Ann. Rev. Pharmacol. Toxicol. 1983. 23:29–44

BETA RECEPTOR BLOCKING AGENTS IN THE SECONDARY PREVENTION OF CORONARY HEART DISEASE

J. Anders Vedin and Claes E. Wilhelmsson

Cardiology Unit and Section for Preventive Cardiology, Department of Internal Medicine, Eastern Hospital, University of Göteborg, S-416 85 Göteborg, Sweden

INTRODUCTION

In the western world coronary heart disease (CHD) constitutes the single most common cause of death from middle age on in both men and women (1). This fact remains despite a recent decline in mortality from the disease in some countries including the USA (2). The magnitude of the problem has induced planning and realization of a number of trials aimed at reducing mortality and new events.

The natural history of CHD is usually divided into two major parts separated by the initial manifestation of the disease. During the period preceding the initial clinical manifestation certain factors have been found to be statistically significantly associated with increased risk of an initial event, i.e. primary risk factors. Measures aimed at these factors are usually included under a common heading, primary prevention. In an analogous way factors associated with increased risk of a second or further events are termed secondary risk factors, and measures aimed at a reduction of these late complications are grouped under the heading secondary prevention. Coronary heart disease has three major clinical manifestations: angina pectoris, acute myocardial infarction, and sudden cardiac death, listed in ascending order of clinical urgency. Despite widespread availability of cardiopulmonary resuscitation, in some areas few victims of sudden cardiac death had been exposed to secondary prevention, and for a number of reasons, despite the high prevalence of the symptom, there have been very few systematic studies or controlled trials of secondary prevention in angina pectoris.

An acute myocardial infarction constitutes a clinical event that defines a subcategory of the population that, in addition to being easy to find, has

a notably increased risk of subsequent deaths and new events in comparison to healthy contemporaries. These facts have led to a large number of secondary prevention studies using various methods of intervention, e.g. hygienic (increased physical activity, cessation of smoking, and dietary modification) or pharmacological, using various therapeutic principles, e.g. anticoagulants, platelet active, lipid lowering, or antiarrhythmic agents. When the literature in each of the different pharmacological fields is compared, only the various studies on beta receptor blocking drugs (beta blockers) provide an overwhelming bulk of evidence urging prophylactic treatment of large categories of patients.

This presentation reviews the secondary prevention studies with various beta blockers and presents the view of the authors with regard to their clinical importance.

Natural History of Myocardial Infarction

It is a well-known fact that a large proportion of patients with acute manifestations of CHD die so soon after onset that the available time alone precludes hospitalization. It is also well known that the rate of death declines exponentially with time after onset of symptoms. The mortality during the hospital stay usually ranges between 10% and 20% in nonselected patient groups below 70 years of age. Obviously hospital mortality is influenced more by the median time it takes for patients to reach hospital after onset of symptoms than by the actual length of the final period of hospitalization. The mortality in unselected patient groups with a similar upper age limit usually amounts to 5–10% during the first year, and during the years thereafter to 3–5% (3). The mortality during the hospitalization and long-term follow-up is associated with and may be predicted by age, the number of previous infarctions, and factors associated with the amount of necrotized tissue (4) and, at least indirectly, the amount of coronary vascular involvement (5). The influence of myocardial involvement is more marked during the relatively early phase, and vascular factors with the relatively late phase. Clearly these two intervals cannot be distinctly separated, and both types of factors play a role throughout the course of the disease. So far, nonfatal reinfarctions have been found to be more difficult to predict, and the risk of a nonfatal reinfarction is not related to age (6).

SECONDARY PREVENTIVE TRIALS

Requirements of Studies in Secondary Prevention

Ideally a secondary preventive trial should prove the effectiveness of the compound and provide a sound scientific basis for future therapeutic recommendations. In order to meet these requirements a number of different aspects have to be covered. Obviously the trials need to include enough patients to comprise a sufficient number of endpoints to allow statistical

analysis at a satisfactory level of significance and provide a sufficient likelihood to reach that result (power). Only an analysis including all randomized patients regardless of subsequent fate is devoid of bias from the preferences and notions of the investigators-analysts (intention to treat). Furthermore, to allow inference from the findings several study properties not always met by the various trials are desirable. A clear presentation of population at risk, the study patients forming a representative sample, clearly presented prerandomization exclusions, a prospectively stratified design, clearly presented withdrawals, and well-defined endpoints all form basic requirements to enhance inference. Needless to say the patients should be entered during not too wide a "window" or interval during the course of the disease, and be treated with relevant doses for suitable periods of time.

It has been argued that beta blockers preclude maintenance of blindness in a study due to their effect on heart rate. It has also been argued that the use of undisputable endpoints, e.g. deaths from any cause, would add to the reduction of bias and make a blinded design unnecessary. Unfortunately both arguments are false and have been used for various reasons to produce study designs that invalidate all findings from these studies. In all the studies of beta blockers the average heart rates in the beta blocker groups have to be lower than in the placebo groups. However, the variance in both treatment groups has always been sufficiently great to cause a large overlap between the two groups. For this reason in every case a precise prediction of the actual treatment becomes uncertain. This holds true also for studies using intravenous administration or exercise tests. In these instances efforts have been made to increase blindness by separating study records and study personnel used during injection-exercise stages of the studies from other parts.

Maintenance of the highest possible degree of blindness was seen to be particularly important when it was shown that already unspecific measures, a good medical practice, may have a substantial impact on reinfarctions and deaths without the use of beta blockers or other specific cardiac agents (7, 8). Thus studies without randomized control groups receiving blind reference treatment cannot be used for proof of therapeutic effectiveness in CHD. Only studies with such control groups are referred to in the subsequent sections of this review. No retrospective studies are considered.

Randomized, Placebo-Controlled Trials

The first placebo-controlled trials, published during 1966–1968, used oral doses today recognized as insufficient for effective clinical beta blockade and produced nonconclusive results. Since then a number of studies have been published. Only very few of these trials meet a large number of the quality requirements listed above. A number of these studies have shown no difference among the many endpoints between the actively and placebo-treated groups. The other studies have produced at least some positive evidence

with regard to one or several important endpoints. For these reasons the published studies have been divided into two categories, nonconclusive and positive studies. Special emphasis will be given to the major points of criticism often raised in connection with the respective trials.

Nonconclusive Trials

The trials published so far are listed in Table 1. Some of the trials have dealt with too few patients, having had too few endpoints, to produce any meaningful results (9, 14, 15). Several studies did not deal with a representative group of patients since the placebo mortality rate was much lower than expected in a nonselected group of patients or the drop-out rates were high (9, 11, 12, 13). In the study by Barber et al (10) a high oral dose was administered as soon as possible after onset of symptoms. There was no significant difference between the practolol and placebo treatment groups. However, in one retrospective analysis patients with high entry heart rates seemed to have an improved survival. If sudden death is used as the major endpoint the late mortality rate is somewhat lower in the practolol group.

Generally it may be concluded that the majority of these trials turned out to be nonconclusive because of the low number of endpoints observed, which in turn may be explained by numbers of patients in the trials or selection of low risk patients.

Positive Studies

Some characteristics of the complete positive long-term studies are listed in Table 2. In the Gothenburg Alprenolol Trial (16, 17), 274 men and women who had experienced a myocardial infarction were screened for eligibility after discharge from hospital. Forty-four patients were excluded due to contraindications either to beta blockade or to participation in a controlled

Table 1 Nonconclusive prospective trials

Author	Year	Number of patients	Compound (mg daily)
Reynolds & Whitlock (9)	1972	87	Alprenolol (400)
Barber et al (10)	1975	484	Practolol (600)
Wilcox et al (11)	1980	388	Atenolol (100) Propranolol (120)
Wilcox et al (12)	1980	473	Disopyramide (450) Oxprenolol (120)
Baber et al (13)	1980	720	Propranolol (120)
Coronary Prevention Research Group (14)	1981	1103	Oxprenolol (80)
McIlymoyle et al (15)	1982	391	Metoprolol n.p.[a]

[a] n.p. = not published.

Table 2 Some characteristics of the positive completed long-term studies with beta blockers

Author	Published	Active drug (dose)	Start after MI	Duration	Age limits	Number of patients	Cumulative placebo mortality (%)	Reduction of total mortality (%)	Reduction of reinfarctions (%)
Wilhelmsson et al (16, 17)	1974	alprenolol (400)	5–8 w	2 yrs	57–67	230	12	50	11
Multicenter International (18)	1975 1977	practolol (400)	1–4 w	1–3 yrs	–70	3053	8[a]	20	23
Andersen et al (19)	1979	alprenolol (10 iv; 400)	acute	1 yr	all ages	282 (198)	20 (35)[b]	55 (+37)[b]	n.p.[c]
Norwegian Study Group (20)	1981	timolol (20)	6–27 days	1–3 yrs (17)	20–75	1884	22	39	28
Hjalmarson et al (21)	1981	metoprolol (15 iv; 200)	acute	3 mos	40–75	1395	9	36	n.p.
Beta blocker Heart Attack Trial (22)	1981	propranolol (120–240)	5–21 days	12–30 mos	30–69	3837	10	26	n.p.
Hansteen et al (23)	1982	propranolol (160)	4–6 days	1 yr	35–70	560	13	32	24
Julian et al (24)	1982	sotalol (320)	5–14 days	1 yr	30–69	1456	9	18	41

[a] Total mortality.
[b] Below and above 65 years of age.
[c] Not published.

trial. The remaining 230 patients were assigned to four different subgroups. In each separate subgroup the patients were randomly allocated to treatment with either 400 mg of alprenolol daily or placebo. Patients below 57 years of age were not available for the present study due to other ongoing projects. On the other hand, an upper age limit was also desirable in order to avoid difficulties of assigning causes of death and problems with multiple diseases in advanced age. The age-range was therefore limited to ages 57–67 to ensure homogeneity. After randomization only eight patients were withdrawn from the placebo and eight from the alprenolol groups. None of these patients died or had a reinfarction before the completion of the follow-up time.

The prospective stratification was successful since there were no deaths in the low risk subgroup either on placebo or alprenolol. Thus, the reduction of the number of sudden deaths was statistically significant when this difference was analyzed for relevant combinations of subgroups. Total mortality was reduced by 50%. The number of nonfatal reinfarctions did not differ between the alprenolol and placebo groups (Table 3).

This study has been criticized mainly for three major reasons: the small number of patients in the study and therefore too low a level of statistical power; a high frequency of digitalis treatment; and the lack of statistical significance for the effect on total mortality. However, although small, the group of patients under study was representative of all the infarction cases in Gothenburg. Standardized criteria were applied for treatment of symptoms and complications in all patients in addition to the trial treatment.

It has been suggested that alprenolol may only reduce fatal digitalis-induced ventricular arrhythmias. Other trials, however, do not publish frequencies of concomitant treatment. Digitalis and alprenolol may, on the other hand, have a synergistic effect, thus producing the decrease of fatal ventricular arrhythmias. It is unlikely, however, that the prevalence of digitalis treatment has any significant effect, since the long-term mortality in Sweden was the same as in other European countries. Also the prevalence of digitalis treatment was the same among survivors and deaths when the alprenolol and placebo groups were compared.

In many countries it is impossible to use cause-specific or mode-specific mortality as endpoints. This is due to the great uncertainty regarding classi-

Table 3 Endpoints in the Gothenburg Alprenolol Trial (16, 17)

	Alprenolol	Placebo
Number of patients	114	116
Nonfatal reinfarctions	16	18
Sudden deaths	3	11
Total number of deaths	7	14

fication of causes of death when the autopsy rate is low. In Gothenburg the autopsy rate was high (90%). It is unlikely that alprenolol has any effect on noncardiac deaths. Therefore, in absolute numbers the difference for total mortality is less than for sudden cardiac mortality. Thus, the reduction of sudden deaths implies a meaningful reduction also of the total mortality.

The Multicentre International Practolol Trial demonstrated a difference regarding both sudden and cardiac mortality among patients maintained in the study (Table 4) (18, 25). When all randomized patients were analyzed the significance no longer remained. The low placebo mortality reflected that the patients were indeed not representative of all postinfarction cases. Since pretrial exclusions have not been detailed it is impossible to generalize from these findings. No prognostic stratification was used. A retrospective analysis was carried out in order to define target patients showing a maximum benefit from treatment with practolol. The analysis indicated that low body weight, low prerandomization diastolic pressures, and site of infarction were important variables in selecting patients. There was a high number of early deaths in the practolol-treated patients who had inferior infarctions (26), and when patients that were included later were analyzed, similar long term mortality reductions were observed regardless of site of infarction. Body weight was inversely correlated with practolol plasma levels, suggesting a dose-response relationship. A major drawback of such a retrospective analysis is, however, that it may never alone serve as a basis for a therapeutic recommendation. It may only serve to initiate new trials, which then have to use a prognostic stratification. It should be stressed, however, that practolol did significantly reduce the total cardiac mortality among all randomized patients.

The aim of the Copenhagen Trial (19) was to study short- and long-term mortality and effects of early treatment and variables associated with infarct size as well as tolerance for alprenolol in elderly patients. Treatment was begun on admission to the coronary care unit, when patients were allocated randomly to treatment with intravenous alprenolol or placebo. Oral maintenance treatment ensued and the patients were followed up for one year after admission. Prognostic stratification was made on the basis of age, heart rate, and degree of impaired consciousness at admission. Pretrial exclusions have been detailed. In age groups below 65 years treatment and placebo groups were comparable. Above 65 years the placebo group was biased towards a

Table 4 Endpoints in the Multicentre International Trial of Practolol (25)

	Practolol	Placebo	$p <$
Number of patients	1524	1514	
Cardiac deaths	83	110	0.04
Total deaths	94	117	0.09

worse prognosis than the alprenolol group (Table 5). For all randomized patients there was a significant 50% reduction of the total mortality below 65 years of age (Table 6). In addition there was a reduction of ventricular arrhythmias (27) and CPK-release (28) among the alprenolol patients, particularly if treatment was instituted soon after onset of symptoms.

The findings were different in patients above 65 years of age. Thus, ethical considerations necessitated an earlier stop of patient intake in this age group. There was no difference between alprenolol and placebo regarding the total mortality. The outcome in the placebo group may be partly expected based on the high number of previous infarctions. However, in patients with first infarctions also there was no reduction of mortality. It has not proved possible to isolate a group of patients in this age group with a beneficial effect of alprenolol. In the entire study a careful follow-up with regard to nonfatal reinfarctions was not possible.

The Norwegian Timolol Trial (20) showed a clear reduction of the total mortality for all randomized patients with similar trends of reduced mortality also for all presented subsets of patients. The design was stratified and the numbers large. The patients were representative of a general population and all pretrial exclusions have been clearly presented. Mortality data also for those patients excluded prior to randomization will become available. The groups were well balanced and analyses ascertained that differences found with regard to patient characteristics of the timolol and placebo groups did not influence the results. Withdrawals were well defined and have been clearly presented. The need to treat patients openly with a beta blocker was the major reason for withdrawing patients from the study. The number of patients was sufficiently large to make an analysis of side effects meaningful. Side effects were more common in the timolol group, but they may be considered minor in view of the reduction of mortality. Timolol

Table 5 The Copenhagen Alprenolol Trial. Patients >65 years, subgroup I–IV (19)

Clinical information	Alprenolol	Placebo
Number of patients	98	100
Males	61 (62%)	55 (55%)
Females	37 (38%)	45 (45%)
Age (mean ± SEM)	74 ± 0.5	74 ± 0.5
Who group I	70 (71%)	61 (61%)
Who group II + III	28 (29%)	39 (39%)
Previous A.M.I.	39 (40%)	28 (28%)
Hypertension Angina pectoris Diabetes mellitus	Equally common in both groups	

Table 6 Findings of the Copenhagen Alprenolol Trial after on year (19)

	Alprenolol	Placebo	p <
⩽ 65 years			
Number of patients	140	142	
Total deaths	13	29	0.01
⩾ 65 years			
Number of patients	98	100	
Total deaths	48	35	n.s.

reduced total mortality by 39% (Table 7), sudden deaths by 45%, and nonfatal reinfarctions by 28%. The effect on witnessed instantaneous deaths was even more marked.

As is clearly presented in Table 2, in addition to the Copenhagen Alprenolol Trial only one other trial (21) has addressed the important question whether early intravenous initiation of treatment has advantages not seen in studies in which treatment was started after several days. In that study the effect of metoprolol and placebo on mortality and variables related to infarct size were studied in patients with a definite or suspected acute myocardial infarction. Treatment was started as soon as possible after arrival in hospital and continued for 90 days. Metoprolol was given as a 15 mg intravenous dose followed by an oral daily dose of 200 mg. After 90 days all patients with a diagnosed definite myocardial infarction were treated openly with metoprolol 100 mg b.i.d. for 2 years. Pretrial exclusions have been carefully detailed and after allocation to one of several risk groups 53% of all eligible patients were randomized to treatment with metoprolol or placebo. 1395 patients were randomized, 809 developed a definite myocardial infarction and 162 a probable infarction according to well chosen and accepted criteria. The number of withdrawals were equal in the two groups (19%) and have been carefully listed. There were 62 deaths in the placebo group (8.9%) and 40 deaths in the metoprolol group (5.7%), a reduction of 36% which was highly significant (Table 8).

Various electrocardiographic and enzymatic variables frequently used as indirect indicators of "infarct size" were reduced in the metoprolol group if treatment was instituted early (<12 hours). However, the reduction of mortality was independent of when treatment was started (29). The mortality difference between the placebo and metoprolol groups after three months

Table 7 Findings of the Norwegian Timolol Trial (20)

	Timolol	Placebo	p <
Number of patients	945	939	
Deaths	98	152	0.001

Table 8 Findings of the Gothenburg Metoprolol Trial (21)

	Metoprolol	Placebo	p <
Number of patients	698	697	
Deaths	40	62	0.03

was maintained after one year or after a further nine months of open treatment. The difference was unchanged in patients included after 12 hours from onset of symptoms but enhanced in patients included earlier. These observations are in agreement with a beneficial late effect possibly associated with a diminution of the index infarction.

Furthermore, metoprolol treatment significantly reduced the number of nonfatal reinfarctions subsequent to the index infarction period and the number of episodes and patients with ventricular fibrillation. Treatment of complications and common clinical states among patients with myocardial infarction followed predetermined guidelines regardless of trial medication. Tolerance and safety was good. Fewer analgesics, diuretics, and antiarrhythmic agents were used in the metoprolol group (Å. Hjalmarson, personal communication.)

After the publication of the timolol and metoprolol trials the results have been corroborated by another large trial using propranolol, the so-called Beta Blocker Heart Attack Trial (BHAT) (22). A total number of 3837 patients were randomized, making it the largest beta blocker postinfarction study so far (Table 9), and pretrial exclusions have been carefully listed. The trial was carefully conducted and withdrawals and side effects were monitored. Apparently, there was a pretrial exclusion of high risk patients and only 23% of all hospitalized patients were included.

This explains the low placebo mortality compared to expected rates based on natural history studies and also in comparison to the Norwegian Timolol Trial. The trial was prematurely interrupted and it has been maintained that this was done according to a decision model formulated in advance, also accounting for the statistical problem of multiple looks.

Further analyses have shown that, in similarity with the timolol trial, there was also a significant 28% reduction of the nonfatal reinfarctions in the propranolol group. Subgroup analyses have failed to identify categories of patients with adverse effects. The beneficial effects were unrelated to age, sex, time of entry, and site of infarction.

Table 9 Finding of BHAT (22)

	Propranolol	Placebo	p <
Number of patients	1916	1921	
Deaths	138	188	0.005

Table 10 Findings of the Norwegian Propranolol Trial

	Propranolol	Placebo	p <
Number of patients	278	282	
Number of deaths	25 [11]	37 [23]	0.12 [0.04][a]

[a] Figures in brackets denote sudden deaths.

Since the publication of the BHAT Trial two more trials have been published, one with propranolol (23) and one with sotalol (24). Both of these trials failed to reduce significantly the total mortality among all randomized patients (Tables 10 and 11). In the sotalol trial the reduction of nonfatal reinfarctions and in the propranolol trial the reduction of sudden deaths reached statistical significance. In the propranolol trial a 30% reduction of all the deaths by one year did not suffice to reach statistical significance due to too small groups. In the sotalol study the reduction of the total mortality was only 18%.

CLINICAL THERAPEUTIC CONSEQUENCES

Thus, many trials have evaluated the effect of beta blockade on survival both during the acute stage of MI and during the long-term follow-up. The methodology of the trials has undergone considerable refinement during the last decade. The bulk of evidence from these trials now may be converted into well founded practical therapeutic recommendations covering a range of clinical issues which are discussed below.

Mortality and Reinfarction Reduction

Eight positive prospective studies now strongly support the concept that chronic beta blockade during the post-infarction period effectively reduces the total mortality and particularly the number of sudden deaths due to myocardial ischemia (Table 2). In order to assess the total experience of beta blockers in postinfarction patients a pooling of all studies that were double-blind and consisted of more than 20 deaths was made. About 17,000 patients have completed randomized placebo-controlled studies. The total mortality reduction is around 25%. For studies with early entry, or before day 5, the situation is not yet clearly resolved. Only one early entry study has conclusively demonstrated a significant lowering of the mortality (21), but gains some support also from another study (19).

Table 11 Findings of the Sotalol Trial

	Sotalol	Placebo	p <
Number of patients	873	583	
Deaths	64	52	0.3

The reduction of mortality (Table 2) varies from 18% to 55% in the different studies. After comparable periods of follow-up the reduction is crudely related to the level of the placebo mortality. The Timolol, BHAT, Gothenburg Metoprolol, and Sotalol studies have established that not only deaths but also nonfatal reinfarctions can be prevented by long-term beta blockade. Since the spontaneous (untreated) mortality never exceeds 50% during several years it is clear that if all patients are treated some may be treated unnecessarily with respect to prevention of deaths. However, in addition to the long-term prophylaxis beta blockers also have other indications such as hypertension and angina pectoris. Approximately 55% of postinfarction patients fullfill such other more conventional indications for beta blockers. The intensity of endpoints is somewhat higher among these patients. Therefore the proportion of patients being unnecessarily treated is much less than is immediately apparent (30).

Selection of Patients

Ideally treatment should be reserved only for patients likely to derive benefit from it. In selecting patients suitable for acute or long-term beta blockade various aspects have to be considered. The conventional contraindications, slightly different in acute and long-term settings, have to be considered. In order to avoid unnecessary treatment of patients with a spontaneously benign outlook it would be desirable to be able to select target patients with high frequencies of endpoints.

TARGET GROUPS Various methods have been applied in order to isolate patients with particularly high risks of mortality. Today precise prediction of mortality is possible by various prognostic models. In one such model a multiple logistic regression analysis was used (4), and 80% of all deaths in 2 years were confined to 30% of all the patients. In order to prevent mortality it should therefore suffice to treat the high risk patients. However, the risk of nonfatal reinfarctions is totally unrelated to these variables and must be associated with other factors (4). Some of these factors are known, e.g. tobacco smoking and hypertension, but it has not yet proved feasible to predict subsequent nonfatal reinfarctions at discharge from hospital or later with a high degree of precision.

Furthermore, when a patient suffers a nonfatal reinfarction he is immediately transferred to a worse prognostic group that has a much higher mortality. Therefore, no distinction of a meaningful group of target patients is indeed feasible. It is difficult to refrain from giving long-term beta blocking therapy to all postinfarction patients without contraindications.

AGE LIMITS In the Danish Alprenolol Study a deleterious effect was suggested in patients above 65 years of age when treatment was instituted early. However, in the trials with metoprolol, propranolol, and timolol no

such untoward effect among elderly patients was observed. A direct comparison between the two trials using early intravenous drug administration shows differences in the prerandomization exclusion criteria (Table 12). There are important differences in terms of heart rates, blood pressures, and other factors, but a more detailed analysis of the difference between the studies is at present impossible, lacking completely published data from both studies. However, by using proper exclusion criteria treatment of patients up to 75 years may be advocated.

CONVENTIONAL CONTRAINDICATIONS In the Gothenburg Metoprolol and Alprenolol Trials some 20 and 15%, respectively, were excluded because of conventional contraindications against acute and long-term beta blockade, respectively. In both studies a somewhat higher number of patients were excluded from participation in the trials prior to randomization, but this was because of administrative criteria making participation in follow-up studies unsuitable or impossible. These figures were also corroborated by the findings of the timolol trial. Other studies have not dealt with equally large proportions of the entire group of eligible patients and therefore generalizations are more difficult.

Start of Treatment

In view of the results from the two trials using early intravenous administration it may yet be too early to conclude that intravenous therapy is routinely indicated. Using other indications, e.g. reduction of pain, tachycardia, and high blood pressure, however, intravenous administration seems safe when standard contraindications are observed. Thus, the recommendation is that beta blocking therapy should be started in all patients after 4–5 days in hospital, and earlier in selected patients. The latter group is likely to expand as familarity with early treatment becomes more widespread.

Table 12 Comparison of different contraindications to participate in the Metoprolol Gothenburg Study and the Alprenolol Danish Study

Metoprolol Gothenburg Study (8)
Systolic blood pressure < 100 mm Hg
Heart rate < 45 beats/min
AV-block (P–Q time > 0.24 sec)
Pulmonary congestion, ausculatory > 10 cm basal rales
Alprenolol Danish Study (6)
Cardiogenic shock (systolic blood pressure < 85 mm, Hg, heart rate > 100 beats/min and cold sweat)
Heart rate < 40 beats/min
AV-block II and III
Pulmonary oedema persisting after 2 h treatment

Duration of Treatment

No study has covered longer follow-up periods than 36 months. Several studies verify that treatment is indicated for a period of 2 years. The relative risk of dying among postinfarction patients declines with time after infarction. The excess morbidity and mortality in comparison to healthy contemporary subjects has been calculated to be 30–50 times during the first 2 years, then to stabilize around 5–10 times and less during the third and subsequent years, respectively (3, 4). The relative importance of prophylactic treatment therefore declines with time. After 2 years patients on prophylactic treatment may be reevaluated on an individual basis. In patients with angina or hypertension treatment may be maintained but may be step-wisely withdrawn in the remaining patients. Some of these patients will then develop usually mild hypertension and angina. Treatment may therefore have to be reinstituted.

Selection of Agents

The mechanisms behind the mortality-reducing effect of the different beta blockers are at present unknown. Therefore, it may be dangerous and too early to generalize the secondary preventive effect to all existing beta blockers. The available beta blockers vary regarding $beta_1$ and $beta_2$ receptor affinity, intrinsic sympathomimetic activity, and membrane stabilization activity. The only single characteristic common to all beta blockers with a positive effect on survival is blockade of the $beta_1$ receptors. It is likely that this effect is the most important, but it need not follow that all compounds with the capacity for $beta_1$ blockade are effective in postinfarction prophylaxis since the detailed mechanisms of neither ischemia nor beta blockade in that situation are sufficiently well known.

Side Effects

So far only three studies have been sufficiently large and been presented in sufficient detail to allow a balanced judgement of the occurrence of side effects (20, 21, 22). It is clear from these trials that the beta blocker indeed causes significantly more side effects than placebo. However, these side effects are benign when the effects on mortality and reinfarction are considered. In a clinical stituation, in an individual patient, the problem may be controlled by changing to another beta blocker.

Community Aspects

After the completion of the Gothenburg Alprenolol trial and the International Multicentre Practolol trials long-term beta blockade was accepted as effective long-term treatment for postinfarction patients in Göteborg. Long-term treatment with beta blockers has been used routinely after infarction since 1975. In order to assess whether this would have any impact on long-term mortality during 1968–1977 an analysis has been made (31). Over

a 10-year period a significant decline in mortality, of around 40% during 2 years after infarction, was observed and remained after adjustments for variations in prehospital, in-hospital mortality, fluctuations in primary cardiovascular risk factor levels, varying patient selection, smoking habits, age, and predicted prognosis. The increase of beta blocker treatment is the most plausible factor explaining the reduction of the postinfarction mortality.

CONCLUSIONS AND SUMMARY

The following conclusions regarding beta blocker use after myocardial infarction may be made:

1. Long-term mortality is reduced at least by alprenolol, timolol, propranolol, and metoprolol. A general claim of this nature for all beta blockers is premature.
2. Recurrent infarctions are reduced by at least timolol, propranolol, metoprolol, and sotalol.
3. Further large scale late entry long-term placebo trials are unethical.
4. No practical, effective, and meaningful selection of target patients for treatment with beta blockers is possible.
5. Treatment starting when patients have stabilized in hospital, after e.g. the fifth day, is well documented. Routine intravenous treatment on arrival to hospital may improve the therapeutic yield but also needs further documentation.
6. Treatment should be maintained for a period of at least two years.
7. Beta blockers are safe and well tolerated when the standard contraindications are observed.

Literature Cited

1. Vedin, A., Wilhelmsson, C., Bolander, A.-M., Werkö, L. 1971. Mortality trends in Sweden 1951–1968 with special reference to cardiovascular causes of death. *Acta Med. Scand. Suppl.* 515:1–76
2. Epstein, F. H., Piza, Z. 1979. International comparisons in ischemic heart disease mortality. In *Proceedings of the Conference on the Decline in Coronary Heart Mortality,* ed. R. J. Halvik, M. Feinlieb, pp. 58–88. NIH Publ. No. 79–1610
3. Vedin, A., Wilhelmsson, C., Elmfeldt, D., Säve-Söderbergh, J., Tibblin, G., Wilhelmsen, L. 1975. Deaths and nonfatal reinfarctions during two years' follow-up after myocardial infarction. A followup study of 440 patients discharged alive from hospital. *Acta Med. Scand.* 198:353–64
4. Vedin, A., Wilhelmsen, L., Wedel, H., Pettersson, B., Wilhelmsson, C., Elmfeldt, D., Tibblin, G. 1977. Prediction of deaths and reinfarctions after initial myocardial infarction. *Acta Med. Scand.* 201:309–16
5. Amsterdam, E. A., Brocchini, R., Vismara, L. A., Mason, D. T. 1974. Sensitivity of portable monitoring and exercise stress in detection of ventricular arrhythmias in coronary patients. *Circulation* 49/50 (Suppl. 3):111–213
6. Bergstrand, R., Vedin, A., Wilhelmsson, C., Wilhelmsen, L. 1982. Incidence and prognosis of acute myocardial infarction among men below age 40 in Göteborg, Sweden. *Eur. Heart J.* In press

7. Vedin, A., Wilhelmsson, C., Tibblin, G., Wilhelmsen, L. 1976. The Post Infarction Clinic in Göteborg, Sweden. A controlled trial of a therapeutic organisation. *Acta Med. Scand.* 200:453–56
8. Kallio, V., Hämäläinen, H., Hakkila, J., Luorila, J. 1979. Reduction in sudden deaths by a multifactorial intervention programme after acute myocardial infarction. *Lancet* 2:1091–94
9. Reynolds, J. L., Whitlock, R. M. L. 1972. Effects of beta-adrenergic receptor blocker in myocardial infarction treated for one year from onset. *Br. Heart J.* 34:252–59
10. Barber, J. M., Boyle, D. M., Chatuverdi, N. C., Singh, N., Walsh, M. J. 1975. Practolol in acute myocardial infarction. *Acta Med. Scand. Suppl.* 587:213–16
11. Wilcox, R. G., Roland, J. M., Banks, D. C., Hampton, J. R. A. 1980. Randomised trial comparing atenolol with propranolol in immediate treatment of suspected myocardial infarction. *Br. Med. J.* 1:885–88
12. Wilcox, R. G., Rowley, J. M., Hampton, J. R., Mitchell, J. R. A., Roland, J. M., et al. 1980. Randomised placebo-controlled trial comparing oxprenolol with disopyramide phosphate in immediate treatment of suspected myocardial infarction. *Lancet* 2:765–69
13. Baber, N. S., Wainwright-Evans, D., Howitt, G., Thomas, M., Wilson, C., et al. 1980. Multicentre post-infarction trial of propra olol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia. *Br. Heart J.* 44:96–100
14. Coronary Prevention Research Group. 1981. An early intervention secondary prevention study with oxprenolol following myocardial infarction. *Eur. Heart J.* 2: 389–93
15. McIlmoyle, L., Eva s, A., Boyle, D. M., Cra , G., Barber, J. M., Elwood, H., Salathia, K., Shanks, R. 1982. Early intervention in myocardial ischaemia. *Br. Heart J.* 47:189
16. Wilhelmsson, C., Vedin, A., Wilhelmsen, L., Tibblin, G., Werkö, L. 1974. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 2:1157–60
17. Vedin, A., Wilhelmsson, C., Werkö, L. 1975. Alprenolol after myocardial infarction. *Acta Med. Scand. Suppl.* 575:1–56
18. A Multicentre International Study. 1975. Improvement i prog osis of myocardial infarction by long-term beta-adrenoceptor blockade using practolol. *Br. Med. J.* 1:735–40
19. Andersen, M. P., Fredriksen, J., Jürgensen, H. J., Pedersen, F., Bechsgaard, P., et al. 1979. The effect of alprenolol on mortality among patients with definite or suspected acute myocardial infarction. *Lancet* 2:865–68
20. Norwegia Study Group. 1981. Timolol-induced reduction in mortality a d reinfarction in patients surviving acute myocardial infarction. *N. Engl. J. Med.* 304:801–7
21. Hjalmarson, Å., Herlitz, J., Malek, I., Ryden, L., Vedin, A., et al. 1981. Effects on mortality of metoprolol in acute myocardial infarction. A double-blind randomized trial. *Lancet* 2:823–27
22. Beta-Blocker Heart Attack Trial Research Group. 1982. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *J. Am. Med. Assn.* 247:1707–14
23. Hansteen, V., Møinicher, E., Lorentsen, E., Andersen, A., Strom, O., et al. 1982. One year's treatment with propra olol after myocardial infarction: preliminary report of Norwegian multicentre trial. *Br. Med. J.* 284:155–60
24. Julian, D. G., Jackson, F. S., Prescott, R. J., Szekely, P. 1982. Controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1:1142–47
25. Hampton, J. R. 1981. The use of beta-blockers for the reduction of mortality after myocardial infarction. *Eur. Heart J.* 2:259–68
26. Chamberlain, D. A. 1978. The effect of beta blockade on mortality after myocardial i farction. In *Beta Blockade 1977,* ed. W. Mäurer, A. Schömig, R. Dietz, P. Lichtlen, pp. 303–10. Stuttgart: Thieme. 374 pp.
27. Pedersen, F., Rasmussen, S. 1983. Prophylactic effect of alprenolol on ventricular arrhythmias during the inpatient phase of acute myocardial infarction. *Acta Med. Scand.* In press
28. Jürgensen, H. J., Fredriksen, J., Hansen, D. A., Pedersen, O., et al. 1981. Limitation of myocardial infarct size in patients less than 66 years treated with alprenolol. *Br. Heart J.* 45:583–88
29. Deleted in proof
30. Wilhelmsson, C., Vedin, A., Wilhelmsen, L. 1982. Costbenefit aspects of postmyocardial infarction intervention. *Acta Med. Scand. Suppl.* 651:317–20
31. Vedin, A., Wilhelmsson, C., Bergstrand, R., Johansson, S., Ulvenstam, G., et al. 1982. *Secular trends in survival after myocardial infarction.* Presented at Am. Heart Assn. Conf. Cardiovasc. Dis. Epidemiol., 22nd, Sa Antonio, Texas