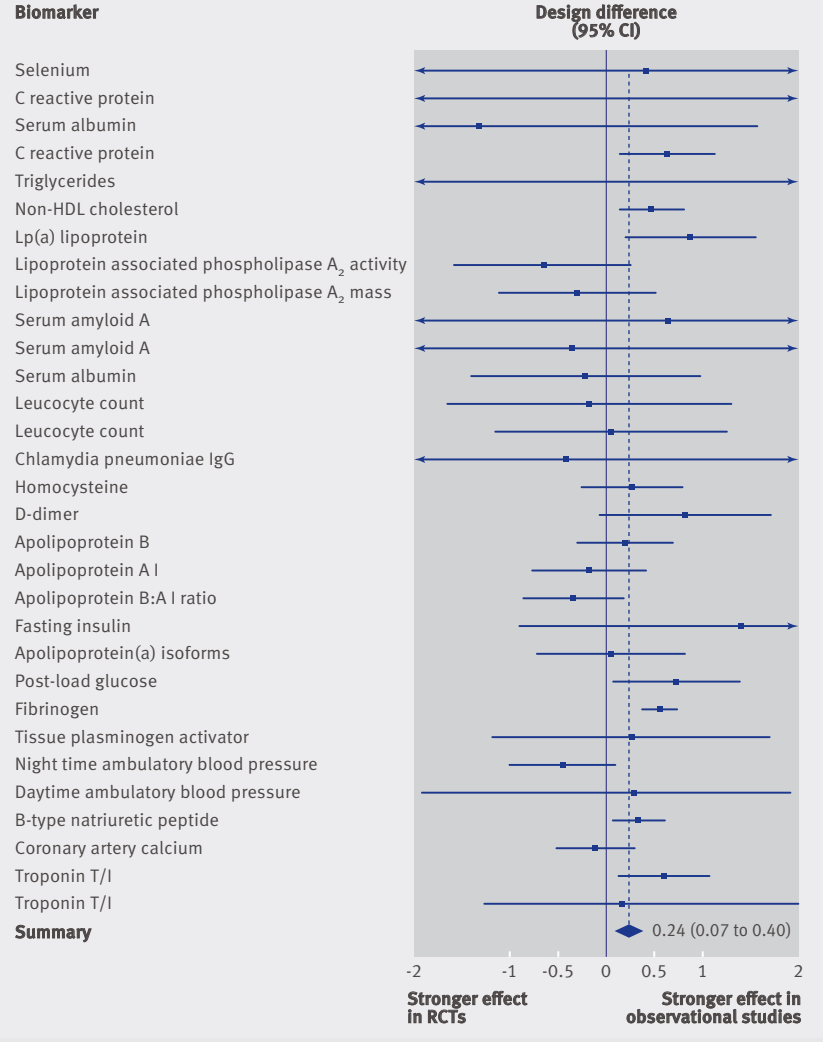
SUMMARY ANSWER

Effect sizes of cardiovascular biomarkers were on average stronger in datasets derived from observational studies than in datasets from randomised controlled trials

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Several cardiovascular disease biomarkers are possible disease predictors, but there is uncertainty about their effect size and their ability to improve prediction. Here we showed that cardiovascular biomarkers often have less promising results in evidence derived from randomised controlled trials than from observational studies.

Comparison of effect sizes from observational studies v randomised controlled trials



Selection criteria for studies

We performed a comprehensive review of meta-analyses of emerging cardiovascular biomarkers (not part of the Framingham risk score) that included datasets from at least one observational study and at least one randomised controlled trial. Meta-analyses were identified through Medline. Biomarkers were eligible regardless of whether they were derived from blood, urine, tissue, or imaging. We excluded meta-analyses of single common genetic variants.

Primary outcome(s)

We performed a review of meta-analyses with end points of cardiovascular disease, coronary heart disease, or cardiovascular mortality.

Main results and role of chance

We identified 31 eligible meta-analyses. The relative relative risk estimate was >1 (suggesting a stronger effect in datasets from observational studies than in those from randomised controlled trials, design difference >0) in 19 out of 31 meta-analyses. For seven major biomarkers (C reactive protein, non-HDL cholesterol, lipoprotein(a), post-load glucose, fibrinogen, B-type natriuretic peptide, and troponins) the prognostic effect was significantly stronger in datasets from observational studies than in datasets from randomised controlled trials. For five of them the effect was less than half as strong in the randomised controlled trial datasets. Across all 31 meta-analyses, on average datasets from observational studies suggested larger prognostic effects than those from randomised controlled trials; from a random effects meta-analysis the estimated average difference in the effect size was 24% (95% CI 7% to 40%), showing that the difference in the effect size amounted to almost a quarter of the overall effect of the biomarker. Based on random effects calculations, the design difference did not differ beyond chance when analyses were performed according to type of observational study, type of meta-analysis, type of randomised controlled trial, statistical significance of the biomarker, and whether the biomarker was recommended for clinical practice.

Bias, confounding, and other reasons for caution

It is unclear whether the results can be extended to any tested biomarker, including those that have only one or a few studies reported on them. However, we studied biomarkers with strong presence in the literature.

Study funding/potential competing interests

We had no funding for this study, and no competing interests.