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Orlistat and the risk of acute liver injury: self controlled case series study in UK Clinical Practice Research Datalink

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EDITORIAL by Wilding

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STUDY QUESTION

Is treatment with orlistat (Xenical; Roche) associated with hepatic injury?

SUMMARY ANSWER

The incidence of acute liver injury was higher in the periods both immediately before and immediately after the start of orlistat treatment.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Since early 2000 reports of liver injury associated with orlistat have accumulated, raising concerns about its safety. In a large population based cohort, the rate of adverse liver events was temporarily increased both immediately before and immediately after treatment with orlistat started, suggesting the risk is associated with underlying health changes associated with the decision to begin treatment rather than a causal effect of the drug.

Participants and setting

Participants were all patients registered in the UK Clinical Practice Research Datalink between 1999 and 2011, receiving prescribed orlistat and having a recorded incident liver injury event.

Design, size, and duration

Of 94 695 patients prescribed orlistat, 988 were identified as having incident liver injury, with a mean observation time of 10.1 years and mean duration of orlistat use of 0.9 years. A self controlled case series analysis compared the incidence of liver injury during periods of orlistat use with periods of non-use.

Main results and the role of chance

An increased incidence of liver injury was detected during the 90 day period before orlistat was first started compared with other periods of non-use of orlistat (incidence rate ratio 1.50, 95% confidence interval 1.10 to 2.06). The incidence remained raised during the first 30 days of treatment (2.21, 1.43 to 3.42), before reverting to baseline levels with prolonged treatment. No increase in the incidence of liver injury was seen when the risk during the first 90 days of treatment was compared with the 90 days preceding first treatment (1.02, 0.67 to 1.56). Over 99% of the events occurring during orlistat use were of raised liver function test results or jaundice, with few cases of severe liver events (one case of hepatitis).

Self controlled case series analysis for orlistat use and risk of liver injury in definite and probable cases (n=988)

Orlistat use	Patient years	No of events	Age adjusted rate ratio (95% CI)
Primary analyses:			
Absence of orlistat	8872	852	—
90 days before prescription	241	42	1.50 (1.10 to 2.06)
1-30 days	81	21	2.21 (1.43 to 3.42)
31-60 days	80	10	1.06 (0.57 to 1.99)
61-90 days	78	12	1.32 (0.75 to 2.34)
>90 days	986	51	0.78 (0.58 to 1.05)
Secondary analyses:			
90 days before prescription	241	42	—
1-90 days	240	43	1.02 (0.67 to 1.56)
30 days before prescription	81	19	—
1-30 days	81	21	1.11 (0.59 to 2.06)

Bias, confounding, and other reasons for caution

We accounted for confounding by using a design where each patient acts as his or her own control, so we can be confident the results are not explained by important differences between participants. Drug use may have been misclassified to some extent, as it is based on prescribing rather than consumption. The most likely effect of this would be to bias the results towards the null.

Generalisability to other populations

The study was UK population based and the results are likely to be generalisable to other similar populations.

Study funding/potential competing interests

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When to remeasure cardiovascular risk in untreated people at low and intermediate risk: observational study

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Research: Comparisons of established risk prediction models for cardiovascular disease (*BMJ* 2012;344:e3318)

STUDY QUESTION

To estimate the probability of becoming at high risk of cardiovascular disease for low and intermediate risk people not receiving treatment for raised blood pressure or lipid levels.

SUMMARY ANSWER

Repeat cardiovascular risk estimation before eight to 10 years is not warranted for most people unless their initial risk is 15-20%, when remeasurement within a year is warranted.

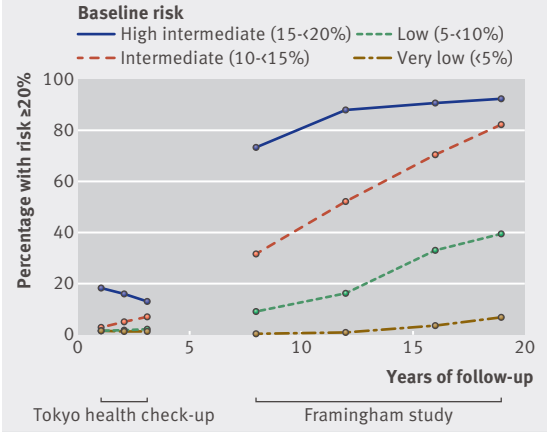
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Increasingly decisions to start blood pressure and lipid lowering treatment are made on the basis of an individual's absolute cardiovascular risk rather than their blood pressure or cholesterol level, and people are regularly screened for a raised risk level.
Remeasurement of cardiovascular risk may be safely done much less often than most guidelines recommend: eight to 10 years for those initially at <10% risk for a cardiovascular event.

Participants and setting

We included 13 757 and 3855 participants of two studies: the Tokyo health check-up and Framingham studies. Included participants were aged 30 to 74 years, had complete data on risk equation covariates, were not receiving blood pressure or lipid lowering treatment, and had an estimated risk of cardiovascular disease within 10 years <20%. We stratified participants on the basis of baseline risk: <5%, 5-<10%, 10-<15%, and 15-<20%.

Probability of crossing 20% cardiovascular disease treatment threshold for 10 year cardiovascular event risk over 19 years of follow-up



Design, size, and duration

Observational study of two cohorts not at high cardiovascular risk at baseline. Follow-up measurements in the Tokyo study were done annually over three years (2006-10), whereas follow-up visits in the Framingham study were done between eight (1968-75) and 19 years (1990-95) after baseline. We used these visit measures to estimate and track changes in the 10 year risk of a cardiovascular event >20% using the Framingham equation for both cohorts.

Main results and the role of chance

At baseline most participants had <5% risk (61% and 46% of Tokyo and Framingham cohorts) or 5-<10% risk (24% and 28%) of a cardiovascular event within 10 years. After three years for both the very low (<5%) and low baseline risk (5-<10%) groups the proportion crossing the treatment threshold was less than 1%. For the intermediate baseline risk (10-<15%) group the proportion crossing the threshold was 5.7% (95% confidence interval 4.5% to 7.0%). By contrast in the high-intermediate baseline risk (15-<20%) group 16.1% (13.4% to 19.0%) had crossed the threshold by one year. After eight years 9.1% (7.1% to 11.3%) of the low baseline risk group had crossed the treatment threshold, whereas for the intermediate and high intermediate baseline risk groups it was over 10% (32.1%, 27.6% to 36.8% and 73.5%, 67.2% to 79.1%, respectively). For those with an initial very low baseline risk, even after 19 years of follow-up the proportion crossing the treatment threshold remained low, with 6.8% (5.5% to 8.2%) crossing the treatment threshold.

Bias, confounding, and other reasons for caution

The findings are based on two separate cohorts with different lengths of follow-up.

Generalisability to other populations

While further examination is warranted in other populations, repeat risk estimation before 8-10 years is not warranted for most people. However, remeasurement within a year seems warranted in those initially at 15-20% risk.

Study funding/potential competing interests

The authors declare that: KJLB, AH, LI, and PG have support from the Australian National Health and Medical Research Council (program grant No 633003, early career fellowship No APP1013390) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Predictive value of S-100β protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis

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Research: Predicting outcome after traumatic brain injury (*BMJ* 2008;336:425)

STUDY QUESTION

Is the concentration of S-100β protein a valid and accurate predictor of prognosis after moderate or severe traumatic brain injury?

SUMMARY ANSWER

Raised serum S-100β protein concentrations are significantly associated with unfavourable prognosis after moderate or severe traumatic brain injury, though optimal discrimination thresholds remain unclear.

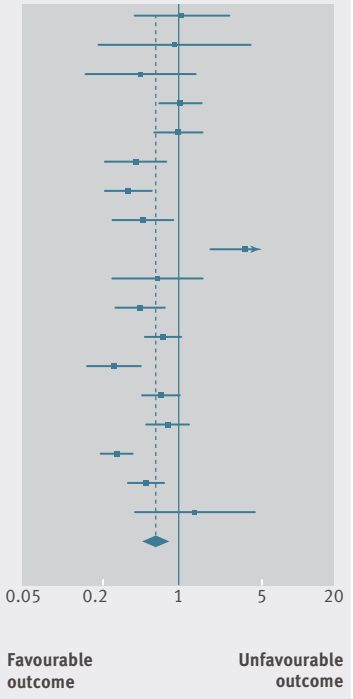
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

S-100β protein concentrations increase in blood and cerebrospinal fluid after a wide range of diseases or conditions leading to brain damage. The review shows that concentrations are significantly correlated with unfavourable prognosis in patients with moderate or severe traumatic brain injury, as defined by mortality, score ≤3 on the Glasgow outcome scale, or brain stem death, with and without concomitant traumatic injuries. This finding could inform a decision aid in the evaluation of patients with traumatic brain injury.

Association between S-100β protein and Glasgow outcome score ≤3 in patients with moderate and severe traumatic brain injury

Study	No of patients by Glasgow outcome score ≤3	No of patients by Glasgow outcome score >3	Mean (SE) difference in ln concentration (μg/L)
Raabe 1998[45]	6	9	1.45 (0.47)
Raabe 1998[46]	20	24	1.30 (0.75)
Jackson 2000[51]	25	5	0.65 (0.54)
Chatfield 2002[54]	8	12	1.42 (0.21)
Woertgen 2002[57]	24	30	1.38 (0.24)
Li 2004[62]	18	22	0.55 (0.30)
Ucar 2004[63]	34	14	0.41 (0.23)
Vos 2004[64]	40	44	0.69 (0.30)
Sawauchi 2005[65]	12	29	2.66 (0.34)
Wang 2006[67]	15	19	0.97 (0.45)
Ghori 2007[68]	13	15	0.64 (0.24)
Lavicka 2007[70]	41	57	1.08 (0.18)
Olivecrona 2009[73]	23	25	0.13 (0.27)
Rainey 2009[74]	50	50	1.04 (0.19)
Wiesmann 2010	38	22	1.17 (0.21)
Murillo-Cabezas 2010[76]	32	55	0.19 (0.16)
Vos 2010[77]	36	43	0.75 (0.18)
Stein 2012[81]	7	16	1.70 (0.59)
Total (95% CI)	442	491	

Test for heterogeneity: τ^2=0.24, χ^2=80.54, df=17, P<0.001, I^2=79%
Test for overall effect: z=7.06, P<0.001



Selection criteria for studies

We included cohort studies and randomised controlled trials evaluating the prognostic value of S-100β protein in patients with moderate or severe traumatic brain injury.

Primary outcomes

Outcomes evaluated were mortality, score on Glasgow outcome scale, and brain stem death.

Main results and role of chance

Forty one studies were eligible for inclusion. There was a significant positive association between S-100β protein concentrations and mortality (12 studies with 770 participants: geometric mean ratio 2.55, 95% confidence interval 2.02 to 3.21, I^2=56%) and Glasgow outcome score ≤3 (18 studies with 933 participants: 2.62, 2.01 to 3.42, I^2=79%). Sensitivity analyses based on sampling time, sampling type, blinding of outcome assessors, and timing of outcome assessment yielded similar results. Ranges of serum threshold values of 1.38-10.50 μg/L and 2.16-14.00 μg/L were associated with 100% specificity for mortality and a Glasgow outcome score ≤3, respectively.

Bias, confounding, and other reasons for caution

We observed significant heterogeneity for all outcomes of interest. Sensitivity analyses did not fully explain the observed heterogeneity for the Glasgow outcome score. We could not perform sensitivity analyses related to age, pupillary reactivity, or the motor component of the Glasgow coma scale, which are known indicators of prognosis in such patients, because of the variable presentations or absence of these data in included studies. The quality of evidence of the association between S-100β protein concentrations and both mortality and neurological outcome was moderate.

Can trial quality be reliably assessed from published reports of cancer trials: evaluation of risk of bias assessments in systematic reviews

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- Research: Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data (*BMJ* 2012;344:d7762)
- Research: Observer bias in randomised clinical trials with binary outcomes (*BMJ* 2012;344:e1119)
- Research Methods and Reporting: The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews (*BMJ* 2010;340:c365)

STUDY QUESTION

How reliable are risk of bias assessments based on publications of randomised controlled trials in cancer, for use in systematic reviews?

SUMMARY ANSWER

Use of trial publications alone to assess risk of bias could be unreliable, therefore systematic reviewers should be cautious about their use as a basis for trial inclusion in meta-analysis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Poor reporting of randomised controlled trials does not necessarily reflect poor methodological quality of the trial design, conduct, or analysis. Obtaining additional information from trials could ensure a more accurate assessment of risk of bias and, if available, summary statistics can reduce or overcome some potential biases.

Participants and setting

We included 95 published randomised controlled trials in cancer that had been included in 13 systematic reviews and meta-analyses based on individual participant data (IPD), and for which publications and completed forms or trial protocols had been collected during the IPD process.

Design

Two authors completed risk of bias assessments using the Cochrane risk of bias tool and following guidance from the Cochrane Handbook. Assessments were conducted for individual domains, and overall for each trial, first using information from trial publications alone and then using supplementary information alongside the published information.

Primary outcome(s)

We compared the two approaches to assessing risk of bias by calculating percentage agreement (low <66%; fair ≥66%; good ≥90%). The approaches were considered to be similarly reliable only when agreement was good.

Main results and the role of chance

Percentage agreement between the two methods for sequence generation and incomplete outcome data was fair. For allocation concealment, selective outcome reporting, and overall risk of bias, percentage agreement was low. Supplementary information reduced the proportion of unclear assessments for all individual domains. This reduced proportion increased the number of trials assessed as having a low risk of bias, and therefore available for inclusion in meta-analyses, from 23 (23%) based on publications alone to 66 (66%).

Bias, confounding, and other reasons for caution

The included cancer trials represented a selected group. Risk of bias assessments were for overall survival—a single, objective and commonly well reported outcome—rather than all possible outcomes, as is recommended. Our results might therefore represent an optimistic view of the reliability of the risk of bias assessments using published information alone. Also, the additional information supplied was sometimes limited; even with additional information, around a third of the included studies were still classified as having unclear risk of bias.

Generalisability to other populations

All of the included trials were cancer trials. These are, in general, well conducted and often well reported. Therefore, for some other healthcare areas, where trials are less well conducted or reported, risk of bias assessments based on publications alone could be even less reliable.

Study funding/potential competing interests

This work was supported by the United Kingdom's Medical Research Council. None of the authors have received support from any organisation for the submitted work, nor do they have any financial relationships with any organisations that might have an interest in the submitted work in the previous three years, or any other relationships or activities that could appear to have influenced the submitted work.

Outcomes and comparison of risk of bias assessments

Risk of bias domain	No of assessments based on publications only			No of assessments based on publications plus supplementary information			Percentage agreement (%; 95% CI)
	Low	Unclear	High	Low	Unclear	High	
Sequence generation	42	53	0	69	26	0	69.5 (60.2 to 78.7)
Allocation concealment	40	55	0	89	6	0	48.4 (38.4 to 58.5)
Incomplete outcome data	74	10	11	90	1	4	80.0 (72.0 to 88.0)
Selective outcome reporting	37	10	48	90	0	5	42.1 (32.2 to 52.0)
Overall risk of bias for trial	23	70	2	64	31	0	54.7 (44.7 to 64.7)