THE LANCET

Long-term and Short-term Beta-blockade after Myocardial Infarction

WHEN a patient is admitted to hospital with a (presumptive) diagnosis of myocardial infarction, beta-blockade may be instituted either intravenously or—with less immediate effect—orally. If and when the patient is discharged, beta-blockers may be prescribed either for an initial "high-risk" period or indefinitely. These four treatment options deserve separate evaluation, for they may have quite different effects on mortality. Evaluation of the use of any drug for an "indefinite" period can, of course, be achieved only indirectly, but direct evaluation of the first three options is possible by randomised trials. At least forty-one such trials, on a total of some 20 000 patients, are now available, and it is time to review what has emerged and what remains to be determined.

At present, the most reliably evaluated effect on mortality is that of moderately prolonged beta-blockade in the period after discharge from hospital. With the report in this issue of the final data from the sotalol study (p. 1142), results are now available from a total of at least eleven randomised trials[1-10] of various types of beta-blocker started orally a week or more after myocardial infarction and continued for some months or years thereafter. Crude examination of this mass of data, involving more than 13 000 patients, suggests that on average the risk of death in these trials was reduced from just over 10% to just under 8%—i.e., that the total number of deaths was reduced by about 25%. Although worldwide a reduction of "only" 25% in the risk of death after discharge from hospital could prevent tens, or perhaps even hundreds, of thousands of deaths each year, such moderate risk reductions are surprisingly difficult to demonstrate in any but the largest clinical trials. For example, even in a trial with 2000 patients, 1000 treated and 1000 not, one might observe about 100 deaths (10%) in the control group and 80 (8%) in the treated group, which would not be statistically significant—and, although the play of chance might increase this difference enough to make it significant, it might equally well dilute or even reverse it. These difficulties are even more acute in smaller trials, so even if the various beta-blockers tested in the eleven different long-term trials actually all reduced the risk of death identically by exactly 25%, one would expect only a few of the trials to indicate a statistically significant benefit, most to indicate a non-significant benefit, and a few to indicate a non-significant harmful effect.

This is exactly what has happened; the 11 observed relative risks (i.e., the odds of death among patients allocated to treatment compared with the odds among those allocated to control groups) range between 0·5 and 1·1. Most of these 11 separate relative risks are not statistically significant, although the "pooled" relative risk of 0·74 is enormously significant (being some five standard errors below unity). (Interestingly, no trial reported a relative risk significantly better than 0·74 and none reported a relative risk significantly worse than 0·74. In formal statistical terms, there was no statistically significant heterogeneity of the 11 relative risks about their pooled value of 0·74.) In this context, even the trial results in which more deaths[9] were observed among the treated than among the control patients do not show that the agent they tested was ineffective. Conversely, even the results from those few trials in which a "statistically significant" benefit happened to be achieved do not show that their particular beta-blocker was more effective than the others. With a few exceptions, the separate trials were hardly large enough to demonstrate on their own that beta-blockade was of any merit, let alone to distinguish reliably between the merits of different types of beta-blockade (although it is noteworthy that the three most widely accepted trial results[1,2,11] have involved three quite different beta-blockers). Likewise, in trials that are hardly big enough to demonstrate a "main effect" there is little prospect of reliably picking out subgroups

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11. Hjalmarson A, Herlitz J, Malek I, et al. Effect on mortality of metoprolol in acute myocardial infarction. *Lancet* 1981; ii: 823–27.

in which treatment is advantageous and subgroups (whether defined by age, by site, or by severity of disease) where it is not. It is therefore unsurprising that even quite striking "subgroup effects" reported in particular studies,[7,12] have not been confirmed by subsequent trials.[1,2]

Consequently, perhaps the most informative use of these eleven trials is to calculate from them some sort of a weighted average of the relative risks suggested by each, and to accept this as an approximate indication of the risk reduction typically conferred by long-term beta-blockade. Clearly, patients in one trial cannot reliably be compared directly with patients in any other trial, but this is avoided as long as an appropriate statistical procedure[13] is used for averaging the treatment effects suggested by the different trials. This[13] leads to the previously cited pooled relative risk estimate of 0·74 (with the very narrow 95% confidence interval 0·65–0·83).

Some indirect support is given to this pooled estimate by the seven trials,[11,14-18] on a total of nearly 4000 patients, in which treatment was scheduled to begin within a few hours or days of admission to hospital and to continue for at least some months thereafter. For, although in those seven trials no material difference in mortality was observed in hospital (where about half the deaths took place), a difference of about the above magnitude was seen in the long-term, post-discharge mortality. A few long-term trials have yet to be published, but even if they have been delayed because they happen to indicate a non-significantly opposite effect no large change in the aggregated results can be expected.

Thus, the aggregated results from these eleven or eighteen trials now add up to conclusive proof that allocation of patients to a regimen of long-term beta-blockade reduces the death rate by about 25%, so the risk reduction among those who actually comply with allocation to such a regimen probably exceeds 25%. This effect will be widely regarded as sufficient to justify routine use of long-term beta-blockade in many patients for perhaps the first year or so after discharge from hospital, unless the side-effects[19] become troublesome. However, the main mechanisms remain unclear, and antiarrhythmic, antihypertensive, and even antiplatelet effects of beta-blockers have been invoked. Partly because of this uncertainty it is not obvious whether the risk reduction varies much depending on the ancillary properties of the beta-blocker that is used; nor, unfortunately, is there good evidence as to how long treatment should continue. More importantly, we do not know whether beta-blockade should be instituted within a few hours of the onset of pain, or whether a few days' delay is acceptable (or even, perhaps, advisable). The theoretical arguments for and against short-term early beta-blockade in the first few hours of coronary care are qualitatively different from the empirical arguments for long-term post-discharge blockade, and the two treatments must therefore be assessed separately. Against early treatment, some have feared that it might precipitate complete heart block or cardiac failure. Reassuringly, however, there has been no excess of these conditions reported in the aggregate of all the trials of early treatment.

The arguments for early treatment depend on its ability, if given intravenously rather than orally, to limit the eventual size of the infarct. The process of infarction of the myocardium is typically spread out over a period of 6–12 hours, or even longer, so at the time of admission to hospital a few hours after the onset of pain a substantial further amount of tissue infarction can still be expected in many patients. Within a few hours more after admission, infarction will usually be largely complete[20] (except, of course, for patients who suffer early reinfarction). Treatments aimed at limiting the eventual size of the infarct should therefore presumably be instituted as soon as possible if they are to have any material effect, and should wherever possible be given intravenously rather than orally, since effective blood levels of beta-blockers are not achieved until several hours after oral administration.[21,22] In experimental infarction and in various randomised clinical trials, intravenous beta-blockers given at most a few hours after coronary ligation or after the onset of pain can substantially reduce the eventual size of the infarct.[14, 23-26] Although

12. Andersen MP, Bechsgaard P, Frederiksen J, et al. Effect of alprenolol on mortality among patients with definite or suspected acute myocardial infarction. *Lancet* 1979; ii. 865–68; see also 868–69
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26. Jurgensen HJ, Frederiksen J, Hansen DA, Pedersen-Bjergaard O. Limitation of myocardial infarct size in patients less than 66 years treated with alprenolol *Br Heart J* 1981; **45:** 583–88.

it is possible that the myocardium thus preserved may be of little functional value (and, indeed, if it remains ischaemic it may even be arrhythmogenic), the limitation of infarct size by early beta-blockade obviously raises the possibility that such intravenous treatment may have an important effect on mortality.

But there is as yet no reliable, direct evidence. Fourteen small randomised trials[27-40] (on a total of only 2000 patients) have involved short-term treatment starting with only an oral beta-blocker but, as noted above, because of the slowness of an oral beta-blocker to take effect, their pooled relative risk (1·07, with standard error 0·14) is not only statistically but also medically uninformative. The seven randomised trials[23-25, 41-44] of short-term treatment that have at least started with an intravenous dose are unfortunately even smaller. So, even if the 1-week mortality in these trials is pooled with that in the three randomised trials[11,13,14] in which intravenous treatment was followed by long-term treatment, this yields a total of only 81/1569 control deaths and 76/1596 treated deaths. This difference is not statistically significant, but the figures do at least suggest that early intravenous beta-blockers need not be as hazardous as was once feared (especially if injected slowly, with close monitoring, into patients without contraindications such as severe failure, second-degree heart block, or unusual risk of bronchospasm).

Unfortunately, the uncertainty as to whether the promise of early intravenous treatment will be fulfilled has not been dispelled even by the excellent study of intravenous metoprolol followed by 13 weeks of oral metoprolol.[11] For, not only was the mean time from onset of pain to intravenous treatment so long (11·3 hours) that the overall mean enzyme reduction was hardly significant, but also the reduction in mortality was chiefly seen not in the first week (23 placebo versus 18 metoprolol deaths) but in weeks 2–13 (39 placebo versus 22 metoprolol deaths). Although mortality in weeks 2–13 might have been favourably affected by early treatment, it is impossible from that study to know whether it really was, or whether only the long-term treatment was important. Moreover, the preliminary results[14] from a similar, though smaller, study of metoprolol are somewhat less promising.

Thus, for the moment it is difficult to disagree with the consensus that emerged from a meeting in New York at which the results from the largest[1] of the long-term beta-blocker trials were presented and discussed. By randomisation in eleven trials of over 13 000 patients, the effects on mortality of long-term beta-blockade after myocardial infarction have now been reliably estimated; but, at present, those of early intravenous short-term beta-blockade during the actual development of myocardial infarction have not. And perhaps they will not be until many thousands of early treatments have also been randomly allocated.

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Brain Damage after Open-heart Surgery

THE mortality-rate for open-heart surgery—2·7% in 15 399 cases of congenital and acquired heart disease managed in six centres[1-6]—is only twice that reported for general surgery in a British teaching unit.[7] In the U.S.A., coronary-vein grafting is now as commonplace as hysterectomy and appendicectomy: some 100 000 are done a year, with a mortality rate of under 1%. Unfortunately, brain damage sometimes arises during these operations. The reported incidence has fallen—from 44% in 1970[8] to 15% in 1975[9]—but much depends on the sensitivity of the tests. Cerebral damage may not be obvious at routine follow-up, showing itself

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