FAST TRACK

Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial

South East Asia Infectious Disease Clinical Research Network

EDITORIAL by Barr and Hurt

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- Research: Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1 9 (*BMJ* 2010;341:c4779)
- Editorial: Tamiflu: 14 flu seasons and still questions (*BMJ* 2013;346:f547)

STUDY QUESTION Are treatment guidelines correct to recommend higher than standard doses of oseltamivir in patients with severe influenza?

SUMMARY ANSWER Double dose oseltamivir has no virological or clinical advantages over standard dose in patients with severe influenza admitted to hospital.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Oseltamivir has clinical and virological benefit particularly when administered within 48 hours of onset of symptoms and is associated with reduced mortality and shorter length of hospital stay. Though several authorities have suggested the use of double doses for patients with severe influenza, this large randomised trial in patients admitted to hospital with severe influenza showed no clinical or virological benefit of double dose oseltamivir over standard dose.

Design

Double blind randomised trial. Clinical Trials NCT00298233.

Participants and setting

Patients aged ≥1 with confirmed severe influenza. Thirteen hospitals in Indonesia, Singapore, Thailand, and Vietnam.

Primary outcome

Viral status according to reverse transcriptase polymerase chain reaction (RT-PCR) for influenza RNA in nasal and throat swabs on day five.

Effect of dose on measures of respiratory compromise, expressed as Kaplan Meier estimates (95% CI)

	Double dose	Standard dose	P value*
Receipt of oxygen			
Median (IQR) time (days)	3 (2-5)	3.5 (2-7)	0.48†
No of patients	50	48	—
% on oxygen on day 3	55.5 (39.7 to 68.7)	60.5 (44.1 to 73.4)	0.72‡
% on oxygen on day 5	36.3 (21.7 to 51.1)	42.8 (26.8 to 57.8)	
% on oxygen on day 7	22.7 (9.6 to 39.1)	28.5 (14.4 to 44.4)	
% on oxygen on day 10	17.0 (5.4 to 34.1)	28.5 (14.4 to 44.4)	
Time in intensive care unit (ICU)			
Median (IQR) time (days)	4.5 (3-6)	5 (2-11)	0.66†
No of patients	27	34	—
% in ICU on day 3	84.7 (64.0 to 94.0)	77.1 (57.8 to 88.5)	0.57‡
% in ICU on day 5	47.4 (23.0 to 68.4)	60.9 (40.1 to 76.4)	
% in ICU on day 7	37.9 (14.5 to 61.5)	38.8 (18.7 to 58.5)	
% in ICU on day 10	25.3 (5.3 to 52.5)	33.2 (14.5 to 53.3)	
Time on ventilation			
Median (IQR) time (days)	2.5 (1-16)	8 (1-16)	0.58†
No of patients	19	21	—
% on ventilation on day 3	89.5 (64.1 to 97.3)	85.7 (62.0 to 95.2)	0.68‡
% on ventilation on day 5	71.6 (26.1 to 92.0)	75.0 (42.4 to 90.8)	
% on ventilation on day 7	71.6 (26.1 to 92.0)	75.0 (42.4 to 90.8)	
% on ventilation on day 10	71.6 (26.1 to 92.0)	45.0 (11.9 to 74.1)	

*For comparison between arms.
†Kruskal-Wallis test.
‡Log rank test.

Main results and the role of chance

Of 326 patients (including 246 (75.5%) children aged <15), 165 and 161 were randomised to double or standard dose oseltamivir, respectively. Of these, 260 (79.8%) were infected with influenza virus A (133 (40.8%) with A/H3N2, 72 (22.1%) with A/H1N1-pdm09, 38 (11.7%) with seasonal A/H1N1, 17 (5.2%) with A/H5N1) and 53 (16.2%) with influenza virus B. Similar proportions of patients were negative for RT-PCR on day five of treatment: 115/159 (72.3%, 95% confidence interval 64.9% to 78.7%) double dose recipients versus 105/154 (68.2%, 60.5% to 75.0%) standard dose recipients; difference 4.2% (−5.9 to 14.2); P=0.42. No differences were found in clearance of virus in subgroup analyses by virus type/subtype, age, and duration of illness before randomisation. Mortality was similar: 12/165 (7.3%, 4.2% to 12.3%) in double dose recipients versus 9/161 (5.6%, 3.0% to 10.3%) in standard dose recipients. No differences were found between double and standard dose arms in median days on supplemental oxygen (3 (interquartile range 2-5) *v* 3.5 (2-7)), in intensive care (4.5 (3-6) *v* 5 (2-11), and on mechanical ventilation (2.5 (1-16) *v* 8 (1-16)), respectively.

Harms

No important differences in tolerability were found.

Bias, confounding, and other reasons for caution

We enrolled a heterogeneous population that included mostly children and also those infected with avian H5N1 or H1N1-pdm09 viruses. Our patients presented a median of five days overall (seven days for H5N1). The heterogeneous population characteristics, geographical differences in recruitment, and the variety of infecting viruses in our trial reflect the clinical circumstances in South East Asia during our study but might be viewed as a limitation. Most of these patients were children and had low or normal body mass index (BMI), and for all patients only about a fifth reported a chronic underlying medical condition.

Generalisability to other populations

Our findings are applicable primarily to the region where the study was conducted and other settings with similar characteristics of influenza epidemiology

Study funding/potential competing interests

The study was conducted by the SEAICRN (www.seaicrn.org/) and supported by the National Institute of Allergy and Infectious Diseases and the Wellcome Trust of Great Britain. The Singapore site was supported by the Singapore National Medical Research Council. Several member of the network have had industry funding in the past. Details are with the full version of this paper on bmj.com.

Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care

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- Research: Association between psychological distress and mortality (*BMJ* 2012;345:e4933)
- Research: The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression (*BMJ* 2012;344:e2598)

STUDY QUESTION Does an intervention to improve treatment of depression in older adults in primary care modify the increased risk of death associated with depression?

SUMMARY ANSWER Patients with major depression in intervention practices were 24% less likely to die than were patients with major depression in usual care practices.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Prospective studies have consistently shown a relation between depression and increased mortality in older adults, but no randomized trials have reported that a depression management program can decrease risk. A depression care manager working with primary care physicians to provide algorithm based care for depression can mitigate the detrimental effects of depression on mortality.

Design
PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial) was a multi-site practice randomized controlled trial of an intervention in which a depression care manager worked with primary care physicians to provide algorithm based care for depression, compared with usual care. This paper reports the long term follow-up.

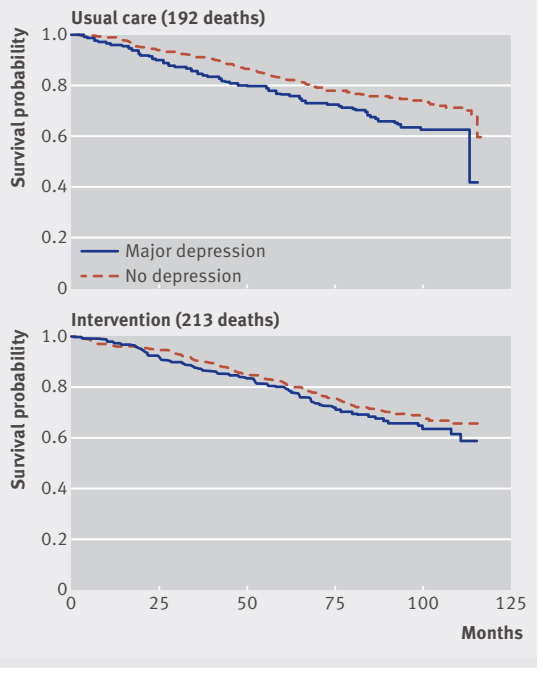
Participants and setting
We identified 1226 participants from 20 primary care practices from New York City, Philadelphia, and Pittsburgh between May 1999 and August 2001 through two stage, age stratified (60-74; ≥75 years) depression screening.

Primary outcome(s)
The primary outcome was mortality risk based on a median follow-up of 98 (range 0.8 to 116.4) months through 2008.

Main results and the role of chance
In baseline clinical interviews, 396 people were classified as having major depression, 203 had clinically significant minor depression, and 627 did not meet criteria for depression. At follow-up, 405 patients had died. Patients with major depression in usual care were more likely to die than were those without depression (hazard ratio 1.90, 95% confidence interval 1.57 to 2.31). Patients with major depression in intervention practices were at no greater risk than were people without depression (hazard ratio 1.09, 0.83 to 1.44). Patients with major depression in intervention practices, relative to usual care, were 24% less likely to have died (79/214 died in intervention practices and 68/182 in usual care practices, hazard ratio 0.76, 0.57 to 1.00; P=0.05).

Harms
No unexpected severe adverse events due to participation in the study were reported.

Survival probability among people with no depression or major depression in practices randomized to usual care or intervention



Bias, confounding, and other reasons for caution
Before randomization, practices were matched on urban location, academic affiliation, size, and population type. Estimates of risk and associated confidence bounds were adjusted for clustering by practice and for patient level characteristics associated with mortality. Comparing the mortality of patients with depression and non-depressed patients from the same sets of practices mitigates the influence of unmeasured characteristics of practices such as the case mix of patients in the practice or the non-specific effects of introducing a person into the practice.

Generalizability to other populations
Because of the sampling strategy, this cohort constituted a representative sample of older patients from the primary care practices participating in PROSPECT. The findings should be applicable to patients in primary care, including patients with a considerable medical burden associated with complex patterns of comorbidity.

Study funding/potential competing interests
Funding was provided by the National Institute of Mental Health (R01 MH065539).

Trial registration number
Clinical trials NCT00000367.

Risk of incident diabetes among patients treated with statins: population based study

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STUDY QUESTION

Are patients treated with HMG-CoA reductase inhibitors (statins) at increased risk of new onset diabetes?

SUMMARY ANSWER

Compared with pravastatin, treatment with higher potency statins, especially atorvastatin and simvastatin, is associated with an increased risk of new onset diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Statins have previously been associated with incident diabetes, though controversy surrounds whether the risk differs among agents. This paper identifies which statins are associated with an increased risk of new onset diabetes.

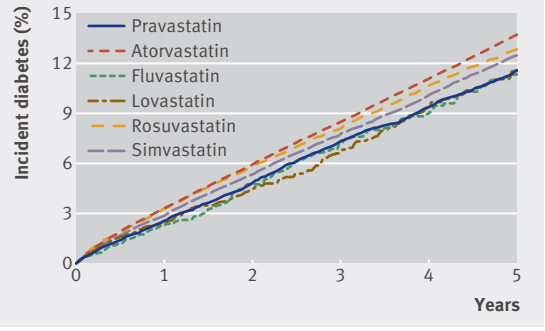
Participants and setting

Patients aged 66 and older without diabetes who started statin treatment from 1 August 1997 to 31 March 2010 were included. Patients with established diabetes before the start of treatment were excluded.

Design, size, and duration

This population based 14 year cohort study used administrative data from Ontario, Canada. The analysis was restricted to 471 250 new users of statins by inclusion only of those people who had at least one year with no prescription for any statin before the start of the study. We identified statin treatment based on prescription for any of atorvastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, or pravastatin during the study period. For each patient, a period of continuous use of each statin was based on successive filling of prescriptions for the same statin within 1.5 times the duration of the preceding prescription. Patients were censored if they experienced the primary outcome, discontinued or switched statin treatment, or died or at the end of the study or after a maximum of five years of follow-up. The primary outcome was incident diabetes, with subgroup analyses according to indication for statin use (primary versus secondary prevention of cardiovascular events) as well as inclusion of potency and time varying analyses of statin dose.

Adjusted survival curves for incident diabetes among new users of statins



Main results and the role of chance

There was an increased risk of incident diabetes with atorvastatin (adjusted hazard ratio 1.22, 95% confidence interval 1.15 to 1.29; diabetes event rate 30 patients per 1000 person years), rosuvastatin (1.18, 1.10 to 1.26; diabetes event rate 34 patients per 1000 person years), and simvastatin (1.10, 1.04 to 1.17; diabetes event rate 26 patients per 1000 person years) compared with pravastatin (diabetes event rate 23 patients per 1000 person years). Our findings were consistent regardless of whether statins were used for primary or secondary prevention of cardiovascular disease. Although similar results were observed when statins were grouped by potency, the risk of incident diabetes associated with use of rosuvastatin became non-significant (adjusted hazard ratio 1.01, 0.94 to 1.09) when dose was taken into account.

Bias, confounding, and other reasons for caution

Although patients treated with the study statins were similar at baseline, potential confounding factors such as weight, ethnicity, or family history could not be determined from the administrative databases.

Generalizability to other populations

These findings are generalizable to older patients newly prescribed statins for primary or secondary prevention.

Study funding/potential competing interests

This study was supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC. MMM has received honorariums from Boehringer Ingelheim, Sanofi-Aventis, Lilly, Pfizer, Bristol-Myers Squibb, Merck and Bayer.

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Research: Use of high potency statins and rates of admission for acute kidney injury (*BMJ* 2013;346:f880)
Research: Unintended effects of statins in men and women in England and Wales (*BMJ* 2010;340:c2197)

Cost effectiveness of the NHS breast screening programme: life table model

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STUDY QUESTION

How cost effective is the breast screening programme conducted by the United Kingdom's health service?

SUMMARY ANSWER

Regular breast screening of 364 500 women aged 50-70 years, with 75% screening uptake and another 15 years of follow-up after the end of screening, was associated with 2040 additional quality adjusted life years (QALYs) gained at an additional cost of £42.5m (€49.8m; $64.7m) in total, or £20 800 per QALY gained.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Despite reports of the incremental cost effectiveness of different screening strategies for breast cancer, no published studies have compared mammographic screening with no screening since the 1986 Forrest report. We have shown that the NHS breast screening programme is moderately likely to be cost effective at the standard cost effectiveness threshold of £20 000 used by the National Institute for Health and Care Excellence (NICE).

Main results

Under the base case scenario (using model input parameters relating to the benefits, harms, and costs of screening and costs of breast cancer treatment), the NHS breast screening programme was predicted to result in 1521 fewer deaths from breast cancer and 2722 overdiagnosed breast cancers. Discounting future costs and benefits at a rate of 3.5% resulted in 6907 added person years of survival in the screened cohort at a cost of 40 946 additional years of survival after a breast cancer diagnosis. The gain in person time survival over 35 years was 9.2 days per person and 2.7 quality adjusted days per woman screened.

Differences in outcomes between screened and unscreened cohorts of 364 500 women (with 75% screening uptake in screened cohort)

	Difference (interquartile range)†
Breast cancer cases	2722 (2153 to 2829)
Breast cancer deaths	−1521 (−1075 to −1600)
Deaths from other causes	729 (546 to 784)
Deaths from all causes	−792 (−525 to −823)
Person years of survival*	6907 (4798 to 7328)
Person years of survival after diagnosis of breast cancer*	40 946 (36 194 to 43 710)
Quality adjusted life years*	2040 (847 to 2974)
Cost (£m)*	42.5 (36.8 to 49.9)

Data are numbers unless stated otherwise.
*Discounted at 3.5% per year.
†Interquartile range for outputs from probabilistic sensitivity analysis.

Design

Life table model.

Sources of effectiveness

Input parameters relating to the benefits and harms of screening were taken from the results of the Independent UK Panel Review of Breast Screening.

Data sources

Data for breast cancer incidence, breast cancer mortality, and all cause mortality were obtained from the Office for National Statistics. The estimated overall cost of the screening programme was obtained from an estimate published by the NHS breast screening programme. Costs of treating primary and metastatic breast cancer were taken from NHS treatment reference costs and NICE. Estimates of the quality of life associated with age and with living after a breast cancer diagnosis were taken from published studies.

Results of sensitivity analysis

We recalculated the model 5000 times, sampling randomly the input parameters from a range of likely values that reflect the uncertainty in those parameter estimates. In 588 (12%) model runs, the screening programme was associated with a reduction in QALYs. In an additional 2152 (43%) runs, the cost per QALY exceeded the £20 000 threshold commonly used by NICE to determine whether an intervention should be funded by the NHS. The probability that the screening programme is cost effective compared with no screening was 45% (2260 scenarios) at a threshold of £20 000 per QALY. This analysis was repeated for another five scenarios for the effect of screening on breast cancer incidence. The more screening advanced the diagnosis of breast cancer, the greater the incremental cost effectiveness ratio. A greater reduction in breast cancer incidence after cessation of screening was associated with a greater reduction in the incremental cost effectiveness ratio.

Limitations

The cost effectiveness estimates were particularly sensitive to the values used for death from breast cancer, relative overdiagnosis of the condition, and long term quality of life after a diagnosis of breast cancer. These are parameters for which there is little evidence from randomised trials of modern digital mammography coupled with modern surgery, radiotherapy, and adjuvant chemotherapy.

Study funding/potential competing interests

This study received no specific funding. NP is a Cancer Research UK clinician scientist fellow.

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- Research: Possible net harms of breast cancer screening (*BMJ* 2011;343:d7627)
- Research methods and reporting: Comparative effectiveness research in cancer screening programmes (*BMJ* 2012;344:e2864)