Conclusions

The incidence of adverse reactions from beta-blockers in patients after myocardial infarction is not insignificant and constitutes an important aspect of the decision whether to treat all patients. While an improvement in mortality of 25% may sound impressive, in reality it represents a change in death rate from eight patients per 100 to six per 100. Since most general practitioners will see fewer than 10 patients with myocardial infarction a year, such statistics may seem unconvincing, especially in the face of a high incidence of adverse effects.

My present practice is to limit treatment with beta-blockers to those patients at high risk after myocardial infarction (for example, those with large infarcts or with pronounced cardiac arrhythmias during the acute phase of their illness) and to those requiring beta-blockers for other reasons, such as hypertension, angina, or arrhythmias after the acute event. Further data are needed on the efficacy of beta-blockers in those patients with small infarcts based on provocative tests such as exercise testing. The prediction of those patients who are more likely to develop severe adverse effects from beta-blockade may become clearer, and this will help define the group of patients in whom beta-blockade is acceptable after myocardial infarction. Present evidence would support the administration of beta-blockers for 12 months, but for longer periods the evidence is not convincing.

References

1 Gillam PMS, Prichard BNC. Propranolol in the therapy of angina pectoris. *Am J Cardiol* 1966;**18**:366-9.
2 Smith SE. Personal view. *Br Med J* 1982;**284**:818.
3 Baber NS, Wainwright Evans D, Howitt G, *et al.* Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia. *Br Heart J* 1980;**44**:96-100.
4 Norwegian Multicentre Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;**301**:801-7.
5 Hjalmarson A, *et al.* Effect on mortality of metoprolol in acute myocardial infarction. *Lancet* 1981;ii:823-6.
6 Hansteen V, *et al.* One year's treatment with propranolol after myocardial infarction; preliminary report of Norwegian multicentre study. *Br Med J* 1982;**284**:155-60.
7 Beta-blocker Heart Attack Trial Research Group. A randomised trial of propranolol in patients with acute myocardial infarction. I Mortality results. *JAMA* 1982;**247**:1707-14.
8 Julian DG, *et al.* A controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1982;i:1142-7.
9 Knarr JW. Impotence from propranolol. *Ann Intern Med* 1976;**85**:259.
10 Miller RA. Propranolol and impotence. *Ann Intern Med* 1976;**85**:682-3.
11 Report of MRC Working Party on mild to moderate hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet* 1981;i:539-43.
12 Day JL, Simpson N, *et al.* Metabolic consequences of atenolol and propranolol in the treatment of essential hypertension. *Br Med J* 1979;i:77-80.
13 Alderman EL, *et al.* Coronary artery syndromes after sudden propranolol withdrawal. *Ann Intern Med* 1974;**81**:625-7.
14 Gerber JG, Nies AS. Abrupt withdrawal of cardiovascular drugs. *N Engl J Med* 1979;**301**:1234-5.
15 Sanders G. Adverse reactions to beta-blocking drugs. *Adverse Drug Reaction Bulletin* 1978;**68**:240-3.
16 Deacon CS, Lennard MS, *et al.* Inhibition of oxidative metabolism by β-adrenoceptor antagonists is related to their lipid solubility. *Br J Clin Pharmacol* 1981;**12**:429-30.
17 Breckenridge A. Joggers blockade. *Br Med J* 1982;**284**:532-3.
18 Alvan G, von Bahr C, *et al.* High plasma concentrations of β-adrenoceptor blocking drugs and deficient debrisoquine hydroxylation. *Lancet* 1982;i:333.
19 McNeer JF, Wallace AG, *et al.* The course of acute myocardial infarction. *Circulation* 1975;**51**:410-3.
20 Theroux P, Waters DD, *et al.* Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;**301**:341-5.

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Part III Some conclusions

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In recent years advances in cardiology have been much more concerned with the investigation of heart disease than with our ability to treat it medically. Clinicians will therefore particularly welcome recent therapeutic advances in beta-blockade, because they improve the balance between investigation and treatment.

In part I Professor Hampton summarised the remarkably numerous clinical trials of beta-blockade after infarction, and in part II Professor Breckenridge reviewed some of the outstanding therapeutic issues. Some important conclusions are now firmly established; but it is equally important to recognise what remains uncertain and to avoid unreasonable extrapolations.

Firstly, treatment with beta-blockers started in the first weeks after myocardial infarction has been shown to reduce the mortality in the next 1-2 years by about 25%. This could amount annually in the UK to about 2500 extra survivors of this high-risk period. (This estimate is based on the treatment of patients under the age of 65; in the aged, side-effects are more troublesome and benefits have not been clearly shown.) The quality of life in these extra survivors is not known, but it is not necessarily worse than average.

Secondly, this reduction in mortality represents a major advance in controlling coronary heart disease. The long-term prognosis of the new survivors is, however, uncertain. Since atherosclerotic disease is generally progressive, most will presumably ultimately die of it. We should speak of lives prolonged, not of lives saved: a man's life has been saved from coronary heart disease only when he dies of something else! If the benefits of the treatment prove to be confined to the first two years after infarction, then the effect on national mortality may not be more than about a 2% reduction. Such a benefit is in no way to be decried; but we must avoid thinking that beta-blockers are the answer to the problem of coronary disease. Major control of this mass disease requires mass primary prevention.

Thirdly, few therapeutic advances in cardiology have been placed so clearly beyond argument. This implies that placebo-controlled trials will no longer be acceptable in the generality of survivors of myocardial infarction. The question for other kinds of treatment (platelet-acting drugs, sulphinpyrazone, surgery) is now simply whether they will confer useful benefit in addition to that proved by beta-blockers. This imposes alarming demands on the size and design of future trials, and there will be no easy answers (and perhaps, for some important questions, no answers at all).

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Fourthly, valuable though these trials have been, it is hard to believe that there needed to be so many. Our trial resources are limited, and this sort of unco-ordinated proliferation has been extremely wasteful. Furthermore, the benefits of beta-blockade after myocardial infarction are not bought cheaply. In the timolol trial, for example, one extra year of life required on average about 30 patient years of treatment with its attendant side effects and drug costs. (This figure, though it may sound alarming, in fact compares favourably with the treatment of hypertension.) On strict statistical principles the trials can be used only to show the average benefit in all treated patients, and a purist is logically correct to conclude that he should now treat all eligible patients. Many clinicians, however, will prefer a selective policy, arguing that low-risk survivors are not going to benefit enough to merit long-term medication.

Fifthly, the trials have not indicated how long the treatment should continue. Beyond 1-2 years the survival curves do not diverge significantly. The only way to tell whether maintenance of advantage depends on maintenance of treatment would have been to stop treatment in a random 50% of patients, and regrettably this was not done. Those doctors who choose to continue treatment beyond 1-2 years are acting on intelligent guesswork not on evidence. The testing of this question is urgently needed.

It could be dangerous to extrapolate the results of the trials to groups of patients other than those studied. Unpublished results from the UK oxprenolol trial suggest that treatment started more than one year after myocardial infarction may have an adverse effect on survival. Also the effect on survival in cases of unstable angina and chronic angina is not known, and it might be either good or bad. Beta-blockers should be given for angina only when they are needed for symptomatic relief and their effects in unconfirmed myocardial infarction remain unknown. Furthermore, the effectiveness of beta-blockers in secondary prevention may not apply to prevention of the first clinical attack. Thus, the recent trials do not show that beta-blockers should be the preferred treatment for hypertension: that judgment must await the outcome of current trials in hypertension.

Finally, the experience of trials in which treatment was started early in the attack of suspected infarction are not consistent. If there is an effect on the size of the infarct, how this will influence long-term disability and prognosis still remains to be discovered.

In the past it has often been difficult to identify an association between the results of clinical trials and changes in clinical practice. It is much to be hoped that this time we shall see an exception. It is now clear that beta-blockade, used correctly, can prevent many deaths after infarction.

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Aspects of Sir Thomas Browne

Sir Thomas Browne: the man and the physician

A BATTY SHAW

Browne's enduring claim to fame rests on his reputation as one of the great writers of English prose, as a moralist, and as a student of the thought and philosophy of his time. Few appraisals have, however, been attempted of his life and work as a physician.

Life and family (fig 1)

Thomas Browne was born in London in 1605. His mother was a relative of the Countess of Devonshire of the day and his father was a City mercer of Cheshire stock who died when Thomas was 8. Browne was educated at Winchester and Broadgates Hall, Oxford, renamed Pembroke College during his second year there. He then spent about three years completing his medical education by study at Montpelier, Rome, Padua, and Vienna, with a final period at Leyden, where he obtained its university's MD in 1633. On returning to England there is debate as to whether he spent the next two years in medical practice at Shipden Vale in Yorkshire or in Oxfordshire, but I believe the former view to be correct. During these two years he wrote the first and most famous of his literary works, *Religio Medici*, though it was not published until 1642 (fig 2), and then in an anonymous and pirated edition; the first authorised edition bearing his name appeared in the following year.

In 1636 Browne settled in Norwich, where he was to remain for the rest of his life, and in the following year he obtained the MD of Oxford University. Norwich at that time would have had its attraction for a young man intending to establish a practice as a physician, for it was still the largest city of the realm after London, as it had been since the Norman Conquest, but his main encouragement to settle there came from his former Oxford tutor, the Reverend Thomas Lushington, who had moved to Norwich in the previous year as chaplain to its Bishop. His European reputation in the worlds of learning, literature, and natural history has tended to overshadow his parallel career as a physician, but many contemporary accounts bear witness to the high professional reputation he achieved during his 46 years of practice in Norwich. He was but one of a number of physicians practising in the city, thus showing the emergence of trained physicians in provincial cities such as Norwich during the seventeenth century and that he was not without his local professional competitors. Browne, however, was the leading physician among them, with a reputation and practice throughout East Anglia, and it is a fortunate consequence of the assiduous attention paid to the collection and editing of his writings for literary ends that much evidence is thereby provided of his life and work as a physician.

As a sign of the respect Browne earned in the eyes of his

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