high. This approach has presumably been used in at least two articles in which individual rates were analysed with non-parametric rank sum tests, indicating that the assumption of normality was not met.[2,3] Obviously, sample size calculations are possible for this kind of variable, and the sample size needed is clearly smaller than that needed in the first approach.

The third method, survival analysis, can cause problems from the clinical point of view. For example, the exact time of occurrence of vertebral fractures is usually unknown. Additionally, the treatment regimens used do not generally affect patients immediately. Thus, fractures during the first months of the study may unnecessarily be regarded as being due to failures of treatment, leading to wrong conclusions and possible loss of relevant data.

Recently a lot of statistical research has been conducted to allow for many events in the same patient during follow up and to take different times to the end points into account. These methods include, for example, random effects models for binary or counted data.[4] To our knowledge, however, these techniques have not yet been included in widely used statistical programs. While waiting for the above models we prefer to choose the second alternative (individual event rate adjusted for follow up time), which fulfils the statistical assumptions, has a clear clinical interpretation, and includes information about all events.

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Can obscure the true risk of certain adverse drug reactions

EDITOR,—The concept of events per person year is not only of limited utility in describing events in osteoporosis.[1] In the study of adverse drug reactions the use of event rates can also be inappropriate and obscure the true risk of certain reactions.

When an event is (or is believed to be) likely to occur at any stage during continuous treatment with a drug then an event rate with a time component (rate per person year, etc) has a true meaning. For example, 1000 patient years' exposure to a drug might be achieved by studying 100 patients for 10 years or 2000 patients for six months, but in both cases the event rate per person year will be the same if the event in question occurs uniformly through the period of exposure to the drug.

If, however, an event is likely to occur either early in a patient's exposure to a drug or not at all (a common situation with idiosyncratic adverse drug reactions) then the use of an event rate with a time component is inappropriate. Extending the example above and assuming that one patient in 50 experiences a specific adverse drug reaction in the first three months of treatment, then the rate per patient year will be 0·002 in the group of 100 patients (=two events in 1000 patient years) and 0·04 in the group of 2000 patients (=40 events in 1000 patient years).

Less commonly, a specific adverse drug reaction may not occur until late in the exposure to a drug, in which case the rate per patient year will be much lower in short term studies than in long term studies.

For adverse drug reactions of this type it is the number of events per patient treated (or per 100 or 1000 patients treated) that is the true rate, reflecting the actual risk to an individual recipient of the drug. Those reporting rates of adverse drug reactions should take careful note of the temporal pattern of reactions and, when risk is not uniform through time, report numbers of events as well as, or even instead of, rates with a time component.

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1 Windeler J, Lange S. Events per person year—a dubious concept. *BMJ* 1995;310:454-6. (18 February.)

Treating heart disease

Estimate of benefit from early thrombolysis in acute myocardial infarction is wrong

EDITOR,—Anthony Hall and D M Humphreys from Boehringer Ingelheim[1] are not alone in uncritically accepting the estimate of the benefit conferred by earlier thrombolysis produced by the Fibrinolytic Therapy Trialists' Collaborative Group.[2] Within five weeks of entry to the trial the loss of benefit per hour of delay to randomisation is given as 1·6/1000 patients. This figure is so low that, if it is true, many would feel that the effort required to expedite thrombolysis, particularly to take it out of hospital into the community, would not be worth while. The data used by the collaborative group, however, do not permit the benefit-time gradient to be measured, and the benefit of earlier thrombolysis is probably much greater than this estimate suggests.

The collaborative group's estimate is derived by retrospective subgroup analysis of randomised placebo controlled trials of thrombolytic treatment. The absolute reduction in mortality with thrombolytic treatment is regressed against delay from onset of symptoms to randomisation. The table, derived from the first two points in the group's figure 2, gives the mortality in the treatment and control groups randomised 0-1 (A) and 2-3 (B) hours after the onset of symptoms and illustrates the fallacy. Death rates within five weeks in patients given thrombolysis at times A and B are not significantly different because the greater efficacy of the treatment with earlier administration is masked by the greater severity of infarction with earlier presentation; the latter is evident from the mortality in the control groups.

To measure the benefit-time gradient we have to know what the mortality would have been for patients presenting at one time and treated at another. The mortality differs significantly between the two control groups, being higher in those who present earlier. The effect of treating patients at time B who present at time A, and vice versa, is not known (because not done) and cannot be inferred by reference back to a control group because there is not one, but there are two control groups that are demonstrably different from each other.

The magnitude of the benefit of earlier thrombolysis can be determined only with a trial in which patients are randomly allotted treatment on presentation or after a deliberate delay. Analysis of trials of such design suggests that the benefit of earlier thrombolysis is at least 10 times the collaborative group's estimate.[3]

Not all readers of the *BMJ* will know that Boehringer Ingelheim makes alteplase, a thrombolytic agent least suited to use in the community. The company therefore has a vested interest in minimising the benefit of earlier thrombolysis, and this conflict of interest should have been declared.

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Authors' reply

EDITOR,—We believe that the views expressed in our letter have been misinterpreted. This may have been because of the subtitle, "Benefits of thrombolysis were overstated," which was chosen without consultation and is certainly not the message that we wished to impart. We firmly believe that thrombolysis is of considerable benefit in acute myocardial infarction. In addition, we recognise that earlier thrombolysis is important, but we consider that the relation between loss of benefit and time from the onset of symptoms to treatment is not linear, being most significant early on. This theory is supported by the "trials of prehospital thrombolysis" discussed by Rawles,[1] although the way in which the time dependency of the benefit was calculated may be criticised.

Our main point of contention was that, in their article, John McMurray and Andrew Rankin[2] reference the graph from the Fibrinolytic Therapy Trialists' Collaborative Group's meta-analysis, which shows a linear loss of benefit per hour of delay of 1·6 lives/1000 patients treated.[3] Thus it is not at all clear from their review how they arrived at their estimate that initiating thrombolysis 30-60 minutes earlier will save about 15 extra lives/1000. Certainly this is not supported by the collaborative group's evidence cited and lacks meaning without a definition when this degree of benefit may occur. Since McMurray and Rankin did not qualify their statement we assumed that they were suggesting that this benefit would apply at any point.

These concepts are in keeping with our belief that early patency is an important determinant of outcome. In support of this the global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries trial showed that the patency grade at 90 minutes was reflected in both measures of left ventricular function (at 90 minutes and 5-7 days) and 30 day mortality, irrespective of which thrombolytic agent was used.[4] It is therefore reasonable to suggest that an agent achieving more rapid and complete lysis is likely to provide additional benefit.

We therefore disagree that Boehringer Ingelheim has a vested interest in belittling the effect of early

Mortality (%) in patients with infarction randomised at times A and B to thrombolysis or control group

Time from onset of symptoms	Thrombolytic treatment	Control	Difference	P value
A (0-1 h)	9·5	13·0	3·5	0·0014
B (2-3 h)	8·2	10·7	2·5	0·00006
Difference	1·3	2·3		
P value	0·11	0·01		