MEDICAL PRACTICE

Occasional Review

Presentation and analysis of the results of clinical trials in cardiovascular disease

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During the past few years numerous clinical trials have been conducted to test the efficacy of various agents in reducing mortality after myocardial infarction. There is considerable confusion about the results of these trials, and no drug or group of drugs is universally accepted by clinicians as being useful for preventing a second infarction. To some extent this confusion results from differences in trial design and to some extent from the inclusion of different types of patient or from treatment being tested during different stages of the illness. Such differences between trials are inevitable and to some extent useful. Nevertheless, it is quite unnecessary for confusion to result from a lack of clarity in the presentation of the results of a trial, or from disagreements about the analysis of these results. Such confusion could be prevented by a standard method of data presentation that makes it clear what was done, makes it easy for one trial to be compared with another, and allows those not directly concerned with the trial to analyse the results in the way they believe most appropriate. Figure 1 shows such a method.

Presentation of trial results

The box on the first line of fig 1 shows the total population from which the patients in the trial were selected. It is essential to know this total, for without it it is impossible to be sure about the applicability of the results of the trial. In any study there are "inclusion" and "exclusion" criteria that superficially appear straightforward, but which may in fact be difficult to apply; other factors, such as the willingness of patients and doctors to co-operate with the study, will also influence the number eventually admitted to the trial. It is characteristic of multicentre trials that the size of the original population of patients is unknown.

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The second box contains the total number of patients included in the trial. A comparison of the numbers in the first two boxes will show the proportion of patients considered suitable for the trial, and this will give an indication of the general applicability of the final results.

It is highly improbable that any treatment will reduce the risk of death after myocardial infarction by as much as 30%, yet few published trials have included enough patients to show with conventional levels of statistical significance such a degree of benefit from treatment. If the number in the box on line 2 appears to be small an explanation must be sought in the text of the paper, and if no adequate reason can be found then the result of the trial must be regarded with some suspicion.

The number of patients randomly allocated to each treatment is shown in the pair of boxes on line 3 of this figure. If the treatment groups are small the text may be scrutinised for evidence that they were well matched, but if these groups of patients were large then good matching is likely.

The boxes on line 4 show the number of patients randomly allocated to each treatment group who continued on that treatment, and the number who were withdrawn from it. In any clinical trial with a double-blind design a patient may be withdrawn from the study if his doctor believes that some undesired event may result from active treatment, or if the doctor believes that active treatment is necessary and fears that his patient may be on a placebo. For example, in a trial using beta-blockers after myocardial infarction hypotension may lead to a patient being withdrawn lest it results from beta-blockade, while the appearance of angina may lead to a patient's withdrawal so that he can electively be treated with a beta-blocker. In some postinfarction trials, and in particular in those when medication was started early in the illness, when symptoms and signs are changing, withdrawal rates have been high in both treated and placebo groups. If the withdrawal rate among patients receiving active treatment is much higher than it is among the patients on placebo the active treatment is unlikely to be useful.

The boxes on the fifth line show the number (and below the numbers, the percentages) of patients who died in each of the subgroups of patients who respectively continued, or withdrew from, the treatment to which they had been assigned. The pair of boxes on line 6 gives the number of deaths among the patients allocated to the two original treatment groups.

Analysis of trial results

Those who believe in the importance of "clinical efficacy" will take the "explicative" approach and look at the number of deaths in line 5 of fig 1. In this method of trial analysis importance is attached to the fact that active treatment cannot help those from whom it is withdrawn; the "treated" fatality rate is therefore calculated from those allocated to active treatment who continued to take this treatment until the end of the study. This fatilaty rate is compared with that in the other groups of patients who were withdrawn from active treatment or who were initially allocated to placebo treatment. This form of analysis is attractive to those who are interested in the mechanisms by which a drug might act, and also to clinicians when a trial necessitates a prolonged period of treatment, when many deaths among "withdrawn" patients may have occurred long after treatment was discontinued, when any possible beneficial or harmful effects should have disappeared.

The alternative approach to trial analysis is based on "all patients—intention to treat," and this is sometimes called "pragmatic" analysis. Here fatality rates are calculated for all those allocated to each treatment group, whether treatment was continued or not. This approach is attractive to the clinician who simply wants to know whether putting his patient on active treatment will reduce mortality within a given period. The numbers in the boxes on line 6 of fig 1 contain the information required for this type of analysis.

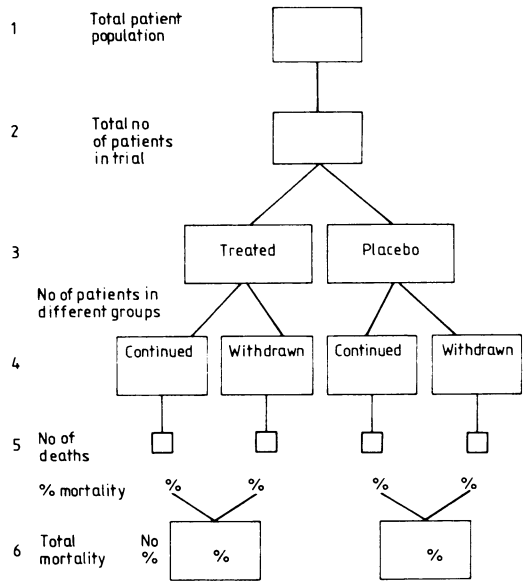

FIG 1—Proposed method for data presentation in cardiovascular trials.

Both approaches to the analysis of trial results have supporters and detractors, and it may well be that at different times each method of analysis will be appropriate. Arguments will and should continue, but they will be much more useful if trial results are presented so that the facts are clear and only their interpretation is in dispute. Presentation of results as suggested in fig 1 makes the facts clear but leaves interpretation open.

Data presentation and analysis in published trials

If the results of published trials are displayed in the way I have described, the advantages become clear: in the examples that follow I have used only data that can be extracted from published reports.

Figure 2 shows the results of a comparison of oxprenolol and disopyramide with placebo in the immediate treatment of patients with suspected myocardial infarction.[1] Because there were three treatment groups the data are complicated, but a modification of the first figure simplifies them considerably. Of 860 patients with suspected infarction admitted to hospital, 473 were included in the trial. The text of the paper shows that the principal reason for exclusion was that the patients were already taking beta-blockers when admitted to hospital. The total number of patients in the trial was relatively small, but the

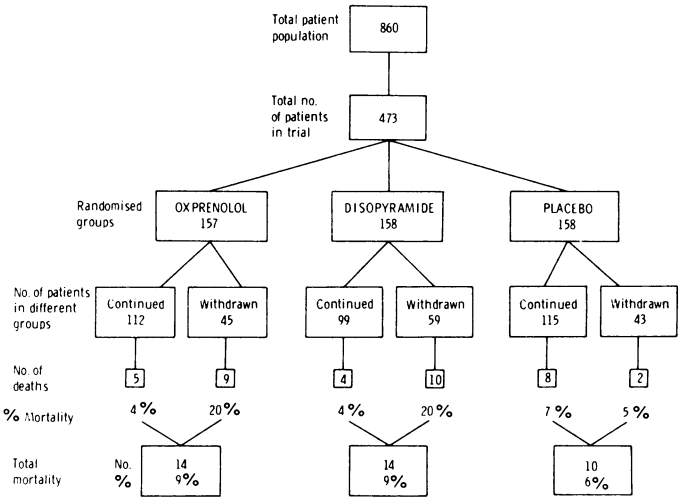

FIG 2—Results of a trial comparing oxprenolol and disopyramide with placebo in patients with acute myocardial infarction.[1]

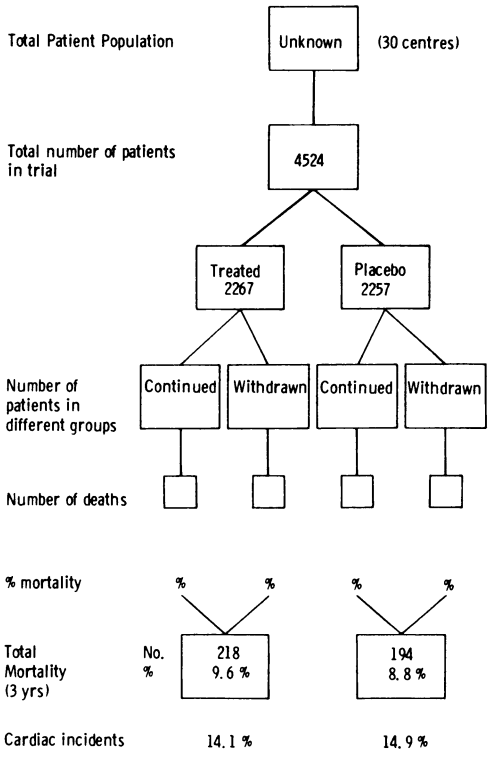

FIG 3—Results of a trial comparing aspirin with placebo in the treatment of patients with myocardial infarction.[2]

text shows that the trial was discontinued prematurely on the advice of an independent review group. Clearly there was a relatively high withdrawal rate in all groups. There was little difference in fatality rate among those subgroups of patients who continued with, or were withdrawn from, placebo treatment (8/115, 7%; 2/43, 5%), but patients continuing on either oxprenolol or disopyramide had considerably lower mortalities (5/112, 4%; 4/99, 4%) than those who were withdrawn from these treatments (respectively 9/45, 20%; 10/59, 20%). These figures may be used for analysis of clinical effectiveness. Analysis by intention to treat is made simple by the figures in the bottom line of the diagram, where the fatality rates in the groups of patients randomly allocated to treatment with oxprenolol, disopyramide, and placebo were respectively 14/157 (9%), 14/158 (9%), and 10/158 (6%). The reasons for the high withdrawal rate, the high mortality among patients withdrawn from active treatment, and the low mortality in all the groups in the intention to treat analysis are all

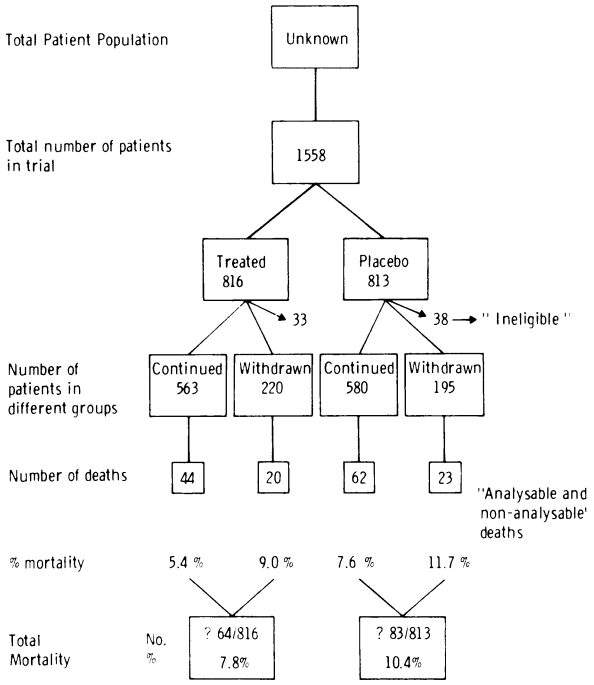

FIG 4—Results of a trial comparing sulphinpyrazone with placebo in the treatment of patients with myocardial infarction.[3]

open to debate. The important point is that the data are clearly presented so that debate is possible.

Figure 3 shows the data from the aspirin myocardial infarction study.[2] The size of the original patient population is unknown, but the randomised groups are large. No mention is made of the number of patients withdrawn from treatment, so that analysis by clinical efficacy is impossible. Analysis by intention to treat shows that there was a similar fatality rate in the treatment and placebo groups. The paper itself is complex, but fig 3 contains most of the essential information.

Figure 4 shows the results of the Anturane reinfarction trial in so far as they can be derived from the published report.[3] The wording of this report is obscure, and it is extremely difficult to fit the data into my standard diagram, but an attempt to do so showed immediately some of the weaknesses of the trial.

The total number of patients from which those in the Anturane reinfarction trial were recruited is unknown, but from the text it is clear that each centre was admitting only a few patients to the trial each month. What distinguished these patients from the others is unknown. The number of patients in the trial was, nevertheless, reasonably large (1558). Of the randomised patients, 33 allocated to active treatment and 38 to placebo were considered "ineligible" and were omitted from the analysis of the results. Figure 4 makes it clear that this was done. For a trial concerning a drug supposedly without important side effects there was a high withdrawal rate in both treated and placebo patients. At this point the wording of the text of the paper is extremely difficult to follow, and it is not clear whether withdrawn patients are those in whom deaths are later described as "non-analysable." I have assumed this to be the case, and fig 4 shows what seems to be the fatality rate in patients who continued, and withdrew from, treatment. The calculation of final mortality rates is impossible because of a lack of information about the ineligible patients; I have added these patients back to the total numbers in each group in the final line of fig 4, but the text does not show how many of them died.

These points were all emphasised by the Food and Drug Administration critique of the Anturane reinfarction trial,[4] which showed that there were more deaths among ineligible patients allocated to sulphinpyrazone than among those allocated to placebo. This narrowed the difference between the overall fatality rates in the randomised groups of patients. No method of data presentation would show some of the other weaknesses in the trial disclosed by the Food and Drug Administration review, but if the results of the Anturane reinfarction trial had initially been presented in the way shown in fig 4 much confusion might have been prevented.

Figure 5 shows that the results of trials of different forms of management can be presented in the same way as the results of drug trials. In the Nottingham study comparing home and hospital care for patients with suspected myocardial infarction[5] 349 such patients were considered and 246 actually included in the trial. Of the 132 randomly allocated to home care, 106 remained at home but 26 were for various reasons later sent to hospital. In these subgroups respectively nine and eight patients died within the six-week study period, giving fatality rates of 8·7% and 31%. None of the 132 patients randomly allocated to hospital care was withdrawn from this form of treatment by premature discharge home; 14 patients allocated to hospital treatment died within the six weeks' study period. Thus if the study is analysed on an all patients-intention to treat basis, the total fatality rate in the home group was 17/132 (13%) and in hospital group 14/132 (11%).

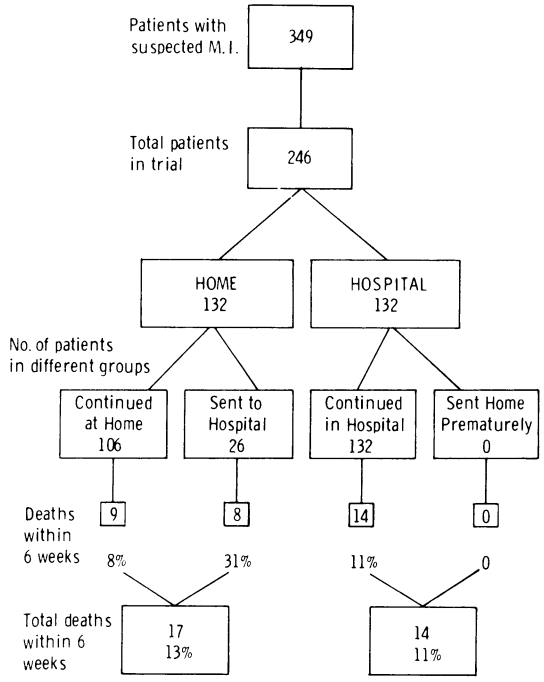

FIG 5—Results of a trial comparing home and hospital care of patients with myocardial infarction.[5]

Conclusions

It is possible to display the results of a variety of clinical trials in a standard format that highlights the good and the weak features of a trial, that makes different forms of analysis possible, and allows one trial to be compared with another. There will always be disagreements about the design of trials and the interpretation of their results, but a standard method of presenting data such as I have described would encourage informed debate about the meaning of undisputed facts.

References

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(*Accepted 20 February 1981*)