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 trials1-10 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 deaths9 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 results1,2,11 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

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, 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 is used for averaging the treatment effects suggested by the different trials. This 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, 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 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 (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. 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. Although
has not been dispelled even by the excellent study of intravenous metoprolol followed by 13 weeks of oral metoprolol. 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 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 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 we will not be until many thousands of early treatments have also been randomly allocated.

Unfortunately, the uncertainty as to whether the promise of early intravenous treatment will be fulfilled

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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—is only twice that reported for general surgery in a British teaching unit. 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 to 15% in 1975—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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3. Griffiths SP, Zarula BM, Courtney D, Spencer FC, Malm JR. Trends in 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%.